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EDITORIAL

Challenges of bone tissue engineering in orthopaedic patients

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Abstract

Bone defects may impede normal biomechanics and the structural stability of bone as an organ. In many cases, the correction of bone defects requires extensive surgical intervention involving the use of bone-grafting techniques and other procedures in which healing is slow, there is a high risk of infection and considerable pain is provoked - with no guarantee of complete correction of the defect. Therefore, the search for surgical alternatives continues to present a major challenge in orthopaedic traumatology. The reamer-irrigator-aspirator (RIA) system, which was devised to avoid the problems that can arise with autograft harvesting from the iliac crest, consists of collecting the product of the femoral canal after reaming. The RIA technique improves osteogenic differentiation of mesenchymal stem cells, compared to bone marrow aspiration or cancellous bone harvesting from the iliac crest using a spoon. Another approach, the Masquelet technique, consists of reconstructing a long bone defect by means of an induced membrane grown onto an acrylic cement rod inserted to fill the defect; in a second surgical step, once the membrane is constituted, the cement rod is removed and cancellous autograft is used to fill the defect. Both in RIA and in the Masquelet technique, osteosynthesis is usually needed. Bone transportation by compression-distraction lengthening principles is commonly implemented for the treatment of large bone loss. However, complications are frequently encountered with these techniques. Among new techniques that have been proposed to address the problem of large bone loss, the application of stem cells in conjunction with tissue engineering techniques is very promising, as is the creation of personalised medicine (or precision medicine), in which molecular profiling technologies are used to tailor the therapeutic strategy, to ensure the right method is applied for the right person at the right time, after determining the predisposition to disease among the general population. All of the above techniques for addressing bone defects are discussed in this paper.

Key words: Bone loss; Mesenchymal stem cells; Reamer-irrigator-aspirator; Autograft; Personalised medicine; Bone transportation; Precision medicine; Masquelet technique

Core tip: This paper discusses the problems created by large bone loss, especially after major trauma, and considers current alternatives to autograft or allograft, such as the reamer-irrigator-aspirator system, the Masquelet technique, bone transportation, or the combination of stem cell therapy and tissue engineering. Future Directions addressed mainly concern the new concepts of personalised medicine and precise medicine.

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INTRODUCTION

High-speed traffic accidents and injuries in the workplace continue to present major orthopaedic trauma challenges, often requiring tissue reconstruction. Worldwide, more than 4.5 million reconstructive surgical procedures are performed annually, in response to accidents, cancer surgery or cosmetic needs. In many countries, too, victims of war or civil conflict must receive complex reconstructive surgery to overcome large tissue losses[1]. Although progress has been made to reduce the incidence of such events (for example, through legislation and improved road safety), orthopaedic procedures for the treatment of large bone loss have not achieved such tangible improvements.

Bone defects can be classified into two different groups: Cavity defects, when the loss does not affect limb biomechanics but nevertheless interferes with osteosynthesis or arthroplasty implantation; and segmental defects, when normal biomechanics are impeded and the structural stability of the bone as an organ may be endangered[2,3]. Reparative surgery is still the treatment of choice for these lesions, and autologous bone grafting is considered the gold standard approach in the clinical setting, in order to harness bone's natural regenerative capacity when a bone defect occurs. Large bone losses, however, are best treated by allograft, despite its less osteogenic nature. In many cases, the correction of bone defects requires extensive surgical intervention using bone-grafting techniques. Numerous surgical procedures may be needed, involving long healing times. These fairly aggressive surgical techniques can produce a high risk of infection; moreover, they provoke substantial pain and do not guarantee complete correction of the defect. The emotional impact on the patient and financial burdens on the healthcare system are further problematic issues. Moreover, substantial donor-site morbidity and limitations on the quantity of bone that can be harvested proscribe its application when large bone loss occurs. In view of these considerations, alternatives to autograft for reconstructive surgery in large bone defects continue to be sought in orthopaedic traumatology.

Cavity defects can be resolved by the application of bone autograft, morselized allograft or bone substitutes. When cavity defects are not too large, they can be treated relatively straightforwardly, and alternative approaches such as combining cavity filling with implants are usually possible. On the other hand, cavity defects - and segmental bone defects in particular - can present major problems. This kind of lesion is often provoked by high-energy trauma, as a result of which the soft tissues are severely affected. Segmental defects may provoke major functional disability and even require amputation. The pelvis is often affected in patients with long-term arthroplasty loosening and also after bone tumour resection, whereas the femur and the tibia are commonly injured by severe trauma. In addition, the long bones of the upper limbs are frequently affected in serious accidents.

In this respect, many surgical techniques have been proposed, and some success has been obtained in treating relatively minor injuries. However, they have proved less effectiveness against large tissue lesions following high-energy trauma. When a large bone defect is experienced, the treatment challenge is twofold. On the one hand, since bone cannot remain uncovered, by skin or muscle, the absence of soft tissue cover will provoke necrosis and the non-viability of any therapeutic attempt; this is very commonly the case with injuries affecting the tibia, when anterior muscle cover is absent or insufficient. Furthermore, even well-covered bone will also need suitable vascularisation of an appropriately-sized, strong graft; otherwise, bone healing will never take place. Apart from these soft tissue and bone problems, function can be severely affected by lesions to tendons and nerves. Therefore, graft size and the vascularisation of bone implantation are of crucial importance for tissue viability, tendon function and nerve physiology.

Current therapies in this field have been developed over many years. The reimplantation of extruded bone segments is uncommon, due to worries about infection and unclear guidelines regarding timing, stabilisation and sterilisation techniques, which have led this procedure to be rejected by the majority of surgeons. The few papers that have been published in this respect have encountered great difficulties in reaching useful conclusions[4]. Another approach is that of autograft harvested from the iliac crest, followed by vascularised autograft - however, the thin shape of this autograft makes it less useful in cases of large bone loss. Bone transportation procedures have also been suggested, together with the induced membrane Masquelet technique, with the creation of an artificial in-situ chamber, after inserting a temporary cement spacer

which will eventually be surrounded by a periostium-like layer. These therapies have been complemented by growth factors - including platelet-derived growth factors and bone morphogenetic proteins (BMPs) - and cell therapies. Synthetic bone has also been included in compound approaches, in a quasi-random combination involving chance as much as science[5].

All of these research lines have sought to focus on the keystone of bone synthesis: Matrix-forming cells. However, although the results of these new therapies are always said to be "promising", they still cannot be managed precisely or combined appropriately with osteosynthesis fixation.

At present, achieving a biomechanically strong, well-vascularised and physiologically-functional bone from the treatment of segmental bone defects continues to pose a major challenge.

Tissue engineering (TE) is a promising technology for secondary reconstruction after severe trauma. TE is an interdisciplinary science combining cellular, engineering, biochemical and physicochemical factors to improve or replace biological functions[6-8], either in combination with, or independently of, an osteosynthesis technique. Different types of cells and bioactive factors have been shown to play an important role during this regeneration. The ideal biomaterial is currently believed to comprise a porous three-dimensional scaffold with patterned substrates, offering vascularisation and regeneration properties[9]. However, the biochemical mediators of this process are imperfectly understood, and their biochemical properties and the sequence in which they act remain to be clarified.

In any case, creating tissue is an unavoidable necessity, as large bone loss cannot be repaired by an *in vivo* physiological mechanism. Whether TE will eventually be capable of replacing normal biological mechanisms has yet to be determined.

BMPs are known to promote cell multiplication and differentiation, but not sufficiently as to provide an alternative to currently-available therapies. Moreover, the sequence pathways of the different molecules remain unknown. Cell therapy, as currently applied, involves three sequential steps: *In vivo* extraction, *ex vivo* manipulation and *in vivo* implantation. After this long and complex procedure, the outcome is still uncertain, especially for large bone defects.

In view of these considerations, the following techniques have been proposed, incorporating the knowledge accumulated from cell therapy principles.

REAMER-IRRIGATOR-ASPIRATOR

The reamer-irrigator-aspirator (RIA) technique is designed to avoid the problems that arise with autograft harvesting from the iliac crest, and consists of collecting the product of the femoral canal after reaming[10-13]. The cells thus collected and cultured present the same properties as those from the iliac crest[14-17]. Studies have shown there are no phenotypical differences between mesenchymal stem cells (MSCs) collected from the pelvic bone and RIA, and that the gene expression alteration found in RIA can be owned to the isolation technique employed[18]. Cell characterisation is similar for adipose-MSCs, bone marrow-MSCs and RIA-MSCs, and the osteogenic potential is similar with *in vitro* and *in vivo* approaches[19,20].

The RIA technique enhances the osteogenic differentiation of MSCs, in comparison with bone marrow aspiration or cancellous bone harvesting with a spoon from the iliac crest[17,18]. A recent study[18] compared harvesting by RIA with iliac crest aspiration and collection with a spoon, and reported that a greater concentration of colony-forming unit-fibroblasts of MSCs was obtained by RIA. Better results were also obtained by RIA for calcium tissue fixation as well as the gene expression of BMP2, SMAD5, runt-related transcription factor 2, osteocalcin and collagen type I alpha 1. Calcium fixation and osteogenic gene expression diminished considerably with higher passage numbers, in every specimen. The authors concluded that the harvesting procedure is critical for MSC differentiation *in vitro*. On the other hand, the CD271 selection of MSCs in RIA also produces a significant rise in MSC pureness and an increase expression of the transcripts implicated in bone synthesis, vessels formation and chemical attraction[20].

Revascularisation takes place within three months of reaming, and bone thickness restoration of the cortex appears normal after 14 mo, allowing the opportunity for further reaming[21].

Although RIA has achieved very promising results with respect to cavity defects, this technique is less useful for segmental ones, for which osteosynthesis supplementation is required. Furthermore, complications can arise in relation to the learning curve, to over-reaming and, in some patients, to cardiac problems produced by rapid blood loss; the latter complication is closely related to previous cardiopathy[22,23].

RIA produces less pressure than intramedullary reaming and nailing, and a lower incidence of micro-embolism, according to studies of animals[24,25] and of humans[26]. However, one clinical study reported different findings from those obtained in animal experimentation, observing no differences in healing complications between intramedullary reaming and RIA, although there was a statistically non-significant tendency for the RIA group to present more complications[27].

Both in conventional reaming for intramedullary nailing and in RIA, the coagulation and fybrinolytic response consists of higher cytokine levels, together with increased IL-6 levels, particularly in intramedullary reaming[28]. However, other authors found no differences between these groups in relation to complications and IL-6 levels[29]. In a biomechanical study of cadavers, under ideal conditions, it was found that RIA did not greatly reduce femoral cortical strength but that careful attention was needed to avoid the catastrophic failure that can occur using this eccentric reamer[30]. In fact, femoral fracture can occur[31], and complications have been reported to affect

31% of cases, including postoperative pain, bone defects, lung embolism, myocardial infarction and iatrogenic fracture[32].

RIA has similar outcomes among all human races[13], and can be performed either antegradely or retrogradely[33,34].

MASQUELET TECHNIQUE

In the original Masquelet technique, a long bone defect is reconstructed by an induced membrane grown onto an acrylic cement rod inserted to fill the defect; in a second surgical step, once the membrane is constituted, the cement rod is withdrawn and the gap is filled with cancellous autograft[35]. In a modification of this technique for tibial fractures, new surgical steps were added, such as the transfer of the soleus muscle island flap, vascularised with retrograde flow on the posterior tibial artery[36]. Further research, on large animals, has shown that the membrane compartmentalises the bone defect, protecting it from the humoral and cellular environment of the muscular layer[37]. The Masquelet technique has become increasingly popular in recent years for the treatment of large bone defects[38]. Good results have been achieved in a large-scale study of bone defects in which autograft harvesting from the iliac crest was replaced by RIA[39], with reduced morbidity in the second step of graft collection.

New research into the Masquelet technique has been conducted in animal studies, but the cell biology of animals is radically different from that of humans[40-43]. In this respect, the paper by Aho *et al*[44] is particularly significant because these authors histologically characterised the induced membrane in humans, finding that greatest vascularisation took place in 30 d old specimens, and that levels diminished by sixty per cent during the following ninety days. Thirty day-old membranes presented the highest expression of vascular endothelial growth factor, interleukin 6 and collagen 1, while sixty day-old membranes expressed less than 40% of these levels. Specific alkaline phosphatase activity, the production of aminoterminal propeptide of type-Ⅰ procollagen and calcium concentration all increased in co-cultures in the presence of a membrane sample. Furthermore, in thirty day-old cultures membranes, the formation of aminoterminal propeptide of type-Ⅰ procollagen was more than twice as high, and calcium fixation was four hundred per cent greater, than in cultures of sixty day-old membranes. The authors concluded that induced membranes present osteogenesis-improving competences but that outcomes gradually worsen, and that the ideal period for carrying out the second step operation is before the second month following the implantation of foreign material[44].

Although many studies have been conducted since the Masquelet technique was first presented in 2000, it is still difficult to predict the outcome of this approach to bone defect reconstruction, as complications are likely among most patients; at the outset, the surgical field is not optimal and the course of reconstruction is long and difficult[45].

Refinements of the Masquelet technique have recently been published by the original authors[46], and further research has been carried out on the basic science for human patients, with multicentre recruitment[47]. It has been shown that effective osseous formation *via* the Masquelet technique only incompletely emulates the cytokine expression of normal biological bone regeneration[47]. Abundant expressions of insulin-like growth factor 1 are associated with successful Masquelet therapy, whereas transforming growth factor β appears to have low contribution. Consequently, the appropriate examination of a successful non-union treatment and of cytokine expression can be made even with a lesser number of cases. Therefore, further research in this field should be aimed at finding a method, based on a small population of patients, for predicting the success or otherwise of treatments for bone loss defects, including the Masquelet technique.

BONE TRANSPORTATION

In 1969, a paper appeared in MEDLINE on the Ilizarov technique aimed to treat "long tubular bones defects by means of one of their fragments"[48]. However, it was published only in Russian and had little impact in Western orthopaedic science. Four years later, an Australian nursing journal published a paper by another Russian author on the Ilizarov technique[49], and during the 1970s more papers appeared on the biomechanics of the Ilizarov apparatus[50]. However, it did not become known worldwide until the 1980s, when Italian authors gave it major prominence[51,52]. The approach described by Ilizarov was more than a single apparatus or technique; it became a new paradigm of the cell biology of bone regeneration, and was amply referred to as such in Russian publications during this decade[53]. By creating a fracture only in the bone cortex ("bone corticotomy"), thus minimising surgical trauma, a callus consolidation process is triggered, and then maintained by means of immobilisation for 7-10 d. Thereafter, continuous slight distraction of less than 1 mm/d is exerted, and over time the gap becomes filled in.

Since its introduction, the Ilizarov technique, with its associated compression-distraction lengthening principles for the treatment of large bone loss, has been applied worldwide, and is now known as bone transportation. It has been shown that during this bone lengthening, the soft tissues also undergo stretching and subsequent physiological metaplasia[54].

However, from the outset it has been apparent that the results obtained with the Ilizarov technique are excellent in some cases, good in others, and only fair in many. Consequences such as persistent infection, deformity, limb shortening, resultant limping, impacts on other joints (for example, equinus), dystrophy and severe pain have led some patients to request amputation. The duration of this treatment and its many negative consequences discourage many therapists from considering bone

transportation in patients with severe osseous loss, and these complex cases are often referred to specialised centres[55]. Outcomes are also compromised by variables such as age older than 20 years, a larger gap magnitude, and diaphyseal rather than metaphyseal loss location[56].

More is now known about the biology underlying Ilizarov bone transportation, and greater experience and better fixators have enabled surgeons to better apply this technique. In addition, new approaches have been tested, mainly in animal experimentation, combining Ilizarov's principles with TE[57-63]. Nevertheless, the technique is still subject to complications and cannot systematically ensure a satisfactory outcome following large bone loss.

COMBINED STEM CELL THERAPY AND TE

Along the last decade, the combined treatment with immature MSCs and growth factors has been considered another promising therapy for bone synthesis. Nonetheless several terminally-differentiated cell lines (keratinocytes, osteoblasts, fibroblasts, osteocytes, chondrocytes and hepatocytes) cannot be used for artificial tissue constructs. Stem cell candidates to build artificial tissues comprise embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and postnatal adult stem cells[64,65]. There are still some limitations to the practical use of ESCs and iPSCs, including the cytogenetic regulation of teratoma development, ethical issues, immune uncertainties in relation to ESCs, and the requirements for genetic manipulation of iPSCs. Multipotent MSCs derived from postnatal adult stem cells (Wharton's jelly cells, adipose tissue, bone marrow and dental pulp) are potentially useful because of their immunocompatibility and the absence of ethical concerns. Bone marrow (BM) and adipose tissue are also good sources of stem cells for clinical use[66,67]. MSCs are cells of mesodermal derivation - different from the hematopoietic linage- existing in various infant and adult organs and conjunctive tissues. Pluripotent MSCs in the BM stromal tissue are capable of differentiating to multiple mesenchymal lines, including osseous and chondral cells. Therefore, it follows that these MSCs could be employed in the restoration of large bone loss caused by traumatisms, surgical procedures or maladies. MSCs from tissue sources such as human dental pulp, exfoliated deciduous teeth (SHED) and periodontal ligaments have similar characteristics to BM-MSCs but are commonly liable to problems such as a short collection of cells and a reduced quantity of collected tissues[68,69]. Other significant drawbacks to the use of MSC in tissue repair include, firstly, the ache and problems associated with BM collection and, secondly, the low income (1 MSC/10^4-10^6 stromal cells), which makes *ex vivo* amplification a necessity[70-72].

The adipose compartment appears to have a rich population of stem cells and, like BM, has a large cellular stroma, constituted of fibroblastic-like cells (the stromal vascular fraction - SVF). This cell segment, obtained from human aspiration of fat, in turn has cells with multiline capabilities, called adipose stem cells (ASCs), which experience adipogenesis, osteogenesis, chondrogenesis and myogenesis *in vitro*. Some experiments have started to study the osteogenic potential of ASCs *in vivo*, in amalgamation with a great diversity of scaffolding materials[73]. The use of human ASCs (hASCs) in scaffolds for osseous TE has been indicated as the alternative approach of the current century to substitute or repair the normal physiology of traumatised, injured or lost bone. The biological relationship between osteoblasts and adipocytes is reflected in their common MSC origin. The accumulation of marrow adipocytes in bone loss may be caused by a shift in the commitment of MSCs from the osteogenic to the adipogenic pathway. hASCs have several characteristics that make them compatible with currently-available strategies for creating new tissue, including cell transfer, induction and the generation of tissue constructs. The MSCs located within adipose tissue are effortlessly harvested in wide amounts, with slight donor site injury or general alterations. Furthermore, human adipose tissue is ubiquitous. Subcutaneous fat tissue fragments can commonly be obtained without general or regional anaesthesia. Present techniques for extracting ASCs are based on collagenase proteolysis after which centrifugal isolation of the SVF from primary adipocytes[74] is performed. Among other features, ASCs present a fibroblast-like phenotype and lack the intercellular lipid precipitations observed in adipocytes[75].

The proliferation capability of ASCs appears to be superior than that of BM-derived MSCs. Studies have revealed that the doubling times of ASCs along the logarithmic phase of growth range between 40 to 120 h, and it changes according to donor age, the nature of fat tissue (white or brown), its placement (subcutaneous or visceral), the harvesting procedure employed, the culture circumstances, the plating concentration and media preparations[76]. Younger donors, have superior proliferation and cell adhesiveness of the ASCs. Cells progressively miss their multiplication capability with passaging. According to the β-galactosidase action, senescence in ASCs is comparable to that seen in BM-derived MSCs. The multiplication of ASCs can be encouraged by a solitary growth factor such as fibroblast growth factors (FGF)-2, EGF, insulin-like growth factor (IGF)-1 or tumor necrosis factor (TNF)-α. FGF-2, in particular, is an effective growth-stimulating factor that is needed for the long-term proliferation and self-renewal of ASCs *via* the extracellular signal-related kinase (ERK) 1/2 signalling pathway[77]. The multiplication of ASCs can likewise be activated by platelet-derived growth factor *via* c-Jun amino-terminal kinase (JNK) activation and by oncostatin M *via* activation of the microtubule-associated protein kinase/ERK and the JAK3/STAT1 pathways. ASC multiplication has also been published to be enhanced by numerous growth factors, which can contain any of the particular growth factors formerly mentioned, complemented by thrombin-activated platelet-rich

plasma, human platelet lysate and human thrombin[78].

ASCs have the capability to differentiate toward a diversity of cell lines, both *in vitro* and *in vivo*. Though ASCs are of mesodermal origin, it is now well known that they can commit themselves into ectoderm and endoderm, as well as mesoderm, lineage cells[79]. Concerning differentiation into cells of the mesodermal line and the regeneration of mesodermal tissues, ASCs may differentiate into adipogenic, osteogenic, chondrogenic, myogenic, cardiomyogenic, angiogenic, tenogenic and periodontogenic lineages. Very little is known about how cell differentiation is affected by aging.

When used combined with a carrying scaffold, the directed osteogenesis of hASCs confirms that adipose tissue is a hopeful autologous font of osteoblastic cells for bone production. This approach provides support for hASC colonisation, migration, growth and differentiation. Few descriptions have been made of purified hASCs in bone engineering, and varying degrees of success have been reported[80-87]. It has not been reported whether cellular free scaffold controls immersed in an osteogenic medium are also capable of achieving bone healing, to any degree[88,89]. Nevertheless, the use of autologous hASCs, managed in the absence of animal-derived materials, following appropriate work in standard unpolluted places, has shown that these cells can be considered safe for uses in tissue engineering, according to European Union standards for clinical cell therapy safety.

Current limitations of hASC for bone TE include the following issues: (1) transitioning from preclinical *in vivo* models to the clinical setting signifies a foremost stride; (2) appropriate serum-free media for these cells must be developed, as foetal bovine serum (FBS) is not suggested for clinical treatments, ought to contamination and infection risk; (3) the *ex vivo* multiplication of cells for two or three weeks renders them vulnerable to possible genomic unpredictability in culture; and (4) appliances that would allow sole-step recruitment, manipulation and grafting are consequently required, to avoid the necessity for cell culture and the associated hazards of utilizing FBS.

Among the challenges to be addressed in hASC bone tissue-engineering for clinical applications, it should be emphasised that the main aim of the ASC TE strategy is to define the real osteogenic capability of ASCs independently of their association with growth factors. Further key challenges to be addressed include the standardising of techniques for recruitment, separating, cultivating and managing hASCs and the publication of procedures for the correct utilisation of carrier materials. Moreover, prospective randomised clinical trials should be conducted to categorize appropriate suggestions for hASC therapies and to validate the clinical results thereby achieved. Finally, ethical and security worries must be determined previous to human use, as the first step in new scaffold usage[90].

As yet, there is little consensus regarding the efficacy of cell-based therapies in skeletal regeneration, or the most effective cell origin type, number, combination or method of delivery[91]. However, better regeneration results have been observed when cells are administered intravenously, subcutaneously or directly to the defect[92-96]. Bone cell progenitors provide bone with its distinctive capacity for repair and regeneration[97], and so their inclusion within a carrier is favoured by most surgeons. Nevertheless, the results obtained in this respect during the last 20 years have been only "promising". Experimental delayed-injection models utilising BM stromal cells have been shown to enhance the repair of injured tissue in relation to "time-of-trauma" cell uses. Time is allowed to elapse between the lesion/bone loss and the injection in order to avoid the early stages of tissue lesions, when the release of cytomodulatory peptides - including TNF-α, interleukins and interferons - and increased concentrations of acute-phase protein in serum appear to diminish the efficacy of stem and precursor populations. Although studies based on experimental spatiotemporal manipulation of cell delivery after the acute inflammatory response have achieved promising results in the field of segmental osseous tissue production[92], it remains apparent that the media and moment of cell delivery significantly influence therapy effectiveness[98].

FUTURE DIRECTIONS

The following main principles of tissue-engineering application in humans are generally accepted: (1) The manipulation of human stem cells for clinical treatment has to be carried out rendering upright laboratory techniques and the guidelines of the Food and Drugs Administration (in United States) or the European Medicines Agency[99]. In this respect, the standardisation of separation and culture processes might raise quality regulations; (2) TE constructs must be considered as medicinal products and their intended use for clinical investigation purposes are subject to European regulations for clinical trials of medical devices and advanced therapies[100]; and (3) Engineered tissue must be structurally and functionally comparable to natural tissue, be of the required size and shape, be able to continue developing after implantation into the body and be able to achieve full integration with the host.

Three components are usually necessary in TE: Cells, extracellular matrices and growth factors to provide molecular signals. The extracellular matrix-scaffold construction is a crucial aspect of bone defect repairing. Recent advances in TE have made available a large number of materials suitable for healing of bone defects and lost bone. Both *in vitro* and *in vivo* formation of bone tissue, using MSCs and 3D scaffolds has been shown[101]. Several scaffolds such as HA/chitosan composites, chitosan or gelatin/TCP constructs, electrospun collagen nanofibres, honeycomb collagen scaffolds and titanium meshes have been used with MSCs. Newly designed scaffolds, resembling the effect of growth factors on adhesion-based mechanisms, need to be further implemented by analyses of the specific "pro-osteogenic" signal

transduction pathways. Osteogenic differentiation relays on cell adhesion and the substrate interaction, which are under the control of integrin complexes interactions. Integrin-matrix interactions can induce numerous signalling pathways, including the MAPK cascade. Although few studies with hASCs have been published, their results show that alternative methods for growth factor stimulation may be fostered to induce hASCs to make and heal bone[102,103].

Regarding signalling systems, it has been suggested that soluble factors produced by ASCs (secretome) are the responsible for the potential clinical impact on different organs/tissues instead of the differentiation capability of hASCs[104]. Analyses from primary hASCs cultures have shown the release of a large series of soluble factors including growth factors such as HGF, VEGF, β-TGF, IGF-1, bFGF, GM-CSF, TNF-α, interleukins (6, 7, 8 and 11), adiponectin, angiotensin, cathepsin D, pentraxin, pregnancy zone protein, retinol-binding protein and CXCL12)[105]. Indeed, HGF expression is increased after the cells have been exposed to bFGF, EGF or ascorbic acid, reinforcing the idea that soluble factors secreted by ASCs can be modulated by exposure to different agents. Thus, transplanted hASCs into inflammatory or ischaemic regions, actively secrete these growth factors, becomes a relevant strategy to promote wound healing and tissue repair. As mentioned previously, the increased bone formation attributed to BMP2-treated ASCs is derived from the osteoconductive and osteoinductive effects of BMP2 or from the ASCs themselves, although this remains to be demonstrated by means of appropriate controls.

Improving the ability of hASCs to generate large quantities of bone to repair bone defect without growth factors represents a major challenge. For that reason signal transduction pathways in adult ASCs need to be explored. Osteogenesis induced by hASCs might employ an alternate signalling pathway for adipogenic and osteogenic fates. Moreover, directed manipulation of downstream signalling paths rather upstream growth factors might be also responsible for stem cell-directed bone regeneration. In this respect, ERK pathways and MAPK signalling in ASC proliferation, migration and apoptosis have been analysed. Bone regeneration has been observed in rabbits with implants of MSCs transduced with Sonic Hedgehog (Shh)-a key protein involved in bone morphogenesis. Furthermore, BMP signalling in ASCs can be modulated by downregulating noggin, using rat ASCs transduced with noggin shRNA, and thus to enhance the differentiation of cells to a osteogenic terminal linage. This noggin suppression + BMP-2 strategy has been confirmed in 3D *in vitro* experiments using complex scaffolds (consisting of chitosan, chondroitin sulphate and an apatite layer) designed to slowly release BMP-2. Wnt signalling pathways are involved in regulation of embryologic patterning, mesenchymal differentiation and stem cell fate[106]. The association of LRP5 gene mutation and the osteoporosis-pseudoglioma syndrome strongly suggests the participation of Wnt signalling in bone formation. Wnt3a induced signalling has been associated with the *in vitro* and *in vivo* inhibition of bone formation[107]. In contrast, increased bone regeneration in bone defects has been observed in MSCs from bone tissues overexpressing Wnt4. This effect may be due to a specific increase in p38 MAPK phosphorylation, which mediates the promotion of bone formation.

TE is considered an advanced therapy medicine product (ATMP), the characterisation of which requires its characteristics (identity, potency, purity and safety) to be defined and measured during product development. ATMP manufacturing activities are mainly focused on the following areas; Pre-Production Activities (patient and donor selection, biopsy procurement, cell/tissue extraction, testing, storage and distribution to Good Manufacturing Practice-GMP-laboratories for production); Production Activities (manufacturing, packaging, labelling, testing, storage and distribution); and Post-Production Activities (testing, storage and administration/implantation of the manufactured product). In the European Union, these activities are mainly regulated by Directive 2004/23EC of the European Parliament[108] which sets quality and safety standards for the main process involved in TE intended for human use (donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells). Other applicable legislation includes Directive 2006/17/EC, Directive 2006/86/EC, Directive 2012/39/EU, Commission Directives (EU) 2015/566 and 2015/565, Regulation (EC) 1394/2007, Directive 2009/120/EC and Directive 95/46/EC[109-116], in addition to EuroGTP guidelines[117].

In ATMPs, preclinical safety/toxicology assays are mandatory for sterility, mycoplasma contamination, endotoxins, aerobic/anaerobic micro-organisms, tumorogenecity and genetic stability. Their design requires specific pre-GMP laboratory activities for the selection and recruitment of stem cell donors and patients. In addition, there are specific regulations for stem cell donors[117]. The clinical problem to be solved with ATMP has two related aspects: On the one hand is the question of individual genetic susceptibility to DNA single nucleotide variants (SNV) related to several pathological conditions, especially tumorigenesis, neoangiogenesis, lymphangiogenesis and cell capacities such as cell adhesion and migration. On the other hand, account must be taken of the gene instability of the cultured and manipulated MSCs used in manufacturing ATMP products.

Among other current limitations to this technique, the potential risk of genomic instability of cells is clearly a main limitation for clinical purposes. This risk appears to increase when e*x vivo* expansion of cells are maintained for more than three weeks. Therefore, much remains to be done to standardise methods and techniques for preparing hASCs for clinical applications and this also must be carried out following GMP, FDA and EMA regulations[118,119]. Indeed, procedures for cells expansion in culture must be according to GMP guidelines for cell manipulation, and their standardisation will facilitate the quality controls, comparative studies,

maximising the reliability and reproducibility of results. In fact, discrepancies have been observed from different studies and from different laboratories, due to variability of the methods and quality of hASC isolation and of the composition of the initial cell culture. hASCs are generally stable (normal diploid karyotype) in long-term cultures, even when they have undergone more than 100 population doublings[120]. However a single report suggests malignant transformation of hASCs cultured for more than four months[121]. Yet, this spontaneous transformation of MSCs may also be due to cross-contamination with malignant cell lines (fibrosarcoma and osteosarcoma)[122]. This controversy on spontaneous hASC transformation requires further experiments and discussion, bearing in mind the needs for a careful manipulation of hASCs, together with long-term follow-up of patients.

As most cells intended for engineering tissues have been subjected to mechanical or enzymatic dissociation, and to rapid proliferation in culture with growth factors and media, among other operations, there is always the possibility that some kind of alteration might be generated within the genetic burden of the cell. Any alteration of these genes could result in tissue dysfunction and a loss of function of the affected tissue.

In this context, the quality control of cell/tissue-engineering should be focused on histomorphology patterns, 3D perfusion seeding, cellular assessments of cell sterility and endotoxins, *in vitro* cellular toxicity, proliferation, adhesion in constructs, genetic quality control for DNA and gene expression and the rheological analysis of scaffolds and new cell/TE. At present, the analysis of tumorogenecity and genetic stability, with respect to chromosomal integrity and mutations of tumour-related genes, is mainly achieved by means of genetic and epigenetic quality controls, to verify at DNA level the absence of any alteration that could lead to malignant transformation, and to ensure that gene expression levels correspond to the functions of native tissues, *via* gene expression analysis of mRNA and proteins.

TE is a novel, complex and specific technology with unexpected risks to public health and to patients. There are three main types of risks to be considered.

Risks to patients arising from the quality of the ATMP product, in particular its components, stability, activity and purity (regarding non-physiological proteins). In the characterisation of a final ATMP product, genetic stability testing is of crucial importance to avoid the risk of clinical side effects due to tumorogenecity, inadequate cell adhesion and/or the increased cell migration capability of expanded/differentiated MSCs seeded onto scaffolds.

Risks derived from the interaction between the ATMP product and the effects on molecular systems of the patient. In this sense it is important to know the immunogenicity, the risks related to genetic modification of cells driving the apoptosis, any change of function, modification of growth and/or differentiation and malignancy. Early and late consequences of homing, grafting, differentiation, migration and proliferation need also to be explored.

Risks related to persistence of the ATMP product in the patient responsible for late complications, such as cancer and autoimmune disorders.

EU legislation requires the genetic analysis of cells to ensure the absence of chromosomal instability and mutations, deletions or translocations in all tissues generated by TE and intended for clinical use.

Personalised medicine/precision medicine (PM) uses molecular profiling technologies to tailor therapeutic strategies, ensuring the right one is delivered to the right person at the right time, and determining the predisposition to disease among the population. Now days, next-generation sequencing (NGS) technologies are more accessible by cost, analytic validity and rapidity. Whole exome sequencing (WES) together with bioinformatics allows the analysis of single nucleotide variants of 85% of coding protein genes (20000 genes, 180000 exons, 1% of the whole genome)[123]. WES sensitivity for known mutations and benign variants reach up to 98.3% and its main clinical use is for the diagnosis of genetic disorders, however, WES also allows phenotype expansion and makes it possible to identify newly mutated genes, undetectable by other techniques.

Taking into account the genetic instability risk of the *ex vivo* expansion of MSCs, we suggest that the standardisation of pre-implant testing of tumorogenic burden, neoangiogenesis and cell adhesion and migration capacities, by means of NGS analysis throughout the differentiation culturing of hASCs, would improve the quality control of artificial bone tissues used for bone repair and help achieve a valid prognosis of full integration within the host of *ex vivo* differentiated hASCs.

Joint exome and transcriptome analysis will help identify a panel of genes involved in hASC proliferation, differentiation, adhesion, migration, and also telomere length control, among other questions, thus constituting a standard genetic stability cell analysis for tissue-engineered bone. This analysis will reinforce the clinical criteria applied in selecting participants for clinical trials with TE, and hence reduce the risk of adverse effects arising from an accumulation of tumour-related gene mutations.

In summary, the clinical reconstruction of large bone defects is a highly challenging procedure, and will probably remain so for the foreseeable future.

REFERENCES

1 **Grasman JM**, Zayas MJ, Page RL, Pins GD. Biomimetic scaffolds for regeneration of volumetric muscle loss in skeletal muscle injuries. *Acta Biomater* 2015; **25**: 2-15 [PMID: 26219862 DOI: 10.1016/j.actbio.2015.07.038]

2 **Paprosky WG**, Perona PG, Lawrence JM. Acetabular defect classification and surgical reconstruction in revision arthroplasty. A 6-year follow-up evaluation. *J Arthroplasty* 1994; **9**: 33-44 [PMID: 8163974]

3 **Paprosky WG**, Cross MB. CORR Insights®: Validity and reliability of the Paprosky acetabular defect classification. *Clin Orthop Relat Res* 2013; **471**: 2266 [PMID: 23613087 DOI: 10.1007/s11999-013-2938-2]

4 **Shanmuganathan R**, Chandra Mohan AK, Agraharam D, Perumal R, Jayaramaraju D, Kulkarni S. Successful reimplantation of extruded

long bone segments in open fractures of lower limb--a report of 3 cases. *Injury* 2015; **46**: 1389-1392 [PMID: 25943294 DOI: 10.1016/j.injury.2015.04.006]

5 **Guerado E**, Fuerstenberg CH. What bone graft substitutes should we use in post-traumatic spinal fusion? *Injury* 2011; **42** Suppl 2: S64-S71 [PMID: 21839997 DOI: 10.1016/j.injury.2011.06.200]

6 **Langer R**, Vacanti JP. Tissue engineering. *Science* 1993; **260**: 920-926 [PMID: 8493529]

7 **MacArthur BD**, Oreffo RO. Bridging the gap. *Nature* 2005; **433**: 19 [PMID: 15635390]

8 **Smith JO**, Aarvold A, Tayton ER, Dunlop DG, Oreffo RO. Skeletal tissue regeneration: current approaches, challenges, and novel reconstructive strategies for an aging population. *Tissue Eng Part B Rev* 2011; **17**: 307-320 [PMID: 21615329 DOI: 10.1089/ten.TEB.2011.0143]

9 **Qazi TH**, Mooney DJ, Pumberger M, Geissler S, Duda GN. Biomaterials based strategies for skeletal muscle tissue engineering: existing technologies and future trends. *Biomaterials* 2015; **53**: 502-521 [PMID: 25890747 DOI: 10.1016/j.biomaterials.2015.02.110]

10 **Hartsock LA**, Barfield WR, Kokko KP, Liles LL, Wind T, Green J, Giannoudis PV. Randomized prospective clinical trial comparing reamer irrigator aspirator (RIA) to standard reaming (SR) in both minimally injured and multiply injured patients with closed femoral shaft fractures treated with reamed intramedullary nailing (IMN). *Injury* 2010; **41** Suppl 2: S94-S98 [PMID: 21144938 DOI: 10.1016/S0020-1383(10)70018-8]

11 **Cox G**, McGonagle D, Boxall SA, Buckley CT, Jones E, Giannoudis PV. The use of the reamer-irrigator-aspirator to harvest mesenchymal stem cells. *J Bone Joint Surg Br* 2011; **93**: 517-524 [PMID: 21464493 DOI: 10.1302/0301-620X.93B4.25506]

12 **Cox G**, Jones E, McGonagle D, Giannoudis PV. Reamer-irrigator-aspirator indications and clinical results: a systematic review. *Int Orthop* 2011; **35**: 951-956 [PMID: 21243358 DOI: 10.1007/s00264-010-1189-z]

13 **Han F**, Peter L, Lau ET, Thambiah J, Murphy D, Kagda FH. Reamer Irrigator Aspirator bone graft harvesting: complications and outcomes in an Asian population. *Injury* 2015; **46**: 2042-2051 [PMID: 26253387 DOI: 10.1016/j.injury.2015.07.027]

14 **van der Bel R**, Blokhuis TJ. Increased osteogenic capacity of Reamer/Irrigator/Aspirator derived mesenchymal stem cells. *Injury* 2014; **45**: 2060-2064 [PMID: 25458067 DOI: 10.1016/j.injury.2014.10.009]

15 **Devine DM**, Arens D, Thalhauser M, Schiuma D, Zeiter S, Nehrbass D. Healing pattern of reamed bone following bone harvesting by a RIA device. *Eur Cell Mater* 2015; **29**: 97-104; discussion 104 [PMID: 25633308]

16 **Sinclair SS**, Horton CO, Jeray KJ, Tanner SL, Burgl KJ. Fat Layer from Medullary Canal Reamer Aspirate for Potential Use as a Supplemental Osteoinductive Bone Graft Material. *J Stem Cells* 2015; **10**: 79-90 [PMID: 27125136]

17 **Crist BD**, Stoker AM, Stannard JP, Cook JL. Analysis of relevant proteins from bone graft harvested using the reamer irrigator and aspirator system (RIA) versus iliac crest (IC) bone graft and RIA waste water. *Injury* 2016; **47**: 1661-1668 [PMID: 27269417 DOI: 10.1016/j.injury.2016.05.030]

18 **Henrich D**, Nau C, Kraft SB, Zollfrank M, Kontradowitz K, Oppermann E, Schultheiss J, Meier S, Frank J, Marzi I, Seebach C. Effect of the harvest procedure and tissue site on the osteogenic function of and gene expression in human mesenchymal stem cells. *Int J Mol Med* 2016; **37**: 976-988 [PMID: 26935410 DOI: 10.3892/ijmm.2016.2489]

19 **Kuehlfluck P**, Moghaddam A, Helbig L, Child C, Wildemann B, Schmidmaier G. RIA fractions contain mesenchymal stroma cells with high osteogenic potency. *Injury* 2015; **46** Suppl 8: S23-S32 [PMID: 26747914 DOI: 10.1016/S0020-1383(15)30051-6]

20 **Cuthbert RJ**, Giannoudis PV, Wang XN, Nicholson L, Pawson D, Lubenko A, Tan HB, Dickinson A, McGonagle D, Jones E. Examining the feasibility of clinical grade CD271+ enrichment of mesenchymal stromal cells for bone regeneration. *PLoS One* 2015; **10**: e0117855 [PMID: 25760857 DOI: 10.1371/journal.pone.0117855]

21 **Rankine JJ**, Hodgson RJ, Tan HB, Cox G, Giannoudis PV. MRI appearances of the femur following bone graft harvesting using the Reamer-Irrigator-Aspirator. *Injury* 2015; **46** Suppl 8: S65-S67 [PMID: 26747921 DOI: 10.1016/S0020-1383(15)30057-7]

22 **Calori GM**, Colombo M, Mazza EL, Mazzola S, Malagoli E, Mineo GV. Incidence of donor site morbidity following harvesting from iliac crest or RIA graft. *Injury* 2014; **45** Suppl 6: S116-S120 [PMID: 25457330 DOI: 10.1016/j.injury.2014.10.034]

23 **Donders JC**, Baumann HM, Stevens MF, Kloen P. Hemorrhagic-Induced Cardiovascular Complications During Reamer-Irrigator-Aspirator-Assisted Femoral Nonunion Treatment. *J Orthop Trauma* 2016; **30**: e294-e298 [PMID: 27124827 DOI: 10.1097/BOT.0000000000000612]

24 **Miller AN**, Deal D, Green J, Houle T, Brown W, Thore C, Stump D, Webb LX. Use of the Reamer/Irrigator/Aspirator Decreases Carotid and Cranial Embolic Events in a Canine Model. *J Bone Joint Surg Am* 2016; **98**: 658-664 [PMID: 27098324 DOI: 10.2106/JBJS.14.01176]

25 **Wang RY**, Li R, Zdero R, Bell D, Blankstein M, Schemitsch EH. The physiologic and pathologic effects of the reamer irrigator aspirator on fat embolism outcome: an animal study. *J Orthop Trauma* 2012; **26**: e132-e137 [PMID: 22377507 DOI: 10.1097/BOT.0b013e318238b22b]

26 **Volgas DA**, Burch T, Stannard JP, Ellis T, Bilotta J, Alonso JE. Fat embolus in femur fractures: a comparison of two reaming systems. *Injury* 2010; **41** Suppl 2: S90-S93 [PMID: 21144937 DOI: 10.1016/S0020-1383(10)70017-6]

27 **Streubel PN**, Desai P, Suk M. Comparison of RIA and conventional reamed nailing for treatment of femur shaft fractures. *Injury* 2010; **41** Suppl 2: S51-S56 [PMID: 21144929 DOI: 10.1016/S0020-1383(10)70010-3]

28 **Husebye EE**, Opdahl H, Røise O, Aspelin T, Lyberg T. Coagulation, fibrinolysis and cytokine responses to intramedullary nailing of the femur: an experimental study in pigs comparing traditional reaming and reaming with a one-step reamer-irrigator-aspirator system. *Injury* 2011; **42**: 630-637 [PMID: 20650454 DOI: 10.1016/j.injury.2010.06.025]

29 **Giannoudis PV**, Tan HB, Perry S, Tzioupis C, Kanakaris NK. The systemic inflammatory response following femoral canal reaming using the reamer-irrigator-aspirator (RIA) device. *Injury* 2010; **41** Suppl 2: S57-S61 [PMID: 21144930 DOI: 10.1016/S0020-1383(10)70011-5]

30 **Silva JA**, McCormick JJ, Reed MA, Morse AS, Heffernan MJ, Lavado RD, Billiar K, Wixted JJ. Biomechanical effects of harvesting bone graft with the Reamer/Irrigator/Aspirator on the adult femur: a cadaver study. *Injury* 2010; **41** Suppl 2: S85-S89 [PMID: 21144935 DOI: 10.1016/S0020-1383(10)70016-4]

31 **Giori NJ**, Beaupre GS. Femoral fracture after harvesting of autologous bone graft using a reamer/irrigator/aspirator. *J Orthop Trauma* 2011; **25**: e12-e14 [PMID: 21245702 DOI: 10.1097/BOT.0b013e3181e39bf4]

32 **Jakma TS**, Röling MA, Punt B, Reynders-Frederix P. More adverse events than expected in the outcome after use of the reamer-irrigator-aspirator. *Eur J Trauma Emerg Surg* 2014; **40**: 337-341 [PMID: 26816069 DOI: 10.1007/s00068-013-0345-8]

33 **Mansour J**, Conway JD. Retrograde reamer/irrigator/aspirator technique for autologous bone graft harvesting with the patient in the prone position. *Am J Orthop* (Belle Mead NJ) 2015; **44**: 202-205 [PMID: 25950533]

34 **Davis RL**, Taylor BC, Johnson N, Ferrel JR, Castaneda J. Retrograde Versus Antegrade Femoral Bone Graft Harvesting Using the Reamer-Irrigator-Aspirator. *J Orthop Trauma* 2015; **29**: 370-372 [PMID: 25635359 DOI: 10.1097/BOT.0000000000000300]

35 **Masquelet AC**, Fitoussi F, Begue T, Muller GP. [Reconstruction of the long bones by the induced membrane and spongy autograft]. *Ann Chir Plast Esthet* 2000; **45**: 346-353 [PMID: 10929461]

36 **Levante S**, Masquelet AC, Nordin JY. [Coverage of chronic osteomyelitis of the ankle and the foot using a soleus muscle island flap, vascularized with retrograde flow on the posterior tibial artery. A seven cases report]. *Ann Chir Plast Esthet* 2009; **54**: 523-527 [PMID: 19195753 DOI: 10.1016/j.anplas.2008.10.003]

37 **Klaue K**, Knothe U, Anton C, Pfluger DH, Stoddart M, Masquelet AC, Perren SM. Bone regeneration in long-bone defects: tissue

compartmentalisation? In vivo study on bone defects in sheep. *Injury* 2009; **40** Suppl 4: S95-102 [PMID: 19895960 DOI: 10.1016/j.injury.2009.10.043]
38 **Apard T**, Bigorre N, Cronier P, Duteille F, Bizot P, Massin P. Two-stage reconstruction of post-traumatic segmental tibia bone loss with nailing. *Orthop Traumatol Surg Res* 2010; **96**: 549-553 [PMID: 20605548 DOI: 10.1016/j.otsr.2010.02.010]
39 **Stafford PR**, Norris BL. Reamer-irrigator-aspirator bone graft and bi Masquelet technique for segmental bone defect nonunions: a review of 25 cases. *Injury* 2010; **41** Suppl 2: S72-S77 [PMID: 21144933 DOI: 10.1016/S0020-1383(10)70014-0]
40 **Henrich D**, Seebach C, Nau C, Basan S, Relja B, Wilhelm K, Schaible A, Frank J, Barker J, Marzi I. Establishment and characterization of the Masquelet induced membrane technique in a rat femur critical-sized defect model. *J Tissue Eng Regen Med* 2016; **10**: E382-E396 [PMID: 24668794 DOI: 10.1002/term.1826]
41 **Gouron R**, Petit L, Boudot C, Six I, Brazier M, Kamel S, Mentaverri R. Osteoclasts and their precursors are present in the induced-membrane during bone reconstruction using the Masquelet technique. *J Tissue Eng Regen Med* 2014; **11**: 382-389 [PMID: 24919776 DOI: 10.1002/term.1921]
42 **Christou C**, Oliver RA, Yu Y, Walsh WR. The Masquelet technique for membrane induction and the healing of ovine critical sized segmental defects. *PLoS One* 2014; **9**: e114122 [PMID: 25461340 DOI: 10.1371/journal.pone.0114122]
43 **Bosemark P**, Perdikouri C, Pelkonen M, Isaksson H, Tägil M. The masquelet induced membrane technique with BMP and a synthetic scaffold can heal a rat femoral critical size defect. *J Orthop Res* 2015; **33**: 488-495 [PMID: 25639666 DOI: 10.1002/jor.22815]
44 **Aho OM**, Lehenkari P, Ristiniemi J, Lehtonen S, Risteli J, Leskelä HV. The mechanism of action of induced membranes in bone repair. *J Bone Joint Surg Am* 2013; **95**: 597-604 [PMID: 23553294 DOI: 10.2106/JBJS.L.00310]
45 **Giannoudis PV**, Faour O, Goff T, Kanakaris N, Dimitriou R. Masquelet technique for the treatment of bone defects: tips-tricks and future directions. *Injury* 2011; **42**: 591-598 [PMID: 21543068 DOI: 10.1016/j.injury.2011.03.036]
46 **Mauffrey C**, Hake ME, Chadayammuri V, Masquelet AC. Reconstruction of Long Bone Infections Using the Induced Membrane Technique: Tips and Tricks. *J Orthop Trauma* 2016; **30**: e188-e193 [PMID: 26618666 DOI: 10.1097/BOT.0000000000000500]
47 **Fischer C**, Doll J, Tanner M, Bruckner T, Zimmermann G, Helbig L, Biglari B, Schmidmaier G, Moghaddam A. Quantification of TGF-ß1, PDGF and IGF-1 cytokine expression after fracture treatment vs. non-union therapy via masquelet. *Injury* 2016; **47**: 342-349 [PMID: 26775211 DOI: 10.1016/j.injury.2015.11.007]
48 **Ilizarov GA**, Lediaev VI. [Replacement of defects of long tubular bones by means of one of their fragments]. *Vestn Khir Im I I Grek* 1969; **102**: 77-84 [PMID: 4904826]
49 **Styazhkin N**. Surgeon Ilizarov and his method. *Australas Nurses J* 1973; **2**: 8 [PMID: 4488965]
50 **Liberman SB**, Semenova VD. Investigation of the strength and rigidity of Kirschner spokes in the apparatus of G. A. Ilizarov. *Biomed Eng* (NY) 1974; **7**: 226-227 [PMID: 4457167]
51 **Landini A**, Confalonieri N, Bagnoli G, Penna G, Pietrogrande V. [Consolidation time in fresh fractures of the leg treated by the Ilizarov method]. *Arch Putti Chir Organi Mov* 1984; **34**: 269-273 [PMID: 6544083]
52 **Confalonieri N**, Penna G, Bagnoli G, Landini A, Pietrogrande V. [Treatment of pseudoarthrosis with the external Ilizarov fixator. Initial experiences]. *Arch Putti Chir Organi Mov* 1984; **34**: 303-308 [PMID: 6544089]
53 **Lavrishcheva GI**, Mikhaĭlova LN. [Histogenesis of skeletogenic tissue in bone regeneration during distraction]. *Biull Eksp Biol Med* 1985; **99**: 198-201 [PMID: 2578836]
54 **Paley D**, Catagni MA, Argnani F, Villa A, Benedetti GB, Cattaneo R. Ilizarov treatment of tibial nonunions with bone loss. *Clin Orthop Relat Res* 1989; **(241)**: 146-165 [PMID: 2924458]
55 **Paley D**. Problems, obstacles, and complications of limb lengthening by the Ilizarov technique. *Clin Orthop Relat Res* 1990; **(250)**: 81-104 [PMID: 2403498]
56 **Fischgrund J**, Paley D, Suter C. Variables affecting time to bone healing during limb lengthening. *Clin Orthop Relat Res* 1994; **(301)**: 31-37 [PMID: 8156692]
57 **Marcacci M**, Kon E, Moukhachev V, Lavroukov A, Kutepov S, Quarto R, Mastrogiacomo M, Cancedda R. Stem cells associated with macroporous bioceramics for long bone repair: 6- to 7-year outcome of a pilot clinical study. *Tissue Eng* 2007; **13**: 947-955 [PMID: 17484701 DOI: 10.1089/ten.2006.0271]
58 **Sunay O**, Can G, Cakir Z, Denek Z, Kozanoglu I, Erbil G, Yilmaz M, Baran Y. Autologous rabbit adipose tissue-derived mesenchymal stromal cells for the treatment of bone injuries with distraction osteogenesis. *Cytotherapy* 2013; **15**: 690-702 [PMID: 23522867 DOI: 10.1016/j.jcyt.2013.02.004]
59 **Nomura I**, Watanabe K, Matsubara H, Hayashi K, Sugimoto N, Tsuchiya H. Uncultured autogenous adipose-derived regenerative cells promote bone formation during distraction osteogenesis in rats. *Clin Orthop Relat Res* 2014; **472**: 3798-3806 [PMID: 24711135 DOI: 10.1007/s11999-014-3608-8]
60 **Ando Y**, Matsubara K, Ishikawa J, Fujio M, Shohara R, Hibi H, Ueda M, Yamamoto A. Stem cell-conditioned medium accelerates distraction osteogenesis through multiple regenerative mechanisms. *Bone* 2014; **61**: 82-90 [PMID: 24389414 DOI: 10.1016/j.bone.2013.12.029]
61 **Dehghan MM**, Baghaban Eslaminejad M, Motallebizadeh N, Ashrafi Halan J, Tagiyar L, Soroori S, Nikmahzar A, Pedram M, Shahverdi A, Kazemi Mehrjerdi H, Izadi S. Transplantation of Autologous Bone Marrow Mesenchymal Stem Cells with Platelet-Rich Plasma Accelerate Distraction Osteogenesis in A Canine Model. *Cell J* 2015; **17**: 243-252 [PMID: 26199903]
62 **Harada Y**, Nakasa T, Mahmoud EE, Kamei G, Adachi N, Deie M, Ochi M. Combination therapy with intra-articular injection of mesenchymal stem cells and articulated joint distraction for repair of a chronic osteochondral defect in the rabbit. *J Orthop Res* 2015; **33**: 1466-1473 [PMID: 26174695 DOI: 10.1002/jor.22922]
63 **Morcos MW**, Al-Jallad H, Hamdy R. Comprehensive Review of Adipose Stem Cells and Their Implication in Distraction Osteogenesis and Bone Regeneration. *Biomed Res Int* 2015; **2015**: 842975 [PMID: 26448947 DOI: 10.1155/2015/842975]
64 **Mechiche Alami S**, Gangloff SC, Laurent-Maquin D, Wang Y, Kerdjoudj H. Concise Review: In Vitro Formation of Bone-Like Nodules Sheds Light on the Application of Stem Cells for Bone Regeneration. *Stem Cells Transl Med* 2016; **5**: 1587-1593 [PMID: 27458265 DOI: 10.5966/sctm.2015-0413]
65 **Medhekar SK**, Shende VS, Chincholkar AB. Recent Stem Cell Advances: Cord Blood and Induced Pluripotent Stem Cell for Cardiac Regeneration- a Review. *Int J Stem Cells* 2016; **9**: 21-30 [PMID: 27426082 DOI: 10.15283/ijsc.2016.9.1.21]
66 **Lo Furno D**, Mannino G, Cardile V, Parenti R, Giuffrida R. Potential Therapeutic Applications of Adipose-Derived Mesenchymal Stem Cells. *Stem Cells Dev* 2016; Epub ahead of print [PMID: 27520311 DOI: 10.1089/scd.2016.0135]
67 **Du WJ**, Reppel L, Leger L, Schenowitz C, Huselstein C, Bensoussan D, Carosella ED, Han ZC, Rouas-Freiss N. Mesenchymal Stem Cells Derived from Human Bone Marrow and Adipose Tissue Maintain Their Immunosuppressive Properties After Chondrogenic Differentiation: Role of HLA-G. *Stem Cells Dev* 2016; **25**: 1454-1469 [PMID: 27465875 DOI: 10.1089/scd.2016.0022]
68 **Tan J**, Xu X, Lin J, Fan L, Zheng Y, Kuang W. Dental Stem Cell in Tooth Development and Advances of Adult Dental Stem Cell in Regenerative Therapies. *Curr Stem Cell Res Ther* 2015; **10**: 375-383 [PMID: 25274563]
69 **Chadipiralla K**, Yochim JM, Bahuleyan B, Huang CY, Garcia-Godoy F, Murray PE, Stelnicki EJ. Osteogenic differentiation of stem cells derived from human periodontal ligaments and pulp of human exfoliated deciduous teeth. *Cell Tissue Res* 2010; **340**: 323-333 [PMID: 20309582 DOI: 10.1007/s00441-010-0953-0]
70 **Mattioli-Belmonte M**, Teti G, Salvatore V, Focaroli S, Orciani M, Dicarlo M, Fini M, Orsini G, Di Primio R, Falconi M. Stem cell origin differently affects bone tissue engineering strategies. *Front Physiol* 2015; **6**: 266 [PMID: 26441682 DOI: 10.3389/fphys.2015.00266]

71 **Li M**, Zhao Y, Hao H, Han W, Fu X. Mesenchymal stem cell-based therapy for nonhealing wounds: today and tomorrow. *Wound Repair Regen* 2015; **23**: 465-482 [PMID: 25877885 DOI: 10.1111/wrr.12304]

72 **Roubelakis MG**, Pappa KI, Bitsika V, Zagoura D, Vlahou A, Papadaki HA, Antsaklis A, Anagnou NP. Molecular and proteomic characterization of human mesenchymal stem cells derived from amniotic fluid: comparison to bone marrow mesenchymal stem cells. *Stem Cells Dev* 2007; **16**: 931-952 [PMID: 18047393 DOI: 10.1089/scd.2007.0036]

73 **Choi JW**, Park EJ, Shin HS, Shin IS, Ra JC, Koh KS. In vivo differentiation of undifferentiated human adipose tissue-derived mesenchymal stem cells in critical-sized calvarial bone defects. *Ann Plast Surg* 2014; **72**: 225-233 [PMID: 23221992 DOI: 10.1097/SAP.0b013e31825f70f5]

74 **Markarian CF**, Frey GZ, Silveira MD, Chem EM, Milani AR, Ely PB, Horn AP, Nardi NB, Camassola M. Isolation of adipose-derived stem cells: a comparison among different methods. *Biotechnol Lett* 2014; **36**: 693-702 [PMID: 24322777 DOI: 10.1007/s10529-013-1425-x]

75 **Yu G**, Floyd ZE, Wu X, Halvorsen YD, Gimble JM. Isolation of human adipose-derived stem cells from lipoaspirates. *Methods Mol Biol* 2011; **702**: 17-27 [PMID: 21082391 DOI: 10.1007/978-1-61737-960-4_2]

76 **Forcales SV**. Potential of adipose-derived stem cells in muscular regenerative therapies. *Front Aging Neurosci* 2015; **7**: 123 [PMID: 26217219 DOI: 10.3389/fnagi.2015.00123]

77 **Kakudo N**, Morimoto N, Ogawa T, Taketani S, Kusumoto K. Hypoxia Enhances Proliferation of Human Adipose-Derived Stem Cells via HIF-1α Activation. *PLoS One* 2015; **10**: e0139890 [PMID: 26465938 DOI: 10.1371/journal.pone.0139890]

78 **Cervelli V**, Scioli MG, Gentile P, Doldo E, Bonanno E, Spagnoli LG, Orlandi A. Platelet-rich plasma greatly potentiates insulin-induced adipogenic differentiation of human adipose-derived stem cells through a serine/threonine kinase Akt-dependent mechanism and promotes clinical fat graft maintenance. *Stem Cells Transl Med* 2012; **1**: 206-220 [PMID: 23197780 DOI: 10.5966/sctm.2011-0052]

79 **Gnanasegaran N**, Govindasamy V, Musa S, Kasim NH. Different isolation methods alter the gene expression profiling of adipose derived stem cells. *Int J Med Sci* 2014; **11**: 391-403 [PMID: 24669199 DOI: 10.7150/ijms.7697]

80 **Dragoo JL**, Choi JY, Lieberman JR, Huang J, Zuk PA, Zhang J, Hedrick MH, Benhaim P. Bone induction by BMP-2 transduced stem cells derived from human fat. *J Orthop Res* 2003; **21**: 622-629 [PMID: 12798061 DOI: 10.1016/S0736-0266(02)00238-3]

81 **Dragoo JL**, Lieberman JR, Lee RS, Deugarte DA, Lee Y, Zuk PA, Hedrick MH, Benhaim P. Tissue-engineered bone from BMP-2-transduced stem cells derived from human fat. *Plast Reconstr Surg* 2005; **115**: 1665-1673 [PMID: 15861072]

82 **Peterson B**, Zhang J, Iglesias R, Kabo M, Hedrick M, Benhaim P, Lieberman JR. Healing of critically sized femoral defects, using genetically modified mesenchymal stem cells from human adipose tissue. *Tissue Eng* 2005; **11**: 120-129 [PMID: 15738667 DOI: 10.1089/ten.2005.11.120]

83 **Chang SC**, Chuang H, Chen YR, Yang LC, Chen JK, Mardini S, Chung HY, Lu YL, Ma WC, Lou J. Cranial repair using BMP-2 gene engineered bone marrow stromal cells. *J Surg Res* 2004; **119**: 85-91 [PMID: 15126087 DOI: 10.1016/j.jss.2003.08.003]

84 **Lieberman JR**, Daluiski A, Stevenson S, Wu L, McAllister P, Lee YP, Kabo JM, Finerman GA, Berk AJ, Witte ON. The effect of regional gene therapy with bone morphogenetic protein-2-producing bone-marrow cells on the repair of segmental femoral defects in rats. *J Bone Joint Surg Am* 1999; **81**: 905-917 [PMID: 10428121]

85 **Tsuda H**, Wada T, Yamashita T, Hamada H. Enhanced osteoinduction by mesenchymal stem cells transfected with a fiber-mutant adenoviral BMP2 gene. *J Gene Med* 2005; **7**: 1322-1334 [PMID: 15926193 DOI: 10.1002/jgm.777]

86 **Mesimäki K**, Lindroos B, Törnwall J, Mauno J, Lindqvist C, Kontio R, Miettinen S, Suuronen R. Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells. *Int J Oral Maxillofac Surg* 2009; **38**: 201-209 [PMID: 19168327 DOI: 10.1016/j.ijom.2009.01.001]

87 **Lendeckel S**, Jödicke A, Christophis P, Heidinger K, Wolff J, Fraser JK, Hedrick MH, Berthold L, Howaldt HP. Autologous stem cells (adipose) and fibrin glue used to treat widespread traumatic calvarial defects: case report. *J Craniomaxillofac Surg* 2004; **32**: 370-373 [PMID: 15555520 DOI: 10.1016/j.jcms.2004.06.002]

88 **Dong SW**, Ying DJ, Duan XJ, Xie Z, Yu ZJ, Zhu CH, Yang B, Sun JS. Bone regeneration using an acellular extracellular matrix and bone marrow mesenchymal stem cells expressing Cbfa1. *Biosci Biotechnol Biochem* 2009; **73**: 2226-2233 [PMID: 19809195 DOI: 10.1271/bbb.90329]

89 **Zuk PA**. Tissue engineering craniofacial defects with adult stem cells? Are we ready yet? *Pediatr Res* 2008; **63**: 478-486 [PMID: 18427291 DOI: 10.1203/PDR.0b013e31816bdf36]

90 **Lim ML**, Jungebluth P, Ajalloueian F, Friedrich LH, Gilevich I, Grinnemo KH, Gubareva E, Haag JC, Lemon G, Sjöqvist S, Caplan AL, Macchiarini P. Whole organ and tissue reconstruction in thoracic regenerative surgery. *Mayo Clin Proc* 2013; **88**: 1151-1166 [PMID: 24079685 DOI: 10.1016/j.mayocp.2013.03.011]

91 **Black CR**, Goriainov V, Gibbs D, Kanczler J, Tare RS, Oreffo RO. Bone Tissue Engineering. *Curr Mol Biol Rep* 2015; **1**: 132-140 [PMID: 26618105 DOI: 10.1007/s40610-015-0022-2]

92 **Berner A**, Henkel J, Woodruff MA, Steck R, Nerlich M, Schuetz MA, Hutmacher DW. Delayed minimally invasive injection of allogenic bone marrow stromal cell sheets regenerates large bone defects in an ovine preclinical animal model. *Stem Cells Transl Med* 2015; **4**: 503-512 [PMID: 25834121 DOI: 10.5966/sctm.2014-0244]

93 **Orlic D**, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Bone marrow cells regenerate infarcted myocardium. *Nature* 2001; **410**: 701-705 [PMID: 11287958 DOI: 10.1038/35070587]

94 **Dreger T**, Watson JT, Akers W, Molligan J, Achilefu S, Schon LC, Zhang Z. Intravenous application of CD271-selected mesenchymal stem cells during fracture healing. *J Orthop Trauma* 2014; **28** Suppl 1: S15-S19 [PMID: 24378433 DOI: 10.1097/BOT.0000000000000063]

95 **Cameron SH**, Alwakeel AJ, Goddard L, Hobbs CE, Gowing EK, Barnett ER, Kohe SE, Sizemore RJ, Oorschot DE. Delayed post-treatment with bone marrow-derived mesenchymal stem cells is neurorestorative of striatal medium-spiny projection neurons and improves motor function after neonatal rat hypoxia-ischemia. *Mol Cell Neurosci* 2015; **68**: 56-72 [PMID: 25828540 DOI: 10.1016/j.mcn.2015.03.019]

96 **Gross JB**, Diligent J, Bensoussan D, Galois L, Stoltz JF, Mainard D. Percutaneous autologous bone marrow injection for treatment of delayed and non-union of long bone: a retrospective study of 45 cases. *Biomed Mater Eng* 2015; **25**: 187-197 [PMID: 25538069 DOI: 10.3233/BME-141235]

97 **Dawson JI**, Kanczler J, Tare R, Kassem M, Oreffo RO. Concise review: bridging the gap: bone regeneration using skeletal stem cell-based strategies - where are we now? *Stem Cells* 2014; **32**: 35-44 [PMID: 24115290 DOI: 10.1002/stem.1559]

98 **Watanabe Y**, Harada N, Sato K, Abe S, Yamanaka K, Matushita T. Stem cell therapy: is there a future for reconstruction of large bone defects? *Injury* 2016; **47** Suppl 1: S47-S51 [PMID: 26768292 DOI: 10.1016/S0020-1383(16)30012-2]

99 **Halme DG**, Kessler DA. FDA regulation of stem-cell-based therapies. *N Engl J Med* 2006; **355**: 1730-1735 [PMID: 17050899 DOI: 10.1056/NEJMhpr063086]

100 **The European parliament and the Council of the European Union**. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 10.12.2007. Official Journal of the European Union. L 324/121, Last Accessed August 2016. Available from: URL: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf

101 **Yousefi AM**, James PF, Akbarzadeh R, Subramanian A, Flavin C, Oudadesse H. Prospect of Stem Cells in Bone Tissue Engineering: A Review. *Stem Cells Int* 2016; **2016**: 6180487 [PMID: 26880976 DOI: 10.1155/2016/6180487]

102 **Timashev P**, Kuznetsova D, Koroleva A, Prodanets N, Deiwick A, Piskun Y, Bardakova K, Dzhoyashvili N, Kostjuk S, Zagaynova E, Rochev Y, Chichkov B, Bagratashvili V. Novel biodegradable star-shaped polylactide scaffolds for bone regeneration fabricated by two-photon polymerization. *Nanomedicine* (Lond) 2016; **11**: 1041-1053 [PMID: 27078220 DOI: 10.2217/nnm-2015-0022]

103 **Sándor GK**. Tissue engineering of bone: Clinical observations with adipose-derived stem cells, resorbable scaffolds, and growth factors. *Ann Maxillofac Surg* 2012; **2**: 8-11 [PMID: 23483030 DOI: 10.4103/2231-0746.95308]

104 **Kapur SK**, Katz AJ. Review of the adipose derived stem cell secretome. *Biochimie* 2013; **95**: 2222-2228 [PMID: 23770442 DOI: 10.1016/j.biochi.2013.06.001]

105 **Senarath-Yapa K**, McArdle A, Renda A, Longaker MT, Quarto N. Adipose-derived stem cells: a review of signaling networks governing cell fate and regenerative potential in the context of craniofacial and long bone skeletal repair. *Int J Mol Sci* 2014; **15**: 9314-9330 [PMID: 24865492 DOI: 10.3390/ijms15069314]

106 **Kokabu S**, Lowery JW, Jimi E. Cell Fate and Differentiation of Bone Marrow Mesenchymal Stem Cells. *Stem Cells Int* 2016; **2016**: 3753581 [PMID: 27298623 DOI: 10.1155/2016/3753581]

107 **Belinsky GS**, Sreekumar B, Andrejecsk JW, Saltzman WM, Gong J, Herzog RI, Lin S, Horsley V, Carpenter TO, Chung C. Pigment epithelium-derived factor restoration increases bone mass and improves bone plasticity in a model of osteogenesis imperfecta type VI via Wnt3a blockade. *FASEB J* 2016; **30**: 2837-2848 [PMID: 27127101 DOI: 10.1096/fj.201500027R]

108 **The European Parliament and the Council of the European Union**. Directive 2004/23/EC of The European Parliament And of The Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union. L 102/48; 7.4.2004. [accessed 2016 Aug]. Available from: URL: http://eur-lex.europa.eu/Lex-UriServ/LexUriServ.do?uri=OJ: L: 2004: 102: 0048: 0058: en: PDF

109 **The European Parliament and the Council of the European Union**. Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. Official Journal of the European Union L 38/40. 9.2.2006. [accessed 2016 Aug]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex: 32006L0017

110 **The European Parliament and the Council of the European Union**. Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union L 294/32. 25.10.2006. [accessed 2016 Aug]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX: 32006L0086

111 **The European Commission**. Commission Directive 2012/39/EU of 26 November 2012 amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells Official Journal of the European Union. L 327/24. 27.11.2012. [accessed 2016 Aug]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX: 32012L0039

112 **The European Commission**. Commission Directive (EU) 2015/565 of 8 April 2015 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells Official Journal of the European Union L 93/43, 9.4.2015. [accessed 2016 Aug]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv: OJ.L_.2015.093.01.0043.01.ENG

113 **The European Commission**. Commission Directive (EU) 2015/566 of 8 April 2015 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells. Official Journal of the European Union L 93/56, 9.4.2015. [accessed 2016 Aug]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX: 32015L0566

114 **The European Parliament and the Council of the European Union**. Regulation (EC) No 1394/2007 of The European Parliament and of The Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. [accessed 2016 Aug]. Available from: URL: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf

115 **The Commission of the European Communities**. Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products. Official Journal of the European Union L 242/3, 5.9.2009. [accessed 2016 Aug]. Available from: URL: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2009_120/dir_2009_120_en.pdf

116 **The European Parliament and the Council of the European Union**. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Official Journal of the European Union L 281/31, 23.11.95. [accessed 2016 Aug]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex: 31995L0046

117 **Governing Regulations CFR - 1270 Series**. [accessed 2016 Aug]. Available from: URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPartFrom=800&CFRPartTo=1299

118 Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Official Journal of the European Union L 262/22, 14.10.2003. [accessed 2016 Aug]. Available from: URL: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf

119 **K. Good Manufacturing Practice**. EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines. [accessed 2016 Aug]. Available from: URL: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

120 **Paula AC**, Martins TM, Zonari A, Frade SP, Angelo PC, Gomes DA, Goes AM. Human adipose tissue-derived stem cells cultured in xeno-free culture condition enhance c-MYC expression increasing proliferation but bypassing spontaneous cell transformation. *Stem Cell Res Ther* 2015; **6**: 76 [DOI: 10.1186/s13287-015-0030-4]

121 **Gimble JM**, Katz AJ, Bunnell BA. Adipose-derived stem cells for regenerative medicine. *Circ Res* 2007; **100**: 1249-1260 [PMID: 17495232 DOI: 10.1161/01.RES.0000265074.83288.09]

122 **Lye KL**, Nordin N, Vidyadaran S, Thilakavathy K. Mesenchymal stem cells: From stem cells to sarcomas. *Cell Biol Int* 2016; **40**: 610-618 [PMID: 26992453 DOI: 10.1002/cbin.10603]

123 **Hedges DJ**, Burges D, Powell E, Almonte C, Huang J, Young S, Boese B, Schmidt M, Pericak-Vance MA, Martin E, Zhang X, Harkins TT, Züchner S. Exome sequencing of a multigenerational human pedigree. *PLoS One* 2009; **4**: e8232 [PMID: 20011588 DOI: 10.1371/journal.pone.0008232]

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THERAPEUTIC ADVANCES

Tips to avoid nerve injury in elbow arthroscopy

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Abstract

Elbow arthroscopy is a technical challenging surgical procedure because of close proximity of neurovascular structures and the limited articular working space. With the rising number of elbow arthroscopies being performed nowadays due to an increasing number of surgeons performing this procedure and a broader range of indications, a rise in complications is foreseen. With this editorial we hope to create awareness of possible complications of elbow arthroscopy, particularly nerve injuries, and provide a guideline to avoid complications during elbow arthroscopy.

Key words: Elbow; Arthroscopy; Complications; Nerve injury; Education; Preventive strategies

Core tip: Elbow arthroscopy is a technical challenging surgical procedure because of close proximity of neurovascular structures and the limited articular working space. With the rising number of elbow arthroscopies being performed nowadays due to an increasing number of surgeons performing this procedure and a broader range of indications, a rise in complications is foreseen. With this editorial we hope to create awareness of possible complications of elbow arthroscopy, particularly nerve injuries, and provide a guideline to avoid complications during elbow arthroscopy.

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INTRODUCTION

A small working space and close by neurovascular structures are the main reasons elbow arthroscopy is a technical challenging surgical procedure[1-12]. Advantages over open surgery may be less scar tissue, decreased risk of infection, less postoperative pain, fast return to work and sports and better visualization of intra-articular pathology[13-17]. Nowadays arthroscopy of the elbow is performed more frequently for an increasing range of indications; loose bodies, primary degenerative and rheumatoid arthritis, posttraumatic contractures, lateral/medial epicondylitis, osteochondral defects, posteromedial impingement, synovial disorders, fractures of the radial head, capitellum and coronoid, and debridement of osteophytes[2,18-22]. With the rising number of elbow arthroscopies being performed nowadays due to an increasing number of surgeons performing this procedure and a broader range of indications, a rise in complications is foreseen.

A range of complications has been described after elbow arthroscopy, such as: Transient neuropraxia[3,6,13,23-45], permanent nerve injury[28,41,46-55], complex regional pain syndrome[31], delayed wound healing[31], superficial wound infection[28,32,37,42,43,56-58], deep wound infection[32], limited range of motion[28,44,59], synovial fistula[28,37], ganglion cyst at portal site[32], granuloma of portal scar[39], heterotopic ossifications[23,32,43] and triceps tendon ossification[32]. One of the most devastating complications is nerve injury[19,60] of which the majority is fortunately transient[13,32].

Recently Desai *et al*[60] conducted a survey among the member of the American Society for Surgery of the Hand to determine which nerves and what kind of nerve injuries were treated after elbow arthroscopy over a five-year period; 222 nerve injuries were identified, an estimated 1.2% occurrence rate. In half of the patients additional surgical intervention was needed; 77%-80% had either partial or no recovery. This seems contradictory with the only 13 cases on permanent nerve injury after elbow arthroscopy published in current literature[28,41,46-55]. Desai *et al*[60] stated that in view of the high number of elbow arthroscopies performed these days permanent nerve injury is probably under-reported. In current literature the ulnar nerve seems most susceptible for nerve injury during elbow arthroscopy[60-62].

The goal of this current concepts review is to raise awareness of possible complications of elbow arthroscopy, in particular nerve injuries, and provide a practical guideline that can help to avoid nerve complications during elbow arthroscopy.

HOW TO AVOID NERVE COMPLICATIONS IN ELBOW ARTHROSCOPY?

A general necessity is thorough knowledge of the anatomy of the elbow in order to comprehend the spatial relation among neurovascular structures and portals and be able to safely perform elbow arthroscopy (Figures 1-3).

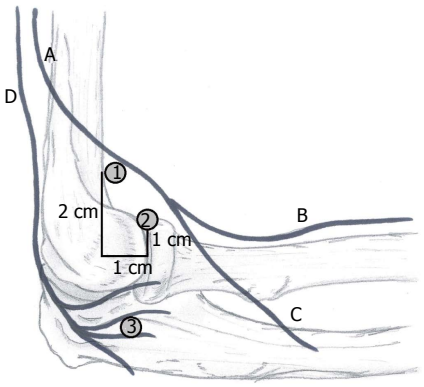

Figure 1 Proximity of nerves and portals: Lateral side view. A: Radial nerve; B: Superficial branch; C: Deep branch; D: Posterior antebrachial cutaneous nerve; 1: Proximal lateral portal; 2: Anterolateral portal; 3: Midlateral portal.

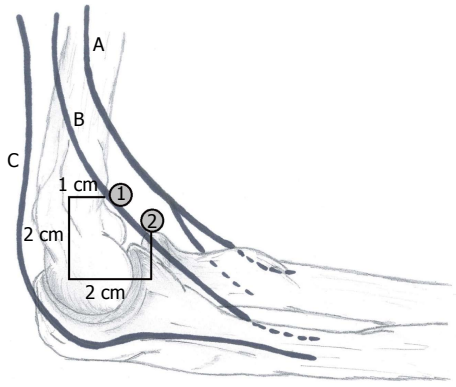

Figure 2 Proximity of nerves and portals: Medial side view. A: Median nerve; B: Medial antebrachial cutaneous nerve; C: Ulnar nerve; 1: Proximal medial portal; 2: Anteromedial portal.

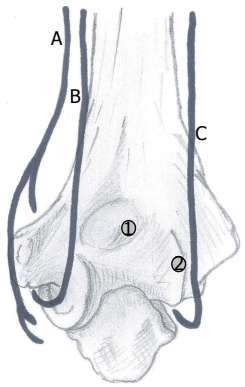

Figure 3 Proximity of nerves and portals: Posterior side view. A: Medial antebrachial cutaneous nerve; B: Ulnar nerve; C: Posterior antebrachial cutaneous nerve; 1: Transtricipital portal; 2: Posterolateral portal.

Work up

Avoiding peri-operative complications starts with a proper work-up. Firstly, there has to be a valid indication for surgery, which starts with patient complaints, history

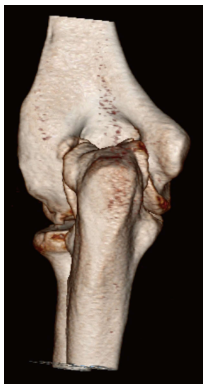

Figure 4 Osteophytes can cause changed anatomy, for example posteromedial osteophytes could push the ulnar nerve out of its groove.

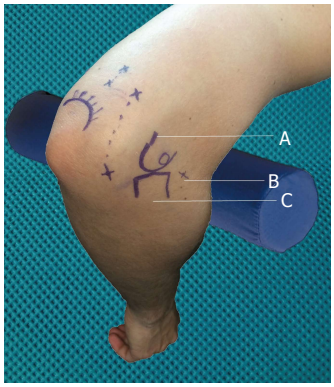

Figure 5 Marking of anatomical structures and portals: Lateral side view. A: Lateral epicondyle; B: Anterolateral portal; C: Radial head.

taking and physical examination. Setting a valid indication prevents unnecessary surgery and subsequently prevents neurological complications. A history of trauma, previous elbow surgery or rheumatoid arthritis, or burns, skingrafts, a subluxing ulnar nerve or congenital deformity of the elbow on physical examination can be complicating factors for surgery due to alteration of the anatomy; for example nerves can be adhered to the capsule[63], the capsule may have less distension capacity and scar tissue may make identifying nerves and vessels difficult. Additional imaging studies (CT, MRI or ultrasound) might be needed to confirm the diagnosis or for careful planning of surgery when expecting changed or difficult anatomy (Figure 4)[25]. For example, a subluxing or previously transposed ulnar nerve. The incidence of a subluxing ulnar nerve is reported to be 11%-21%[64,65] and not recognizing its presence preoperatively may lead to iatrogenic ulnar nerve injury. Dodson *et al*[19] suggested that arthroscopic surgery should be avoided if the patient had undergone previous ulnar nerve transposition. In order to prevent missing a not physiological ulnar nerve course it is recommended to routinely report if patients had a ulnar nerve transposition or are diagnosed with a subluxing ulnar nerve during physical examination in the outpatient setting.

Preoperative preventive measures

Prior to incision and distension of the joint, preoperative

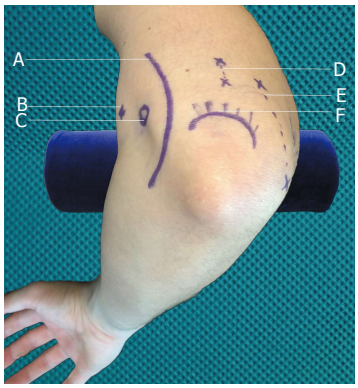

Figure 6 Marking of anatomical structures and portals: Medial side view. A: Ulnar nerve; B: Proximal medial portal; C: Medial epicondyle; D: Transtricipetal portals; E: Posterolateral portals; F: Olecranon.

examination under anesthesia, marking of anatomic landmarks and portal sites, and palpation of the course of the ulnar nerve are of great importance to obtain good orientation and avoid complications[3,18,28,66] (Figures 5 and 6). In cases with changed ulnar nerve anatomy a possible safe anteromedial approach depending on with what certainty the course of the ulnar nerve can be determined is described by Sahajpal *et al*[66]. If the course is unequivocal a safe anteromedial approach is possible by placing the portal 1cm from the nerve, if the course is equivocal portal placement should be 1 cm from the nerve by mini-incision, or by open approach *via* an incision of 2- to 4-cm in order to identify the nerve and subsequently place the portal if localization of the nerve is impossible. However, in the opinion of the authors the safest approach of an elbow with a subluxing or transposed ulnar nerve is an immediate open approach and starting elbow arthroscopy after identifying the ulnar nerve. Whenever establishing or re-entering the portal the ulnar nerve should be fixated posteriorly of the medial epicondyle.

Anesthesia

Most surgeons prefer general anesthesia with total muscle relaxation because of patient comfort and the disabling of unexpected patient movement, and it allows for supine positioning[2,18]. Some surgeons prefer to add regional anesthesia, for optimal reduction of postoperative pain. However, in a randomized controlled trial performed by Wada *et al*[67] no additional pain relief was observed using a supplemental axillary nerve block over general anesthesia alone. In addition, regional anesthesia has a small risk for nerve injury with an incidence of 3:10000 based on two large prospective studies[68-70].

Patient positioning

Several alternatives are available in positioning of the patient: The most common are the lateral decubitus position and the supine-suspended position with the use of a limb positioner (Figure 7). An advantage of the lateral decubitus position over the supine-suspended position

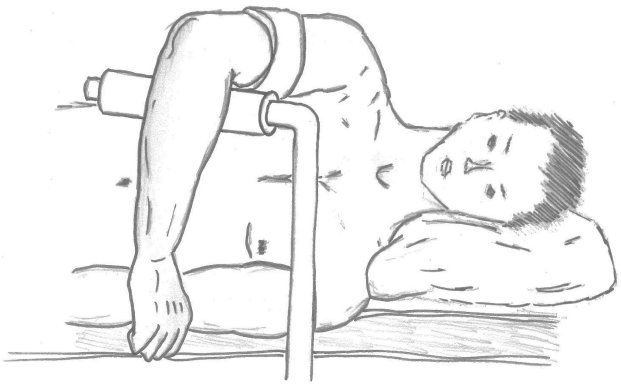

Figure 7 Lateral decubitus position.

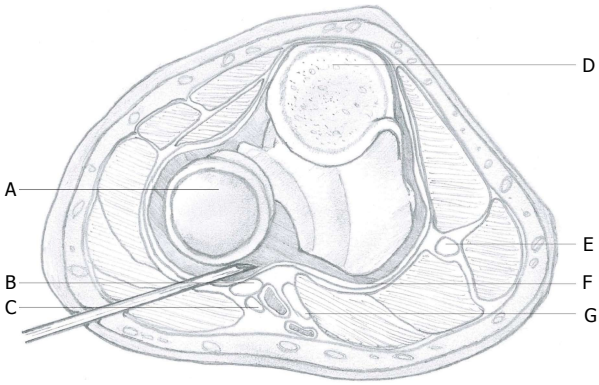

Figure 8 Non-distended joint. A: Head of radius; B: Radial nerve; C: Lateral antebrachial nerve; D: Cross-section of olecranon; E: Ulnar nerve; F: Capsule; G: Median nerve.

is that gravity assists in displacing the neurovascular structures away from the anterior capsule and from the anterior working field. Furthermore, the lateral decubitus position facilitates easy access to all compartments. A stable and comfortable patient position can be achieved by use of vacuum beanbag immobilizer.

Joint distension

When proper orientation of the surgical landmarks and patient positioning has been acquired, the next step is fluid distension (20-30 mL) of the joint *via* the midlateral soft spot or *via* a posterior approach. The latter approach is preferred by the authors because of the absence of cartilage in addition to the absence of nerves. Fluid distension of the elbow joint space moves the neurovascular structures away from the surgical field by expanding the joint capsule[3-5,10,45,71-75] (Figures 8 and 9). It is very important to realize that the nerve-to-capsule distance does not increase with joint distension, but only nerve-to-portal distance and the nerve to osseous structures distance[3,5,75,76]. Therefore, joint distension probably reduces the chance of nerve injury during joint entry *via* the portals and during intra-articular surgical procedures, but not during performance of capsular procedures. Since the capsule may rupture at pressures below 50 mmHg, it is advised to use gravitational force

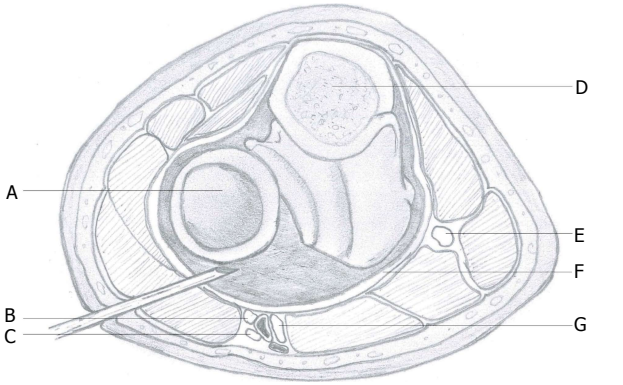

Figure 9 Distended joint joint. A: Head of radius; B: Radial nerve; C: Lateral antebrachial nerve; D: Cross-section of olecranon; E: Ulnar nerve; F: Capsule; G: Median nerve.

only, and avoid pressurized infusion, to keep the joint distended. Higher pressures occurring in fluid pumps cause fluid to flow extra-articular decreasing joint visibility[76,77]. Saline-infusion of 5 mL or less indicates a decreased displacement of neurovascular structures and less working space, for example in elbow contractures, making surgery more complicated[1]. Successful joint insufflation of the elbow with fluid will cause an extension movement.

Elbow positioning

It is advised to flex the elbow to 90 degrees as it displaces the brachial artery and the anterior nerves anteriorly[4,9], maximizing the distance between the joint capsule and the brachial artery, and the nerve-to-capsule distance[3,73]. The distance between the portals and the medial and radial nerves is doubled solely by elbow flexion, in combination with the aforementioned joint distension this distance even triples[72]. Furthermore, capsular capacity is maximized by flexion, increasing arthroscopic working space and minimizing the chance of neurovascular complications[1,3-5,73,78]. Disorders as rheumatoid arthritis, stiff and posttraumatic elbows may compromise the distension capacity of the capsule, thus raising the risk of neurovascular complications[1,3,5,13,38,52]. For maximal range of flexion, compression of the flexion crease due to supportive arm holders should be avoided.

Portal placement

Portal placing can cause nerve injury[13,18,46,62]. The above-mentioned preventive measures are meant to minimize the risk of neurovascular injury during the placing of portals. Mini-incision of the skin, avoiding incision of subcutaneous tissue, and the use of a blunt trocar or clamp are the first two preventive measures to avoid injury to the antebrachial nerves[9,75]. Furthermore, recognize that portals placed proximally of the joint have the tendency of being safer[9,79]. Pronation (in addition to flexion) of the elbow protects the posterior interosseous nerve when placing lateral portals. The elbow should be in midpronation at least. This way the nerve is brought

Table 1 Recommendations in short

Step	Phase	Recommendations
1	Work-up	Determine a valid indication. Identify possible complicating factors. If needed obtain additional imaging studies for careful planning of surgery
		Routinely report a subluxing or previously transposed ulnar nerve for all patients in the outpatient clinic setting previous of elbow arthroscopy
		Critical assessment of CT-studies to determine if osteophytes compress or mobilize the nerves (Figure 4)
2	Preoperative preventive measures	Examination under anesthesia (ROM)
		Marking of anatomic landmarks and portal sites (Figures 5 and 6)
		Palpation of the ulnar nerve course
3	Anesthesia	General anesthesia is recommended because of patient comfort and disabling unexpected patient movement
4	Patient positioning	Lateral decubitus position is recommended because of additional gravitational displacement of nerves away from the anterior capsule and easy access to all compartments (Figure 7)
		Use a bean bag for stable patient positioning
5	Joint insufflation	Increases nerve-to-portal distance by expanding the joint space en pushing the neurovascular structures away from the surgical field. Recognize that joint insufflation does not increase nerve-to-capsule distance (Figures 8 and 9)
6	Elbow positioning	Elbow flexion increases distension capacity of the joint and increases nerve-to-portal distance
		Supportive arm holders should not compress the flexion crease
7	Portal placement	Portals proximal to the joint tend to be safer
		Mini-incision of the skin only and the use of a blunt trocar or clamp prevents injury to the antebrachial nerves
		Pronation and flexion of the elbow protects the posterior interosseous nerve when placing lateral portals
		Avoid use of the posteromedial portal as the posterolateral and midposterior portals are good alternatives when inspecting the posterior compartment
8	Use of instruments	Always visualize the tip of the instrument
		Avoid suction when in the vicinity of a nerve or against the capsule
		Use a retractor to lift the capsule away from the debriding instrument, particularly in compartments at risk
		The use of hooded burrs instead of unhooded burrs is recommended as it help prevent the burr tangling up in the soft tissues
		No suction while shaving
		Availability of different shaver sizes during surgery

more anteromedial and the portal-to-nerve distance has increased[4,78,80]. When assessing the anterior compartment of the elbow it is advised to start with an anteromedial portal subsequently placing a lateral portal using the camera because this possibly reduces the risk of radial nerve, *i.e.*, posterior interosseous nerve (PIN), injury[7,9,10,12]. The proximal medial portal might even be a superior alternative compared to the anteromedial portal due to greater distance to the medial antebrachial nerve and no difference in arthroscopic view[9,81]. When placing the proximal medial portal stay anterior of the medial intermuscular septum to keep the ulnar nerve posterior of the portal and avoid ulnar nerve injury[9,82]. A method to reduce neurovascular injury when placing the proximal medial portal is by using a blunt hemostat or clamp after the usual mini-incision of the skin and place it on the anterior aspect of the humerus and aim it at the coronoid. By sliding downward over the humerus the capsule will be reached with small chance of injuring the median nerve, medial antebrachial nerve or brachial artery[81]. When assessing the posterior compartment of the elbow avoid using the posteromedial portal as it brings risk for ulnar nerve injury; posterolateral and midposterior portal are good alternatives[81].

Use of instruments

Once safe entry to the joint has been established it is important to always keep your instrument tips within sight even under hard conditions and keep clear of using suction when working in the proximity of a nerve or the capsule to prevent within-out- injury[75]. Never use suction while shaving. Another way of preventing within-out injury is using a retractor, *via* a separate portal, to keep the capsule away from a debriding instrument[75]. This particularly applies to the posteromedial and the anterolateral compartment because of limited distance to the ulnar nerve and radial nerve respectively. Other advantages of using a retractor, aside from preventing within-out injury, are better visualization and exposure of the elbow joint. Lastly, to prevent a burr from getting entangled in the surrounding soft tissues and causing damage to an adjacent nerve hooded burrs are advised. Availability of different sizes of shavers during surgery is obligatory, so you can adjust the shaver size to the specific circumstances and avoid within-out-injury due to usage of a too large shaver.

All aforementioned recommendations are summarized in Table 1.

DISCUSSION

Thorough knowledge of the anatomy of the elbow in health and various diseases, handling of arthroscopic instruments and number of performed elbow arthroscopies

are of influence on one's arthroscopic expertise[13,20,31,83,84]. There still is no consensus on the minimal number of elbow arthroscopies that has to be performed to become an experienced arthroscopist. However it is apparent that elbow arthroscopy has a long(er) learning curve. Savoie[20] states that a minimal number of 100 performed elbow arthroscopies is necessary to become an experienced elbow arthroscopist. After the first 15 arthroscopies Kim *et al*[84] observed a significant decrease in surgical time in elbow arthroscopy.

It is common sense that with more experience comes a decreased complication rate. This seems to be confirmed when comparing the study of Claessen *et al*[83] with the studies of Marti *et al*[31] and Elfeddali *et al*[28]. Claessen *et al*[83], observed a 30% complication rate in portal placement by novice surgeons whom were trained by a single didactic lecture and a single cadaveric training and found the complication rate significantly higher when compared to studies in current literature by experienced elbow arthroscopists. Marti *et al*[31] found 6 minor complications (5%) in a series of 100 elbow arthroscopies done by 1 fellowship trained surgeon with only previous cadaveric experience, however no correlation could be found between the complication rate and the learning curve. Elfeddali *et al*[28], found a 7.5% complication rate in 200 elbow arthroscopies over 8 years all performed by a single surgeon; due to the sample size it was not possible to detect any significant learning effect.

Following out of the aforementioned studies is that inexperienced surgeons are more likely to cause iatrogenic complications during elbow arthroscopy. A "young" surgeon should undergo extensive training with as much hands-on exposure as possible, comprehending guidance by an experienced elbow arthroscopist, computer-simulated hands-on courses, pre-clinical hands-on cadaveric courses preferably yearly and in line with the current opinion of arthroscopy experts and Claessen *et al*[83] fellowship training.

In current literature the prevalence of neurologic injury after elbow arthroscopy, transient and permanent, is reported to range between 0% and 14%[8,13,14,32,34,42,45,63,85-88]. As stated by Desai *et al*[60] the reported prevalence is probably underreported. Possible causes of nerve injury underreporting after elbow arthroscopy are; the lack of a national registration for nerve injuries like there is for orthopedic implants, loss-to-follow-up due to the diagnosis and treatment of nerve injury by another specialty, and the possible reluctance or fear of the consequences when reporting iatrogenic nerve injury.

The goal of this editorial is to make one aware of the complications that can occur when performing elbow arthroscopy and more importantly stress the difficulty of performing elbow arthroscopy. The abovementioned instructions are to be a general guideline in order to help avoid complications during elbow arthroscopy. We believe a proper and thorough work-up and awareness of the possible severe complications throughout all steps of the procedure is the key for a successful elbow arthroscopy.

No matter the experience of an elbow arthroscopist, for every indication a surgeon should assess if he is capable to perform the procedure as a surgeon's experience is directly related to the incidence of complications[20].

REFERENCES

1 **Gallay SH**, Richards RR, O'Driscoll SW. Intraarticular capacity and compliance of stiff and normal elbows. *Arthroscopy* 1993; **9**: 9-13 [PMID: 8442838 DOI: 10.1016/s0749-8063(05)80336-6]

2 **Abboud JA**, Ricchetti ET, Tjoumakaris F, Ramsey ML. Elbow arthroscopy: basic setup and portal placement. *J Am Acad Orthop Surg* 2006; **14**: 312-318 [PMID: 16675625 DOI: 10.5435/00124635-200605000-00007]

3 **Lynch GJ**, Meyers JF, Whipple TL, Caspari RB. Neurovascular anatomy and elbow arthroscopy: inherent risks. *Arthroscopy* 1986; **2**: 190-197 [PMID: 3768116 DOI: 10.1016/s0749-8063(86)80067-6]

4 **Marshall PD**, Fairclough JA, Johnson SR, Evans EJ. Avoiding nerve damage during elbow arthroscopy. *J Bone Joint Surg Br* 1993; **75**: 129-131 [PMID: 8421009]

5 **Miller CD**, Jobe CM, Wright MH. Neuroanatomy in elbow arthroscopy. *J Shoulder Elbow Surg* 1995; **4**: 168-174 [PMID: 7552673 DOI: 10.1016/s1058-2746(05)80047-3]

6 **Morrey BF**. Arthroscopy of the elbow. *Instr Course Lect* 1986; **35**: 102-107 [PMID: 3819396]

7 **Omid R**, Hamid N, Keener JD, Galatz LM, Yamaguchi K. Relation of the radial nerve to the anterior capsule of the elbow: anatomy with correlation to arthroscopy. *Arthroscopy* 2012; **28**: 1800-1804 [PMID: 23079289 DOI: 10.1016/j.arthro.2012.05.890]

8 **Small NC**. Complications in arthroscopic surgery performed by experienced arthroscopists. *Arthroscopy* 1988; **4**: 215-221 [PMID: 3166663 DOI: 10.1016/s0749-8063(88)80030-6]

9 **Stothers K**, Day B, Regan WR. Arthroscopy of the elbow: anatomy, portal sites, and a description of the proximal lateral portal. *Arthroscopy* 1995; **11**: 449-457 [PMID: 7575879 DOI: 10.1016/0749-8063(95)90200-7]

10 **Verhaar J**, van Mameren H, Brandsma A. Risks of neurovascular injury in elbow arthroscopy: starting anteromedially or anterolaterally? *Arthroscopy* 1991; **7**: 287-290 [PMID: 1750938 DOI: 10.1016/0749-8063(91)90129-I]

11 **Field LD**, Altchek DW, Warren RF, O'Brien SJ, Skyhar MJ, Wickiewicz TL. Arthroscopic anatomy of the lateral elbow: a comparison of three portals. *Arthroscopy* 1994; **10**: 602-607 [PMID: 7880349 DOI: 10.1016/s0749-8063(05)80055-6]

12 **Lindenfeld TN**. Medial approach in elbow arthroscopy. *Am J Sports Med* 1990; **18**: 413-417 [PMID: 2403191 DOI: 10.1177/036354659001800414]

13 **Kelly EW**, Morrey BF, O'Driscoll SW. Complications of elbow arthroscopy. *J Bone Joint Surg Am* 2001; **83-A**: 25-34 [PMID: 11205854]

14 **Kim SJ**, Kim HK, Lee JW. Arthroscopy for limitation of motion of the elbow. *Arthroscopy* 1995; **11**: 680-683 [PMID: 8679028 DOI: 10.1016/0749-8063(95)90109-4]

15 **Savoie FH**, Nunley PD, Field LD. Arthroscopic management of the arthritic elbow: indications, technique, and results. *J Shoulder Elbow Surg* 1999; **8**: 214-219 [PMID: 10389075 DOI: 10.1016/s1058-2746(99)90131-3]

16 **Kim SJ**, Shin SJ. Arthroscopic treatment for limitation of motion of the elbow. *Clin Orthop Relat Res* 2000; **(375)**: 140-148 [PMID: 10853163 DOI: 10.1097/00003086-200006000-00017]

17 **Andrews JR**, St Pierre RK, Carson WG. Arthroscopy of the elbow. *Clin Sports Med* 1986; **5**: 653-662 [PMID: 3768970]

18 **Baker CL**, Jones GL. Arthroscopy of the elbow. *Am J Sports Med* 1999; **27**: 251-264 [PMID: 10102110]

19 **Dodson CC**, Nho SJ, Williams RJ, Altchek DW. Elbow arthroscopy. *J Am Acad Orthop Surg* 2008; **16**: 574-585 [PMID: 18832601 DOI: 10.5435/00124635-200810000-00003]

20 **Savoie FH**. Guidelines to becoming an expert elbow arthroscopist. *Arthroscopy* 2007; **23**: 1237-1240 [PMID: 17986413 DOI: 10.1016/j.arthro.2007.04.013]

21 **Adams JE**, King GJ, Steinmann SP, Cohen MS. Elbow arthroscopy: indications, techniques, outcomes, and complications. *Instr Course Lect* 2015; **64**: 215-224 [PMID: 25745907 DOI: 10.5435/jaaos-22-12-810]

22 **Yeoh KM**, King GJ, Faber KJ, Glazebrook MA, Athwal GS. Evidence-based indications for elbow arthroscopy. *Arthroscopy* 2012; **28**: 272-282 [PMID: 22244102 DOI: 10.1016/j.arthro.2011.10.007]

23 **Adams JE**, Wolff LH, Merten SM, Steinmann SP. Osteoarthritis of the elbow: results of arthroscopic osteophyte resection and capsulectomy. *J Shoulder Elbow Surg* 2008; **17**: 126-131 [PMID: 18069006 DOI: 10.1016/j.jse.2007.04.005]

24 **Blonna D**, Lee GC, O'Driscoll SW. Arthroscopic restoration of terminal elbow extension in high-level athletes. *Am J Sports Med* 2010; **38**: 2509-2515 [PMID: 20847224 DOI: 10.1177/0363546510376727]

25 **Blonna D**, Wolf JM, Fitzsimmons JS, O'Driscoll SW. Prevention of nerve injury during arthroscopic capsulectomy of the elbow utilizing a safety-driven strategy. *J Bone Joint Surg Am* 2013; **95**: 1373-1381 [PMID: 23925741 DOI: 10.2106/jbjs.k.00972]

26 **Dolderer JH**, Prandl EC, Kehrer A, Beham A, Schaller HE, Briggs C, Kelly JL. Solitary paralysis of the flexor pollicis longus muscle after minimally invasive elbow procedures: anatomical and clinical study of the anterior interosseous nerve. *Plast Reconstr Surg* 2011; **127**: 1229-1236 [PMID: 21364424 DOI: 10.1097/PRS.0b013e3182043ac0]

27 **El Hajj F**, Hoteit M, Ouaknine M. Elbow arthroscopy: An alternative to anteromedial portals. *Orthop Traumatol Surg Res* 2015; **101**: 411-414 [PMID: 25910702 DOI: 10.1016/j.otsr.2015.03.011]

28 **Elfeddali R**, Schreuder MH, Eygendaal D. Arthroscopic elbow surgery, is it safe? *J Shoulder Elbow Surg* 2013; **22**: 647-652 [PMID: 23590887 DOI: 10.1016/j.jse.2013.01.032]

29 **Lattermann C**, Romeo AA, Anbari A, Meininger AK, McCarty LP, Cole BJ, Cohen MS. Arthroscopic debridement of the extensor carpi radialis brevis for recalcitrant lateral epicondylitis. *J Shoulder Elbow Surg* 2010; **19**: 651-656 [PMID: 20541097 DOI: 10.1016/j.jse.2010.02.008]

30 **Lee BP**, Morrey BF. Arthroscopic synovectomy of the elbow for rheumatoid arthritis. A prospective study. *J Bone Joint Surg Br* 1997; **79**: 770-772 [PMID: 9331033 DOI: 10.1302/0301-620x.79b5.7466]

31 **Marti D**, Spross C, Jost B. The first 100 elbow arthroscopies of one surgeon: analysis of complications. *J Shoulder Elbow Surg* 2013; **22**: 567-573 [PMID: 23419603 DOI: 10.1016/j.jse.2012.12.001]

32 **Nelson GN**, Wu T, Galatz LM, Yamaguchi K, Keener JD. Elbow arthroscopy: early complications and associated risk factors. *J Shoulder Elbow Surg* 2014; **23**: 273-278 [PMID: 24332953 DOI: 10.1016/j.jse.2013.09.026]

33 **Nguyen D**, Proper SI, MacDermid JC, King GJ, Faber KJ. Functional outcomes of arthroscopic capsular release of the elbow. *Arthroscopy* 2006; **22**: 842-849 [PMID: 16904581 DOI: 10.1016/j.arthro.2006.04.100]

34 **O'Driscoll SW**, Morrey BF. Arthroscopy of the elbow. Diagnostic and therapeutic benefits and hazards. *J Bone Joint Surg Am* 1992; **74**: 84-94 [PMID: 1734016]

35 **Papilion JD**, Neff RS, Shall LM. Compression neuropathy of the radial nerve as a complication of elbow arthroscopy: a case report and review of the literature. *Arthroscopy* 1988; **4**: 284-286 [PMID: 2852940 DOI: 10.1016/s0749-8063(88)80046-x]

36 **Park JY**, Cho CH, Choi JH, Lee ST, Kang CH. Radial nerve palsy after arthroscopic anterior capsular release for degenerative elbow contracture. *Arthroscopy* 2007; **23**: 1360.e1-1360.e3 [PMID: 18063186 DOI: 10.1016/j.arthro.2006.11.021]

37 **Pederzini LA**, Nicoletta F, Tosi M, Prandini M, Tripoli E, Cossio A. Elbow arthroscopy in stiff elbow. *Knee Surg Sports Traumatol Arthrosc* 2014; **22**: 467-473 [PMID: 23435987 DOI: 10.1007/s00167-013-2424-0]

38 **Rosenberg BM**, Loebenberg MI. Elbow arthroscopy. *Bull NYU Hosp Jt Dis* 2007; **65**: 43-50 [PMID: 17539761]

39 **Schubert T**, Dubuc JE, Barbier O. A review of 24 cases of elbow arthroscopy using the DASH questionnaire. *Acta Orthop Belg* 2007; **73**: 700-703 [PMID: 18260480]

40 **Tanaka N**, Sakahashi H, Hirose K, Ishima T, Ishii S. Arthroscopic and open synovectomy of the elbow in rheumatoid arthritis. *J Bone Joint Surg Am* 2006; **88**: 521-525 [PMID: 16510817 DOI: 10.2106/jbjs.e.00472]

41 **Thomas MA**, Fast A, Shapiro D. Radial nerve damage as a complication of elbow arthroscopy. *Clin Orthop Relat Res* 1987: 130-131 [PMID: 3802628 DOI: 10.1097/00003086-198702000-00018]

42 **Vavken P**, Müller AM, Camathias C. First 50 Pediatric and Adolescent Elbow Arthroscopies: Analysis of Indications and Complications. *J Pediatr Orthop* 2016; **36**: 400-404 [PMID: 25851678 DOI: 10.1097/bpo.0000000000000461]

43 **Wu X**, Wang H, Meng C, Yang S, Duan D, Xu W, Liu X, Tang M, Zhao J. Outcomes of arthroscopic arthrolysis for the post-traumatic elbow stiffness. *Knee Surg Sports Traumatol Arthrosc* 2015; **23**: 2715-2720 [PMID: 24832692 DOI: 10.1007/s00167-014-3032-3]

44 **Somanchi BV**, Funk L. Evaluation of functional outcome and patient satisfaction after arthroscopic elbow arthrolysis. *Acta Orthop Belg* 2008; **74**: 17-23 [PMID: 18411597]

45 **Andrews JR**, Carson WG. Arthroscopy of the elbow. *Arthroscopy* 1985; **1**: 97-107 [PMID: 4091924 DOI: 10.1016/s0749-8063(85)80038-4]

46 **Carofino BC**, Bishop AT, Spinner RJ, Shin AY. Nerve injuries resulting from arthroscopic treatment of lateral epicondylitis: report of 2 cases. *J Hand Surg Am* 2012; **37**: 1208-1210 [PMID: 22459658 DOI: 10.1016/j.jhsa.2012.01.038]

47 **Murphy RK**, Ray WZ, Mackinnon SE. Repair of a median nerve transection injury using multiple nerve transfers, with long-term functional recovery. *J Neurosurg* 2012; **117**: 886-889 [PMID: 22978538 DOI: 10.3171/2012.8.jns111356]

48 **Gay DM**, Raphael BS, Weiland AJ. Revision arthroscopic contracture release in the elbow resulting in an ulnar nerve transection: a case report. *J Bone Joint Surg Am* 2010; **92**: 1246-1249 [PMID: 20439672 DOI: 10.2106/jbjs.i.00555]

49 **Dumonski ML**, Arciero RA, Mazzocca AD. Ulnar nerve palsy after elbow arthroscopy. *Arthroscopy* 2006; **22**: 577.e1-577.e3 [PMID: 16651181 DOI: 10.1016/j.arthro.2005.12.049]

50 **Gupta A**, Sunil Tm Tm. Complete division of the posterior interosseous nerve after elbow arthroscopy: a case report. *J Shoulder Elbow Surg* 2004; **13**: 566-567 [PMID: 15383817 DOI: 10.1016/s1058274604000503]

51 **Reddy AS**, Kvitne RS, Yocum LA, Elattrache NS, Glousman RE, Jobe FW. Arthroscopy of the elbow: a long-term clinical review. *Arthroscopy* 2000; **16**: 588-594 [PMID: 10976118 DOI: 10.1053/jars.2000.8953]

52 **Haapaniemi T**, Berggren M, Adolfsson L. Complete transection of the median and radial nerves during arthroscopic release of post-traumatic elbow contracture. *Arthroscopy* 1999; **15**: 784-787 [PMID: 10524831 DOI: 10.1016/s0749-8063(99)70015-0]

53 **Hahn M**, Grossman JA. Ulnar nerve laceration as a result of elbow arthroscopy. *J Hand Surg Br* 1998; **23**: 109 [PMID: 9571498 DOI: 10.1016/s0266-7681(98)80236-2]

54 **Ruch DS**, Poehling GG. Anterior interosseus nerve injury following elbow arthroscopy. *Arthroscopy* 1997; **13**: 756-758 [PMID: 9442332 DOI: 10.1016/s0749-8063(97)90014-1]

55 **Jones GS**, Savoie FH. Arthroscopic capsular release of flexion contractures (arthrofibrosis) of the elbow. *Arthroscopy* 1993; **9**: 277-283 [PMID: 8323612 DOI: 10.1016/s0749-8063(05)80422-0]

56 **Cefo I**, Eygendaal D. Arthroscopic arthrolysis for posttraumatic elbow stiffness. *J Shoulder Elbow Surg* 2011; **20**: 434-439 [PMID: 21397792 DOI: 10.1016/j.jse.2010.11.018]

57 **Grewal R**, MacDermid JC, Shah P, King GJ. Functional outcome of arthroscopic extensor carpi radialis brevis tendon release in chronic lateral epicondylitis. *J Hand Surg Am* 2009; **34**: 849-857 [PMID: 19410988 DOI: 10.1016/j.jhsa.2009.02.006]

58 **Krishnan SG**, Harkins DC, Pennington SD, Harrison DK, Burkhead WZ. Arthroscopic ulnohumeral arthroplasty for degenerative arthritis of the elbow in patients under fifty years of age. *J Shoulder Elbow Surg* 2007; **16**: 443-448 [PMID: 17254810 DOI: 10.1016/j.jse.2006.09.001]

59 **McLaughlin RE**, Savoie FH, Field LD, Ramsey JR. Arthroscopic

treatment of the arthritic elbow due to primary radiocapitellar arthritis. *Arthroscopy* 2006; **22**: 63-69 [PMID: 16399463 DOI: 10.1016/j.arthro.2005.10.013]

60 **Desai MJ**, Mithani SK, Lodha SJ, Richard MJ, Leversedge FJ, Ruch DS. Major Peripheral Nerve Injuries After Elbow Arthroscopy. *Arthroscopy* 2016; **32**: 999-1002.e8 [PMID: 26853949 DOI: 10.1016/j.arthro.2015.11.023]

61 **Blonna D**, Bellato E, Marini E, Scelsi M, Castoldi F. Arthroscopic treatment of stiff elbow. *ISRN Surg* 2011; **2011**: 378135 [PMID: 22084755 DOI: 10.5402/2011/378135]

62 **Dwyer T**, Henry PD, Cholvisudhi P, Chan VW, Theodoropoulos JS, Brull R. Neurological Complications Related to Elective Orthopedic Surgery: Part 1: Common Shoulder and Elbow Procedures. *Reg Anesth Pain Med* 2015; **40**: 431-442 [PMID: 26192546 DOI: 10.1097/aap.0000000000000178]

63 **Schneider T**, Hoffstetter I, Fink B, Jerosch J. Long-term results of elbow arthroscopy in 67 patients. *Acta Orthop Belg* 1994; **60**: 378-383 [PMID: 7847086]

64 **Childress HM**. Recurrent ulnar-nerve dislocation at the elbow. *Clin Orthop Relat Res* 1975; **(108)**: 168-173 [PMID: 1139823 DOI: 10.1097/00003086-197505000-00027]

65 **Van Den Berg PJ**, Pompe SM, Beekman R, Visser LH. Sonographic incidence of ulnar nerve (sub)luxation and its associated clinical and electrodiagnostic characteristics. *Muscle Nerve* 2013; **47**: 849-855 [PMID: 23625811 DOI: 10.1002/mus.23715]

66 **Sahajpal DT**, Blonna D, O'Driscoll SW. Anteromedial elbow arthroscopy portals in patients with prior ulnar nerve transposition or subluxation. *Arthroscopy* 2010; **26**: 1045-1052 [PMID: 20678701 DOI: 10.1016/j.arthro.2009.12.029]

67 **Wada T**, Yamauchi M, Oki G, Sonoda T, Yamakage M, Yamashita T. Efficacy of axillary nerve block in elbow arthroscopic surgery: a randomized trial. *J Shoulder Elbow Surg* 2014; **23**: 291-296 [PMID: 24439245 DOI: 10.1016/j.jse.2013.11.022]

68 **Auroy Y**, Benhamou D, Bargues L, Ecoffey C, Falissard B, Mercier FJ, Bouaziz H, Samii K. Major complications of regional anesthesia in France: The SOS Regional Anesthesia Hotline Service. *Anesthesiology* 2002; **97**: 1274-1280 [PMID: 12411815 DOI: 10.1097/00000542-200211000-00034]

69 **Auroy Y**, Narchi P, Messiah A, Litt L, Rouvier B, Samii K. Serious complications related to regional anesthesia: results of a prospective survey in France. *Anesthesiology* 1997; **87**: 479-486 [PMID: 9316950 DOI: 10.1097/00132586-199806000-00031]

70 **Brull R**, McCartney CJ, Chan VW, El-Beheiry H. Neurological complications after regional anesthesia: contemporary estimates of risk. *Anesth Analg* 2007; **104**: 965-974 [PMID: 17377115 DOI: 10.1213/01.ane.0000258740.17193.ec]

71 **Adams JE**, Steinmann SP. Nerve injuries about the elbow. *J Hand Surg Am* 2006; **31**: 303-313 [PMID: 16473695 DOI: 10.1016/j.jhsa.2005.12.006]

72 **Hackl M**, Lappen S, Burkhart KJ, Leschinger T, Scaal M, Müller LP, Wegmann K. Elbow Positioning and Joint Insufflation Substantially Influence Median and Radial Nerve Locations. *Clin Orthop Relat Res* 2015; **473**: 3627-3634 [PMID: 26152782 DOI: 10.1007/s11999-015-4442-3]

73 **Adolfsson L**. Arthroscopy of the elbow joint: A cadaveric study of portal placement. *J Shoulder Elbow Surg* 1994; **3**: 53-61 [PMID: 22959642 DOI: 10.1016/s1058-2746(09)80110-9]

74 **Baker CL**, Brooks AA. Arthroscopy of the elbow. *Clin Sports Med* 1996; **15**: 261-281 [PMID: 8726317]

75 **Morrey BF**. Complications of elbow arthroscopy. *Instr Course Lect* 2000; **49**: 255-258 [PMID: 10829181]

76 **O'Driscoll SW**, Morrey BF, An KN. Intraarticular pressure and capacity of the elbow. *Arthroscopy* 1990; **6**: 100-103 [PMID: 2363775 DOI: 10.1016/0749-8063(90)90007-z]

77 **Ogilvie-Harris DJ**, Weisleder L. Fluid pump systems for arthroscopy: a comparison of pressure control versus pressure and flow control. *Arthroscopy* 1995; **11**: 591-595 [PMID: 8534302 DOI: 10.1016/0749-8063(95)90137-x]

78 **Unlu MC**, Kesmezacar H, Akgun I, Ogut T, Uzun I. Anatomic relationship between elbow arthroscopy portals and neurovascular structures in different elbow and forearm positions. *J Shoulder Elbow Surg* 2006; **15**: 457-462 [PMID: 16831651 DOI: 10.1016/j.jse.2005.09.012]

79 **Nowicki KD**, Shall LM. Arthroscopic release of a posttraumatic flexion contracture in the elbow: a case report and review of the literature. *Arthroscopy* 1992; **8**: 544-547 [PMID: 1466720 DOI: 10.1016/0749-8063(92)90024-6]

80 **Diliberti T**, Botte MJ, Abrams RA. Anatomical considerations regarding the posterior interosseous nerve during posterolateral approaches to the proximal part of the radius. *J Bone Joint Surg Am* 2000; **82**: 809-813 [PMID: 10859100]

81 **Raphael BS**, Weiland AJ, Altchek DW, Gay DM. Revision arthroscopic contracture release in the elbow resulting in an ulnar nerve transection: surgical technique. *J Bone Joint Surg Am* 2011; **93** Suppl 1: 100-108 [PMID: 21411691 DOI: 10.2106/jbjs.j.01272]

82 **O'Holleran JD**, Altchek DW. The thrower's elbow: arthroscopic treatment of valgus extension overload syndrome. *HSS J* 2006; **2**: 83-93 [PMID: 18751853 DOI: 10.1007/s11420-005-5124-6]

83 **Claessen FM**, Kachooei AR, Kolovich GP, Buijze GA, Oh LS, van den Bekerom MP, Doornberg JN. Portal placement in elbow arthroscopy by novice surgeons: cadaver study. *Knee Surg Sports Traumatol Arthrosc* 2016; Epub ahead of print [PMID: 27351547 DOI: 10.1007/s00167-016-4186-y]

84 **Kim SJ**, Moon HK, Chun YM, Chang JH. Arthroscopic treatment for limitation of motion of the elbow: the learning curve. *Knee Surg Sports Traumatol Arthrosc* 2011; **19**: 1013-1018 [PMID: 21127837 DOI: 10.1007/s00167-010-1334-7]

85 **Guhl JF**. Arthroscopy and arthroscopic surgery of the elbow. *Orthopedics* 1985; **8**: 1290-1296 [PMID: 4094963]

86 **Rodeo SA**, Forster RA, Weiland AJ. Neurological complications due to arthroscopy. *J Bone Joint Surg Am* 1993; **75**: 917-926 [PMID: 8314834]

87 **Savoie FH**, 3rd. Complications. In: Arthroscopy of the elbow. New York: Churchill Livingstone, 1996: 151-156

88 **Ward WG**, Anderson TE. Elbow arthroscopy in a mostly athletic population. *J Hand Surg Am* 1993; **18**: 220-224 [PMID: 8463583 DOI: 10.1016/0363-5023(93)90350-c]

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MINIREVIEWS

Total knee arthroplasty and fractures of the tibial plateau

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Abstract

Tibial plateau fractures are common injuries that occur in a bimodal age distribution. While there are various treatment options for displaced tibial plateau fractures, the standard of care is open reduction and internal fixation (ORIF). In physiologically young patients with higher demand and better bone quality, ORIF is the preferred method of treating these fractures. However, future total knee arthroplasty (TKA) is a consideration in these patients as post-traumatic osteoarthritis is a common long-term complication of tibial plateau fractures. In older, lower demand patients, ORIF is potentially less favorable for a variety of reasons, namely fixation failure and the need for delayed weight bearing. In some of these patients, TKA can be considered as primary mode of treatment. This paper will review the literature surrounding TKA as both primary treatment and as a salvage measure in patients with fractures of the tibial plateau. The outcomes, complications, techniques and surgical challenges are also discussed.

Key words: Arthroplasty; Knee; Tibia; Intra-articular fractures; Fracture fixation

Core tip: It is well known that patients undergoing open reduction and internal fixation (ORIF) following tibial plateau fracture have a high rate of post-traumatic arthritis (PTOA) requiring total knee arthroplasty (TKA) in the future. Currently, ORIF is the standard of care for all patients requiring operative management. Small groups of select patients have shown good results with TKA as primary treatment of tibial plateau fracture. This group includes elderly patients with poor bone stock who are shown to have high rates of post-traumatic arthritis and fixation failure. In younger and more active patients, the options for salvage TKA in the case of PTOA is discussed, as this procedure is more complex than primary TKA.

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INTRODUCTION

Tibial plateau fracture is a common injury of the lower extremity that is seen in the population with a bimodal age distribution. These injuries are often categorized using the Schatzker classification, which can be been used to classify the fracture pattern and oftentimes dictate treatment. Type Ⅰ, Ⅱ and Ⅲ fractures involve the lateral plateau. Type Ⅳ fractures involve the medial plateau, while type Ⅴ describes bicondylar involvement. In type Ⅵ fractures, there is complete metadiaphyseal dissociation. In younger patients with more robust bone stock, tibial plateau fractures are generally the result of high energy mechanisms, whereas low energy mechanisms are usually observed in the elderly, osteoporotic population. Due to the mechanical axis of the lower extremity, with the lateral plateau higher and in 3 degrees of varus, the medial tibial plateau receives 60% of the load placed on the knee, creating stronger subchondral bone. As a result, lower energy injuries more commonly injure the lateral plateau. Therefore, medial injuries are not simply the counterpart to lateral injuries, but rather represent a much higher energy impact, and therefore associated injuries *(i.e.*, ACL and MCL) are more common with this pattern[1]. Approach to the patient should commence with evaluation of the soft-tissue envelope and neurovascular exam. In Schatzker Ⅳ-Ⅵ fractures, clinicians should be especially sensitive to the possibility of vascular injuries and compartment syndrome[1]. Computed tomography imaging in addition to standard radiographs are important in both fracture classification and operative planning.

Options for the management of these fractures range from conservative methods including bracing and limited weight bearing to surgical management, most commonly open reduction and internal fixation. The decision to pursue surgery is based upon the characteristics of the fracture. Regardless of patient age and bone quality, fractures with significant displacement or fragment depression require surgical management for a successful outcome. Instability and fracture displacement usually require an operative approach to restore joint surface congruity. A major factor when considering surgical management in the acute period following the injury is concomitant damage to the soft tissue structures surrounding the knee. If there is significant soft tissue damage or swelling precluding acute open reduction and internal fixation (ORIF), external fixation using a spanning frame with delayed surgical management of 2-3 wk is usually pursued. Goals of articular fracture management include restoration of the articular surface, normalization of the mechanical axis, stable fixation, early range of motion and delayed weight bearing in most cases. Lansinger *et al*[2] determined that long-term outcomes correlate better with restoration of joint axis in the sagittal and coronal planes than exact articular reduction. Achieving these goals gives patients the best chance of restoring their pre-injury level of function and avoiding the complications associated with these types of injuries[1,3].

Complications of tibial plateau fractures may require arthroplasty as a salvage procedure. Complications of operative management of tibial plateau fractures include infection, knee stiffness, non-union, fixation failure, and most relevant to this discussion, post-traumatic osteoarthritis (PTOA). Infections may be a frequent complication of ORIF of tibial plateau fractures with rates ranging from 2%-11%[4]. With optimal handling of the soft tissue envelope and appropriate decision-making by the surgeon, rates of infectious complication can be kept to a minimum. Infection should be avoided at all costs because patients who suffer infection following ORIF incur on average an additional five surgeries[5]. Factors associated with infection after tibial plateau fracture include smoking, compartment syndrome requiring fasciotomy and fractures requiring dual incisions with dual plating[6]. Knee stiffness is thought to be the result of post-operative immobilization. Patients with higher-energy fracture patterns are noted to be more likely to experience unsatisfactory knee motion following ORIF of the tibial plateau. This is also the case in patients with longer periods of immobilization. Three to four weeks of immobilization *vs* immediate ROM is associated with higher rates of stiffness and flexion contracture[4]. Fixation failure can be loosely defined as loss of reduction resulting in either step off of > 3 mm or malalignment of the extremity of greater than 5 degrees, loosening or breaking of implants. The rates of fixation failure range from between 1%-31%[7].

PTOA is caused mainly by articular incongruity and joint instability, although direct damage to the articular surface at the time of injury may play a role. PTOA is seen in 23%-44% of patients following tibial plateau fracture, even in those with stable knees. In one study, the rate of secondary OA was seen in 44% of patients who suffered PTOA and were followed up at an average of 7.6 years. An important point was that after 7 years, the rate of OA development did not increase significantly[8,9]. Weigel *et al*[10]'s 20-year follow-up of patients with high energy tibial plateau fractures found that after 2-4 years of follow-up, there was not a significant change in the rate or grade of arthrosis. There is a higher rate of PTOA in patients who undergo meniscectomy during fracture repair, and therefore preservation of menisci should be a priority during surgical management of these patients. Ligamentous injury also correlates with the development of secondary arthritis, as does residual tilt of the tibial plateau. Seventy-five percent of patients with ligamentous injury at the time of surgery developed secondary osteoarthritis *vs* 27% of those with no evidence of ligamentous injury or instability at the time of repair[8]. Not surprisingly, age is also a predictor of development of PTOA, with older patients being more likely to suffer secondary OA following trauma. Risk of degenerative change increases significantly with greater age at time of

injury[4,9,10]. It should be noted that there does not seem to be a difference in the rate of PTOA between those managed operatively *vs* non-operatively[8].

For patients who develop post-traumatic arthrosis of the knee, total knee arthroplasty (TKA) is a widely accepted treatment option, just as prosthetic replacement is considered for patients who develop primary osteoarthritis of the knee. In fact, the risk of TKA in patients with previous fracture of the tibial plateau is 5-times higher than matched controls from the general population, at 7.3% in the 10-year period following injury[11]. Age of the patient, activity level and the status of bone mineralization are some of the major factors that are involved in treatment of PTOA. Non arthroplasty options for physiologically younger patients generally include osteotomy and arthrodesis, however in most patients, especially older patients, TKA should be considered the optimal treatment for end stage PTOA[12].

In contrast to TKA for salvage in patients who suffered complications of tibial plateau fractures, TKA is potentially a primary treatment option for elderly patients with lower demands along with fracture patterns and bone quality that make ORIF a less desirable option. Elderly, osteopenic patients present several unique issues in the management of tibial plateau fractures. Fractures in this patient population are generally lower-energy injuries than seen in younger patients. Due to poor bone quality, fracture patterns are often complex with significant displacement and damage to the articular surface. As such, there is an association between patient age and failure of fracture fixation. Patients older than 60 have an increased risk of fixation failure and radiographic evidence of osteoporosis is a major predictor of failed fixation. One study reported a 79% rate of radiographic fixation failure in elderly patients *vs* 7% in the younger group of patients[7]. Second, fracture fixation in elderly patients will often times prevent early weight-bearing following surgical intervention. Delayed weight bearing in elderly patients is associated with higher morbidity and mortality than in younger populations. The earlier you can get an elderly patient mobile following surgery, the better the outcome and more likely the return to preoperative functional status, which should be the ultimate goal in management of these injuries. Therefore, investigators selecting patients to undergo TKA acutely following tibial plateau fracture used evidence of osteopenia or osteoarthritis as indications for TKA. This allows the identification of patients who are at risk for either failed fixation or later requirement of TKA. Some groups specified an age range, for instance, Vermeire *et al*[13] limited participants to over 70 years of age with evidence of poor bone stock or over 55 with severe, debilitating pre injury osteoarthritis.

Finally, as some studies have indicated, delayed TKA presents a greater challenge both in the operating room and during recovery than primary TKA, and complications can often be more dramatic in elderly patients. Considering these ideas, several papers are presented here that have examined groups of patients with tibial plateau fractures treated primarily with TKA and examined the outcomes and complications experienced by these patients.

APPROACH TO TKA IN TIBIAL PLATEAU FRACTURES

Total knee arthroplasty for PTOA

Arthroplasty in patients with prior fixation about the knee can present major challenges. It is more technically demanding and is associated with higher rates of complication than arthroplasties performed in patients with primary OA[14]. When planning TKA for patients with prior fixation of tibial plateau fracture, surgeons must consider several factors. First of all, patients should undergo a standard and thorough preoperative evaluation. This includes a medical evaluation, full length alignment radiographs along with an infectious and nutrition workup. Next the surgeon should take into consideration the previous repair and hardware present in the knee. Prior hardware may be removed intraoperatively or the removal can be staged it if will require extensive incisions or dissection, which can predispose to infection if performed simultaneously with TKA[15]. Additionally, not all hardware requires removal. Some authors suggest removing only the hardware that is going to directly interfere with the prosthesis[12].

In addition to challenges posed by the fracture, alterations to the soft tissue environment imposed by previous surgeries can complicate wound healing. Prior incisions should be approached carefully by using the most lateral incision and taking care not to create acute angles across prior transverse incisions. Careful attention should be taken to preserve the medial skin flap, as this is where the perforators arise. Other issues that can be encountered in this population is surgically constructed flaps and grafts which have a tenuous blood supply of their own. Surgeons should have a low threshold for consulting a plastic surgeon for management of the soft tissues in patients with prior soft tissue reconstruction. Careful consideration in this regard is necessary to preventing skin necrosis and wound healing complications.

Exposure of the knee can be difficult, as PTOA patients often have stiff knees. Certain maneuvers can be employed in different scenarios to provide excellent exposure as well as to manage injury to extensor mechanism and collateral ligaments. These include quadriceps, snip, VY turndown, tibial tubercle osteotomy and lateral retinacular release. Weiss *et al*[16] performed lateral release in 28% of their patients to facilitate their approach while Saleh *et al*[17] performed the same maneuver in 33% of their patients. Civinini *et al*[18] performed quadriceps snip and tibial tubercle osteotomy to facilitate exposure in 12% and 16% of their patients, respectively. It must be pointed out that these maneuvers are not without morbidity. Lateral release is generally benign and doesn't require any additional post-operative rehabilitation. Tubercle osteotomy can be more problematic, and mechanical

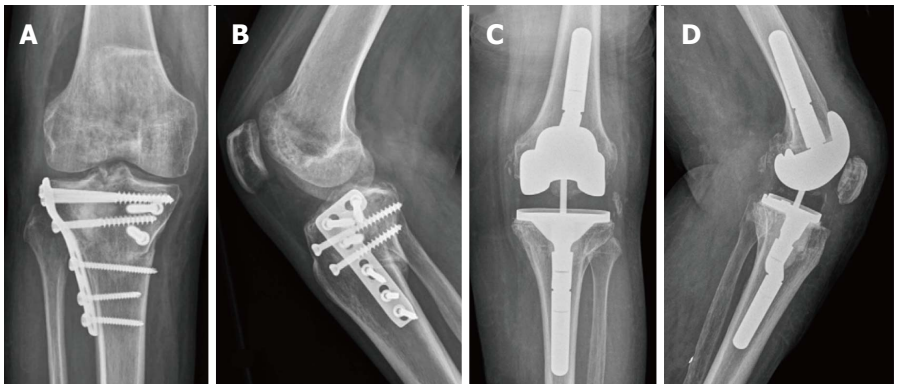

Figure 1 Total knee arthroplasty following open reduction and internal fixation of the tibial plateau. A and B: Radiographs of a 61-year-old woman made 3 years after ORIF for tibial plateau fracture; C and D: Radiographs at 7-year follow-up after constrained PS prosthesis with offset and stem in both components. ORIF: Open reduction and internal fixation.

complications relation to the procedure include disruption of the extensor mechanism or resultant fracture, with rates around 15%[19]. Quadriceps snip and VY turndown are soft tissue techniques that evolved as an alternative to tibial tubercle osteotomy, however they also pose a minor threat to the extensor function[20]. One study identified factors in their patient population that predicted patellar tendon rupture and these includes diabetes mellitus, steroids, trauma and patella baja[17]. Managing bony loss in these patients involves techniques similar to those for revision TKA including cement filling, morselized bone grafting and metal wedge augmentation, among others[12] (Figure 1).

Device selection should take into account ligament integrity and bone quality. A general rule is to use the least amount of prosthesis constraint necessary while allowing symmetric and balanced flexion and extension of the knee[12]. The high rate of constrained implant use in these patients makes this procedure more similar to revision TKA than primary standard TKA. The choice of implant should take into account the stability of the knee and existing bony defects. The most common implants types were varus/valgus constrained, hinged and PCL-retaining prostheses. Most but not all groups performed patellar resurfacing and required long-stems in certain patients to bypass fracture areas.

There is a well-known benefit to using computer assistance (CAS) in total knee arthroplasty. Kini *et al*[21] examined the use of CAS in acute TKA for a group of elderly patients with proximal tibial fractures, 6 of which were Schatzker type Ⅱ. Mean time to walking was 2 d and all patients returned to preoperative functional status. There were no major complications or revisions. Successful TKA relies on restoration of mechanical axis, which is improved with CAS. All patients in this sample had mechanical axis restored to within 3 degrees, which prevents off-axis loading and can lead to greater implant survivability. This study, while small, suggests that navigation systems for TKA can play a role in delivering acceptable outcomes to patients undergoing primary TKA for tibial plateau fracture. While CAS is an option for TKA in tibial plateau fractures, it is certainly not the standard of care[21].

TKA AS PRIMARY TREATMENT

Most authors evaluating this approach comment on the technical aspects of arthroplasty as the primary treatment for tibial plateau fracture. Preoperative planning as always is the first major step in ensuring an optimal outcome. Implant type and level of constraint should be determined based on pre-operative radiographs, assessing whether or not the fracture line likely compromises the medial or lateral collateral ligaments. In this case, a rotating hinge prosthesis should be selected. In terms of timing of surgery, all authors discussed the immediate post-injury period as ideal for surgery, as the primary goal of arthroplasty was early mobilization to prevent the sequelae of prolonged non-weightbearing. One study reported a mean surgical delay of 7.5 d, while another reported 4 d of mean surgical delay[22]. While it makes sense to allow a modest period of time for soft-tissue healing to prevent infection, we recommend allowing no more than three weeks before definitive repair. In most cases, unless prevented by the fracture site, medial parapatellar approach to the joint was used. Some authors utilized tibial tubercle osteotomies in all patients as a protocol[13], while other authors managed to avoid it entirely. For the bony cuts, the distal femoral cut should be 2.5 cm distal to the epicondyles and the tibial cut should allow joint line positioning 1 cm above the fibular head[19]. In terms of selecting prostheses, the choice between a hinged system and posterior-stabilized is made based on the integrity of the ligaments. In the studies evaluated, constrained, PS, rotating hinge and super stabilized prostheses were all used. If the fracture line is compromising the stability of the medial or lateral collateral ligaments, a rotating hinge prosthesis is best option[22]. Vermeire *et al*[13] has noted equally satisfactory results in using PS modular prostheses and cemented rotating hinge implants. This group also used stemmed cemented components, which allowed early weight bearing in these elderly patients. In series published on this topic, more attention should be paid

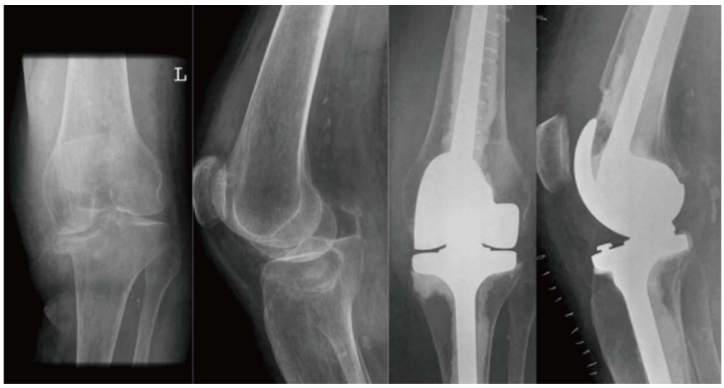

Figure 2 Primary total knee arthroplasty following tibial plateau fracture. Proximal tibial fracture with poor bone stock and post-operative radiograph showing rotating hinge prosthesis.

in the future to discussing the reasoning behind implant selection. As most studies were retrospective in nature, surgeon preference was often cited as the reasoning behind surgical decisions. Patellar resurfacing was variable between studies, with some groups performing this step systemically in all patients, others in select patients, and other groups not at all. In terms of managing bony loss, usually in osteoporotic or comminuted fractures most authors made use of wedges, augments and bone grafts to deal with osseous defects in these patients. One paper expanded on this and recommended wedges or cone shaped metallic augments or the patient's own bone for fixing defects[22]. Fracture reduction and joint alignment to determine pre-injury joint congruity and rotation, making use of diaphyseal landmarks is one approach used by Boureau *et al*[23]. If this cannot be performed accurately, surgeons should elect to approach the case as a revision TKA with major bone loss[22]. Simultaneous bony stabilization was used by all authors in this review (Figure 2).

RESEARCH RESULTS

TKA for ptoa following tibial plateau fracture

A number of studies exist in the literature that identified patients who underwent TKA following tibial plateau fractures that were managed operatively and nonoperatively Most of these series have looked at outcomes in terms of function and pain scores, patient satisfaction as well as stability, survivability of prosthesis, and incidence of common complications of TKA, such as infection, component loosening or periprosthetic fracture. Weiss *et al*[16] found improvements in KSS for pain and function in a group of 62 patients, with excellent or good results in 48 of those patients. Optimal component positioning had a positive impact on outcome. Civinini *et al*[18] had a good result in 18 of 25 patients undergoing TKA for this indication. Alternatively, poor outcome was related to complications in this group of patients. Range of motion and stability was significantly improved in this group. Saleh *et al*[17] reported HSS knee scores that improved from 51 pre-operatively to 80 post-operatively. Twelve/fifteen outcomes were considered good or excellent in their paper. Scott *et al*[14] matched the patients undergoing TKA for prior tibial plateau fracture with controls undergoing TKA for primary OA. Absolute OKS scores did not differ significantly between the two groups at five years. This is in sharp contrast to other studies of this nature which highlight poorer knee outcomes based on KSS and HSS knee scores. The authors here suggest that OKS is a more-patient centered scale that is based on the experience of the patient, while the HSS and KSS scales may be reporting more physician-centered data that might ignore the fact that patients are actually satisfied with their implants despite clinically discouraging measures such as range of motion, contracture and instability[14]. Lizaur-Utrilla *et al*[15] performed a similar comparison. The authors of this study challenged the notion that the outcomes between TKA for PTOA and routine TKA are significantly different. This study had a homogenous surgical and postoperative protocol not seen in most of its contemporaries. Functional outcomes including WOMAC pain score, KSS knee and function scores, ROM, SF12 physical and mental scores did not differ significantly between the two groups. The authors posited that a protocolized surgical scheme, which involved separate removal of hardware and standardized exposure strategy, can improve outcomes for patients undergoing TKA for PTOA secondary to tibial plateau fracture[15]. Abdel *et al*[24] followed 46 patients over 15 years and found that KSS and ROM both improved significantly from pre-operative values.

TKA as primary treatment

More recently in the literature is a group of studies analyzing the success of TKA as a primary treatment of tibial plateau fractures in elderly patients. Considering that TKA for PTOA is a more established concept than primary TKA for tibial plateau fracture, the series presented in this section are also smaller. The first small series performed primary TKA on four elderly patients with tibial plateau fractures. Excellent results were obtained in three cases and a fair result in one. No reoperations were required, and radiographic follow up showed optimal alignment with no evidence of loosening[25]. Vermeire *et al*[13] selected 12 patients who underwent primary TKA within 3 wk of tibial plateau fracture. Seven patients had outcomes rated as excellent and median final knee score was 78 and function score was 58. The authors concluded that primary TKA for tibial plateau fracture is an acceptable alternative to fracture fixation in patients with difficult fractures or poor

bone quality who would likely end up requiring a TKA[22]. Malviya *et al*[26] studied a group of elderly patients who underwent primary TKA for either tibial plateau or distal femoral fractures. Eighty-one percent of elderly patients with fractures about the knee returned to preoperative functional status. Patient satisfaction was similarly excellent although KSS were not overall excellent (90.2 knee and 35.5 for function). The authors remind us to consider that this patient population likely did not have excellent knee function to begin with[26]. Haufe *et al*[27] limited their series to only patients with fractures of the tibial plateau. They found improved mean knee scores for patients undergoing the procedure. Their paper contended that in the elderly population, tibial plateau fractures represent a great technical challenge in primary repair and primary TKA can avoid this challenge while presenting the patient an opportunity for full weight-bearing in the early postoperative period, which is likely to reduce some of the morbidity associated with delayed weight-bearing following ORIF. An interesting finding in this paper was that the subgroup of patients treated in the later part of the series (2013-2014) showed better functional results than the overall group, potentially indicating that we can expect improved results for this procedure as experience and technology progress[27]. Another group examining the outcomes of TKA as primary treatment of periarticular fractures about the knee in elderly patients did not find evidence to support the idea that primary TKA in these patients preserves patient autonomy as widely suggested. Patient autonomy was measured using the Parker Score of mobility, and found a significant decline following surgery (7.2 pre op to 4.6 post op). Moreover, autonomy decline was evidenced by only 7/15 patients returning to pre-operative level of independence and only 11/15 patients returning home following surgery. While this group did stratify proximal tibial from distal femoral fractures, the knee scores did not differ significantly between the groups, allowing us to generalize these results to our specific discussion of tibial plateau fractures[23]. Parratte *et al*[22] highlighted 16 cases of tibial plateau fractures treated primarily with TKA in a multicenter retrospective trial in France from 1990-2010. While functional results of the knee were considered good, there was a significant loss of autonomy in this group of patients, as seen in other studies of its nature[22].

COMPLICATIONS

TKA for PTOA

Despite an acceptable functional outcome, Weiss *et al*[16] showed a great deal of complications. Twenty-six percent of patients encountered post-operative complications, most commonly stiffness and wound breakdown. Of note, there were 5 intraoperative patellar tendon ruptures in this sample, all of which were repaired successfully during surgery. For Civinini *et al*[18] 8 of 25 knees encountered complication, including patellar tendon rupture and two implant failures. Saleh *et al*[17] also reported a high rate of postoperative complications, 11/15 patients experienced some sort of complication. There were two early patellar tendon ruptures and three patients requiring treatment for early wound complications with prolonged drainage and oral antibiotics. For the controlled trial conducted by Scott *et al*[14], rates of intraoperative complication were higher in in the PTOA cohort although the incidence of early and late complications failed to differ significantly. In the trial conducted by Lizaur-Utrilla *et al*[15], the PTOA group did have significantly more complications than the primary patients, including patellar tendon rupture and wound infection, however they weren't serious enough to affect the functional outcomes. Shearer *et al*[28] determined that in patients with soft tissue graft coverage, more common in this population, outcomes were poorer.

In all series reviewed, a number of patients experienced post-operative stiffness, some requiring manipulation under anesthesia. In the papers reviewed, the rates of manipulation under anesthesia for persistent stiffness ranged from 3.44%-20%[14-18]. Several papers reported repeat manipulations. Stiffness is therefore a major complication associated with arthroplasty following previous ORIF of the tibial plateau. Another common complication experienced throughout the literature is intra-operative avulsion of the patellar tendon and/or the MCL, owing to exposure difficulty in knees with significant scar tissue from previous surgery.

Overall, the type of complications encountered were similar and reflected the complex nature in performing TKA in knees with prior injury. Methods to avoid patellar tendon rupture and to preserve the delicate soft tissue are recommended to avoiding some of the common problems encountered by these authors. In Abdel *et al*[24]'s 15-year follow-up, they found that from the 5 to 15 year follow-up, there were only 2 additional complications (periprosthetic fracture and periprosthetic infection), leading the authors to conclude that if the early complications of TKA can be avoided, long-term survivorship free from aseptic loosening and revision (96% and 82%, respectively) can be achieved in pts undergoing TKA for this indication[24].

Primary TKA

The overall complication rate for primary TKA following tibial plateau fracture is higher than that for primary TKA in the general population but lower than that for TKA following operative repair of the tibial plateau by ORIF[23]. Overall complication rates of the studies included ranged from 9.5%-33%. The most commonly reported complications were infectious and wound complications, stiffness and flexion contracture, as well as periprosthetic fracture. All authors reported at least one case of wound complications, with many patients requiring re-operation for debridement or revision. Parratte *et al*[22] and Boureau *et al*[23] both reported problems with knee stiffness with 8% and 19% requiring closed manipulation under anesthesia, respectively. Component loosening was seen radiographically in one patient who required reoperation. Vermeire *et al*[13] discussed the case of a patient with a

periprosthetic fracture which was repaired using plates and screws. Other less common complications, which were not unique to this procedure, included hematoma formation and DVT/PE, reported in several papers. In the 12-patient analysis by Vermeire *et al*[13], three developed spontaneously resolving hematomas and one developed a lower extremity DVT treated with low-molecular weight heparin.

DISCUSSION

The discussion of TKA in patients with fractures of the tibial plateau is two-fold. First, patients who develop complications of fracture management, most commonly post-traumatic osteoarthritis of the knee, can be managed with arthroplasty. It is most commonly considered in older patients with less demand, as arthroplasty is usually not preferred in younger patients who may require several revisions throughout their lifetime. Our review shows that while good results may be achieved, complication rates are high and the procedure requires thoughtful decision making and careful attention to avoid complications. Avoiding the early complications can result in acceptable function and survivability. The body of literature regarding this topic is well-rounded, and will benefit in future years from longer-term data on patients and evolving technology in total joint replacement. While recognizing that there is no argument to be made for primary TKA replacing ORIF for primary treatment of tibial plateau fractures, there is a certain group of patients for whom a primary TKA may be indicated. It has been demonstrated in this literature review that fixation failure is more common in elderly patients with poor bone stock. In patients with low demand, poor bone stock in whom we can predict a high rate of TKA, primary arthroplasty should be considered as a primary treatment for fractures of the tibial plateau.

With that in mind, the second discussion is that of TKA as primary treatment for tibial plateau fractures, which is usually carried out in these older, osteoporotic patients. Most series on this topic are small in number and carried out in Europe. While theoretically well-understood to avoid complications of delayed weight-bearing and poor outcomes of fracture fixation, the overall body of literature for this indication is lacking. Currently, the literature which has discussed the use of acute TKA for this injury has been limited to series of elderly patients with poor bone quality. Perhaps expanding the indications for primary TKA in tibial plateau fracture to outside of the group with obviously poor bone may prove to be beneficial for a wider group of patients. However, at this time there is no reason to consider expanding in the indications for primary TKA following a fracture to the tibial plateau. At the same time, it should also be recognized that a high percentage of patients who undergo successful ORIF will need prosthetic knee replacement down the road. This is well established and accepted in the world of orthopaedic trauma. Refining the indications and technique for performing a primary TKA after tibial plateau fracture is an important task. Future effort should be placed in identifying patients with high risk of poor outcome (either failed fixation or PTOA) and evaluating TKA as an alternative to fixation in this group. Our paper shows clearly that for the elderly patients selected, primary TKA is a potentially valuable option to address their injury. Slowly expanding the indications with future series will possibly show that younger patients with healthier bone can benefit as well. For now, ORIF remains the standard of care for these patients. Large cohort, multi-center data, as well as head-to head comparison of the two methods is going to be required to determine the true benefit of primary TKA for patients with fractures of the tibial plateau.

REFERENCES

1 **Berkson EM**, Virkus WW. High-energy tibial plateau fractures. *J Am Acad Orthop Surg* 2006; **14**: 20-31 [PMID: 16394164 DOI: 10.007/978-1-4471-0691-3_24]

2 **Lansinger O**, Bergman B, Körner L, Andersson GB. Tibial condylar fractures. A twenty-year follow-up. *J Bone Joint Surg Am* 1986; **68**: 13-19 [PMID: 3941115 DOI: 10.2106/00004623-198668010-00003]

3 **Schatzker J**, McBroom R, Bruce D. The tibial plateau fracture. The Toronto experience 1968--1975. *Clin Orthop Relat Res* 1979; **(138)**: 94-104 [PMID: 445923]

4 **Papagelopoulos PJ**, Partsinevelos AA, Themistocleous GS, Mavrogenis AF, Korres DS, Soucacos PN. Complications after tibia plateau fracture surgery. *Injury* 2006; **37**: 475-484 [PMID: 16118010 DOI: 10.1016/j.inury.2005.06.035]

5 **Young MJ**, Barrack RL. Complications of internal fixation of tibial plateau fractures. *Orthop Rev* 1994; **23**: 149-154 [PMID: 8196973]

6 **Morris BJ**, Unger RZ, Archer KR, Mathis SL, Perdue AM, Obremskey WT. Risk factors of infection after ORIF of bicondylar tibial plateau fractures. *J Orthop Trauma* 2013; **27**: e196-e200 [PMID: 23287757 DOI: 10.1097/BOT.0b013e318284704e]

7 **Ali AM**, El-Shafie M, Willett KM. Failure of fixation of tibial plateau fractures. *J Orthop Trauma* 2002; **16**: 323-329 [PMID: 11972075 DOI: 10.1097/00005131-200205000-00006]

8 **Honkonen SE**. Degenerative arthritis after tibial plateau fractures. *J Orthop Trauma* 1995; **9**: 273-277 [PMID: 7562147 DOI: 10.1097/00005131-199509040-00001]

9 **Volpin G**, Dowd GS, Stein H, Bentley G. Degenerative arthritis after intra-articular fractures of the knee. Long-term results. *J Bone Joint Surg Br* 1990; **72**: 634-638 [PMID: 2380219]

10 **Weigel DP**, Marsh JL. High-energy fractures of the tibial plateau. Knee function after longer follow-up. *J Bone Joint Surg Am* 2002; **84-A**: 1541-1551 [PMID: 12208910 DOI: 10.2106/00004623-200209000-00006]

11 **Wasserstein D**, Henry P, Paterson JM, Kreder HJ, Jenkinson R. Risk of total knee arthroplasty after operatively treated tibial plateau fracture: a matched-population-based cohort study. *J Bone Joint Surg Am* 2014; **96**: 144-150 [PMID: 24430414 DOI: 10.2106/JBJS.L.01691]

12 **Bedi A**, Haidukewych GJ. Management of the posttraumatic arthritic knee. *J Am Acad Orthop Surg* 2009; **17**: 88-101 [PMID: 19202122 DOI: 10.5435/00124635-200902000-00005]

13 **Vermeire J**, Scheerlinck T. Early primary total knee replacement for complex proximal tibia fractures in elderly and osteoarthritic patients. *Acta Orthop Belg* 2010; **76**: 785-793 [PMID: 21302577]

14 **Scott CE**, Davidson E, MacDonald DJ, White TO, Keating JF. Total knee arthroplasty following tibial plateau fracture: a matched cohort study. *Bone Joint J* 2015; **97-B**: 532-538 [PMID: 25820894 DOI: 10.1302/0301-620X.97B4.34789]

15 **Lizaur-Utrilla A**, Collados-Maestre I, Miralles-Muñoz FA, Lopez-Prats FA. Total Knee Arthroplasty for Osteoarthritis Secondary to Fracture of the Tibial Plateau. A Prospective Matched Cohort Study. *J Arthroplasty* 2015; **30**: 1328-1332 [PMID: 25795233 DOI: 10.1016/j.arth.2015.02.032]

16 **Weiss NG**, Parvizi J, Trousdale RT, Bryce RD, Lewallen DG. Total knee arthroplasty in patients with a prior fracture of the tibial plateau. *J Bone Joint Surg Am* 2003; **85-A**: 218-221 [PMID: 12571297]
17 **Saleh KJ**, Sherman P, Katkin P, Windsor R, Haas S, Laskin R, Sculco T. Total knee arthroplasty after open reduction and internal fixation of fractures of the tibial plateau: a minimum five-year follow-up study. *J Bone Joint Surg Am* 2001; **83-A**: 1144-1148 [PMID: 11507121 DOI: 10.2106/00004623-200108000-00002]
18 **Civinini R**, Carulli C, Matassi F, Villano M, Innocenti M. Total knee arthroplasty after complex tibial plateau fractures. *Chir Organi Mov* 2009; **93**: 143-147 [PMID: 19711154 DOI: 10.1007/s12306-009-0033-3]
19 **Wolff AM**, Hungerford DS, Krackow KA, Jacobs MA. Osteotomy of the tibial tubercle during total knee replacement. A report of twenty-six cases. *J Bone Joint Surg Am* 1989; **71**: 848-852 [PMID: 2745481 DOI: 10.2106/00004623-198971060-00008]
20 **Garvin KL**, Scuderi G, Insall JN. Evolution of the quadriceps snip. *Clin Orthop Relat Res* 1995; **(321)**: 131-137 [PMID: 7497658 DOI: 10.1097/00003086-199512000-00020]
21 **Kini SG**, Sathappan SS. Role of navigated total knee arthroplasty for acute tibial fractures in the elderly. *Arch Orthop Trauma Surg* 2013; **133**: 1149-1154 [PMID: 23771128 DOI: 10.1007/s00402-013-1792-8]
22 **Parratte S**, Bonnevialle P, Pietu G, Saragaglia D, Cherrier B, Lafosse JM. Primary total knee arthroplasty in the management of epiphyseal fracture around the knee. *Orthop Traumatol Surg Res* 2011; **97**: S87-S94 [PMID: 21802385 DOI: 10.1016/j.otsr.2011.06.008]
23 **Boureau F**, Benad K, Putman S, Dereudre G, Kern G, Chantelot C. Does primary total knee arthroplasty for acute knee joint fracture maintain autonomy in the elderly? A retrospective study of 21 cases. *Orthop Traumatol Surg Res* 2015; **101**: 947-951 [PMID: 26589193 DOI: 10.1016/j.otsr.2015.09.021]
24 **Abdel MP**, von Roth P, Cross WW, Berry DJ, Trousdale RT, Lewallen DG. Total Knee Arthroplasty in Patients With a Prior Tibial Plateau Fracture: A Long-Term Report at 15 Years. *J Arthroplasty* 2015; **30**: 2170-2172 [PMID: 26195353 DOI: 10.1016/j.arth.2015.06.032]
25 **Nourissat G**, Hoffman E, Hémon C, Rillardon L, Guigui P, Sautet A. [Total knee arthroplasty for recent severe fracture of the proximal tibial epiphysis in the elderly subject]. *Rev Chir Orthop Reparatrice Appar Mot* 2006; **92**: 242-247 [PMID: 16910606]
26 **Malviya A**, Reed MR, Partington PF. Acute primary total knee arthroplasty for peri-articular knee fractures in patients over 65 years of age. *Injury* 2011; **42**: 1368-1371 [PMID: 21763651 DOI: 10.1016/j.injury.2011.06.198]
27 **Haufe T**, Förch S, Müller P, Plath J, Mayr E. The Role of a Primary Arthroplasty in the Treatment of Proximal Tibia Fractures in Orthogeriatric Patients. *Biomed Res Int* 2016; **2016**: 6047876 [PMID: 26885510 DOI: 10.1155/2016/6047876]
28 **Shearer DW**, Chow V, Bozic KJ, Liu J, Ries MD. The predictors of outcome in total knee arthroplasty for post-traumatic arthritis. *Knee* 2013; **20**: 432-436 [PMID: 23313556 DOI: 10.1016/j.knee.2012.12.010]

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MINIREVIEWS

Failed medial patellofemoral ligament reconstruction: Causes and surgical strategies

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Abstract

Patellar instability is a common clinical problem encountered by orthopedic surgeons specializing in the knee. For patients with chronic lateral patellar instability, the standard surgical approach is to stabilize the patella through a medial patellofemoral ligament (MPFL) reconstruction. Foreseeably, an increasing number of revision surgeries of the reconstructed MPFL will be seen in upcoming years. In this paper, the causes of failed MPFL reconstruction are analyzed: (1) incorrect surgical indication or inappropriate surgical technique/patient selection; (2) a technical error; and (3) an incorrect assessment of the concomitant risk factors for instability. An understanding of the anatomy and biomechanics of the MPFL and cautiousness with the imaging techniques while favoring clinical over radiological findings and the use of common sense to determine the adequate surgical technique for each particular case, are critical to minimizing MPFL surgery failure. Additionally, our approach to dealing with failure after primary MPFL reconstruction is also presented.

Key words: Medial patellofemoral ligament; Failed medial patellofemoral ligament reconstruction; Trochleoplasty; 3D-CT in patellofemoral surgery

Core tip: An increasing number of revision surgeries of the reconstructed medial patellofemoral ligament (MPFL) will be seen in the foreseeable future. There are several reasons for this trend: (1) The increasing number of primary MPFL reconstructions; (2) The fact that more and more orthopedic surgeons perform this surgical technique; and (3) The high percentage of patients returning to sport after this type of surgery and thereby put the reconstructed ligament at risk. Our paper tries to answer a crucial question: What must we do to reduce the number of failed MPFL reconstructions? Furthermore, we analyze our approach to dealing with failure after MPFL reconstruction.

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INTRODUCTION

What is a failure of a medial patellofemoral ligament (MPFL) reconstruction? A MPFL reconstruction in patients with chronic lateral patellar instability (CLPI) fails when there is either recurrence of the instability, disabling anterior knee pain (AKP) or a combination of both. While this usually demands a revision surgery, there are some more questionable cases. It ultimately depends on the activity level and how much this instability or AKP affects a patient with the same ligament deficiency. The higher the physical requirements are the greater the disability caused by the malfunctioning MPFL. Patients with low physical requirements will tolerate instability much better and will have less instability and/or pain. In addition, standard scales (Kujala, IKDC) used to measure results in "normal" people are not practical for athletes due to their low sensitivity. Instead, functional tests that includes specific sporting gestures (cutting, pivoting, stopping, *etc*.)[1] should be used in this specific group of patients.

Shah *et al*[2], in a systematic review (meta-analysis-level of evidence Ⅱ) of complications and failures associated with the MPFL reconstruction in patients with a CLPI, found that the complication rate associated with this procedure (26%) is not at all insignificant even though MPFL has a high success rate. Therefore, it is important to inform the patient of the potential risks of this surgery before the surgery. These authors also showed that instability represents 32% of all the complications (52/164) found in MPFL reconstruction[2]. This recurrence of instability may be secondary to a ruptured or elongated MPFL graft, or secondary to the failure to recognize other risk factors for instability. However, Parikh *et al*[3] found a slightly smaller rate of complications (16%) in a case series (level of evidence Ⅳ). Surprisingly enough, almost half of those complications resulted from technical problems or surgical errors. Ultimately, most failed MPFL reconstructions result from surgeon-dependent factors. Schneider *et al*[4] reported a low rate of reoperations after an isolated MPFL reconstruction, specifically 3.1% (95%CI: 1.1%-5.0%), in a systematic review and meta-analysis published in 2016. However, this study only reported on short term results. Similarly, the recurrence of instability and the persistence of apprehension was 1.2% (95%CI: 0.3%-2.1%) and 3.6%, respectively (95%CI: 0%-7.2%).

The increasing number of primary surgeries will lead to a higher number of MPFL revision surgeries in upcoming years. Schneider *et al*[4] showed that 84.1% (95%CI: 71.1%-97.1%) of patients return to sports after an isolated MPFL reconstruction. Thus, the return to sports puts the reconstructed ligament at risk and so its break again due to an indirect trauma to the knee.

This paper tries to answer a crucial question: What must we do to reduce the number of failed MPFL reconstruction? An approach to dealing with failure after primary MPFL reconstruction is also presented.

MPFL RECONSTRUCTION FAILURE DUE TO AN INCORRECT SURGICAL INDICATION - INAPPROPRIATE SURGICAL TECHNIQUE/PATIENT SELECTION

The first requirement for a successful MPFL reconstruction is, logically, to properly select the patient. The ideal indication of an isolated MPFL reconstruction would be a CLPI with at least two documented episodes of dislocation, and confirmation of dislocation with examination under anesthesia, in a patient with a TT-TG distance of less than 20 mm, a positive apprehension test up to 30° of knee flexion, a patellar Caton-Deschamps index of less than 1.2 and trochlear dysplasia grade A[5]. A double-bundle MPFL reconstruction is recommended given that it is associated with a lower failure rate than single bundle reconstruction[6].

On the other hand, an MPFL reconstruction is not indicated in patients with AKP without patellar instability. Neither is it indicated for excessive lateral patellar tilt and/or lateral patellar subluxation on imaging without a history and a physical examination for CLPI. Lateral patellofemoral instability, with at least 2 documented episodes of patellar dislocations and a physical examination demonstrating patellar dislocation, is the primary indication for an MPFL reconstruction[5]. Pain and "giving out" episodes are not sufficient criteria for establishing this diagnosis. Examination under anesthesia may be necessary to confirm lateral patellar instability objectively (Figure 1). A MPFL reconstruction should not be performed if the patella cannot be laterally dislocated.

An MPFL reconstruction is not aimed at "pulling"

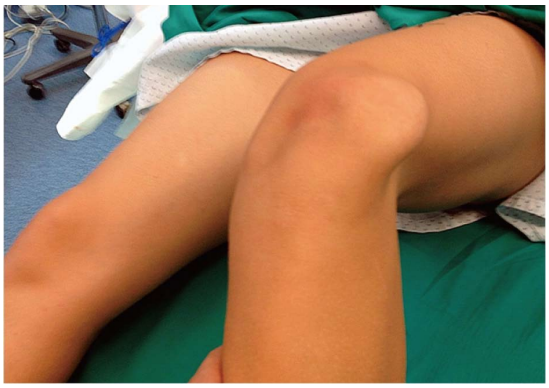

Figure 1 With the patient under anesthesia, we verify that the patella can be dislocated laterally.

the patella into position, but rather at stabilizing it once the patellofemoral tracking has been corrected. That is so once the patella is in an adequate position within the trochlear groove. Therefore, an isolated MPFL reconstruction is not indicated to eliminate patella J-tracking.

Finally, an isolated MPFL reconstruction should not be performed with fixed lateral patellar dislocation in knee flexion (Figure 2). In this situation, the main problem is the retraction of the extensor mechanism of the knee and a flat lateral condyle, factors that contribute to secondary MPFL insufficiency[7]. Therefore, the correct treatment for these cases would be a lateral retinaculum lengthening, lengthening of the rectus lateralis tendon and quadriceps tendon lengthening[7]. If needed, the lateral condyle may be raised. Then, an MPFL reconstruction may be performed as the final surgical step[7].

MPFL RECONSTRUCTION FAILURE DUE TO A TECHNICAL ERROR

According to Parikh *et al*[3], 47% of the complications that occur after MPFL reconstructive surgery are related to technical errors.

The most frequent and significant technical mistake that can lead to MPFL reconstruction failure is to position the femoral tunnel incorrectly although we can see both an incorrect femoral fixation point associated with an incorrect patellar fixation point in some cases (Figure 3). Femoral fixation point is crucial as it determines the length change behavior of the graft and therefore the graft tension at different angles of knee flexion, that is, it determines the kinematic behavior of the graft[8]. A normal MPFL is tighter in extension than in flexion. If the graft tightens when the knee is flexed, stiffness, pain and patellar overload will occur[8]. This situation typically occurs when the femoral fixation point is placed excessively anterior. In the mid-term, it may produce a severe patellar chondropathy (Figure 4) and patellofemoral osteoarthritis in the long-term (Figure 5). Therefore, it is essential to accurately check the femoral tunnel placement intra-operatively.

An incorrect femoral fixation point can lead to excessive obliquity of the graft, making it ineffective in preventing an excessive lateral patellar displacement in the first 40 degrees of knee flexion. This would explain a persistent lateral dislocation of the patella with a healthy graft. In this case, correction of the instability can be accomplished simply by modifying the fixation points despite the presence of additional anatomical factors predisposing to lateral instability such as severe trochlear dysplasia (Figure 6).

Schöttle *et al*[9] have recommended the used of intraoperatory fluoroscopy to more accurately placed the femoral tunnel. Obtaining a true lateral image intraoperatively is imperative when using this radiographic method. Unfortunately, this is not always easily accomplished. In addition, several authors have observed that Schoettle's radiological method, universally accepted as the gold standard, does not guarantee a true anatomical fixation point in many cases[10] even with the use of a true lateral radiograph[11]. The radiological method is only an approximation and should not be the sole basis for femoral attachment location. The most accurate method for pinpointing anatomic placements is to perform a large enough incision to identify the most relevant anatomic landmarks. In this case, it is the adductor magnus tendon (AMT). The AMT is readily identified and leads right to the MPFL origin on the femur, situated 10.6 ± 2.5 mm distal to the apex of the adductor tubercle and parallel to the long axis of the femur[12]. The great variability in the location of the adductor tubercle (Figure 7) explains the variability in the location of the femoral insertion of the MPFL. This explains the large number of errors when using Schoettle's method to identify the femoral anatomic fixation point of the MPFL.

Relative to the MPFL patellar insertion site, Kikuchi *et al*[13] have recently shown that it is largely consistent. Most of its fibers insert more into the vastus medialis obliquus (VMO) and vastus intermedius than into the patella. Unlike the femoral fixation point, accuracy in placing the patellar fixation has been shown to be less important[8]. In fact, the MPFL length changes depend on the femoral attachment site more than on the patellar attachment site[8].

Another technical error that can lead to surgical failure is excessive graft tension. The concept of "tensioning" the MPFL graft is not correct from a conceptual point of view given that in its native state the MPFL is not under constant tension[5]. It only comes under tension when a lateral force acts on the patella displacing it laterally. Philip Schoettle makes a very intelligent simile, comparing the MPFL to a dog leash. The leash is loose most of the time, except when the dog (the patella) wants to run away (dislocate), and then it becomes tight. If the leash (the MPFL) were tight all the time, it would choke the dog. Continuing with our simile, it would create a high patellofemoral pressure that would lead to osteoarthritis. *In vivo*, MPFL kinematic studies have shown that MPFL length was longest from 0° to 60° of knee flexion and decreased significantly during flexion from 60° to 120°,

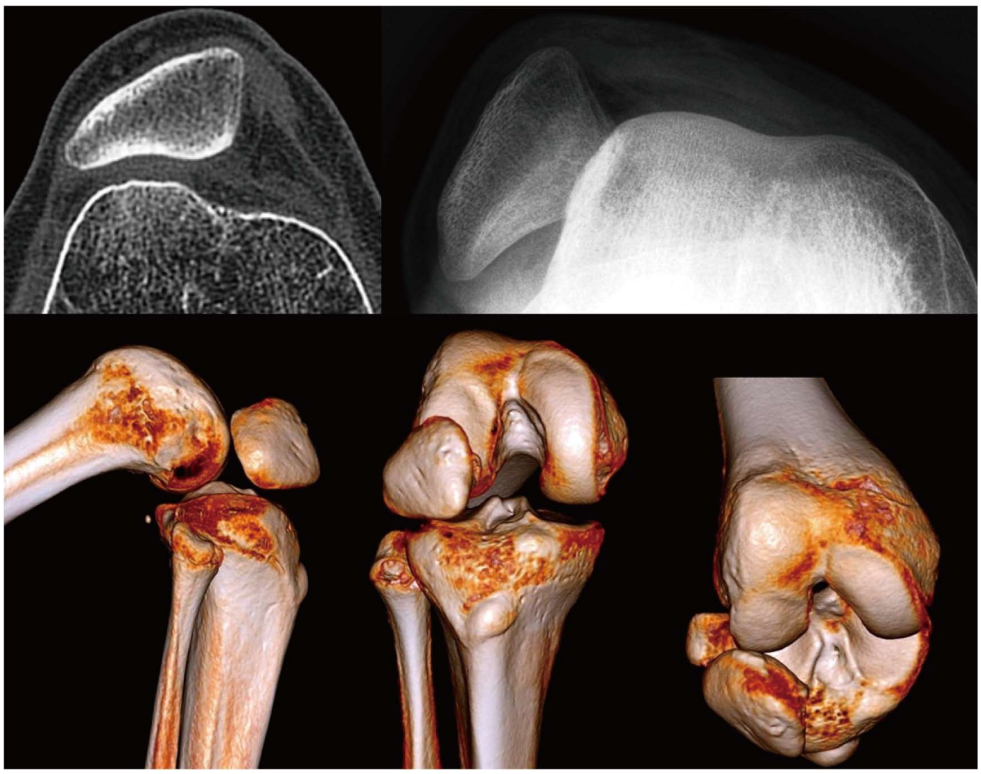

Figure 2 Lateral patellar instability in flexion. The patella dislocates laterally beyond 40º of knee flexion.

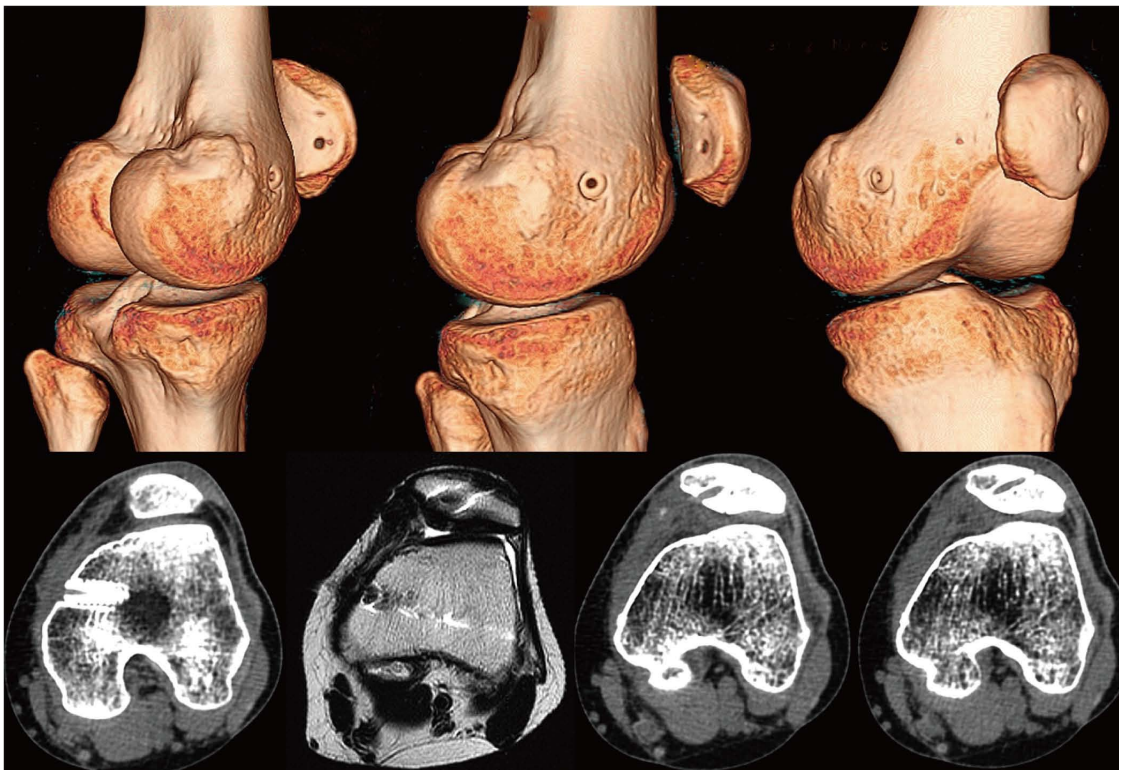

Figure 3 The femoral tunnel is non-anatomic. A very serious mistake when performing patellar tunnels. We can see that the patellar tunnels are drilled through the medial facet articular surface and exit through the central dorsal aspect of the patella.

thereby checking excessive patellofemoral compression force during high degrees of knee flexion[8]. Additionally, the MPFL is not tight when the patella is not subject to a lateral displacing force[5].

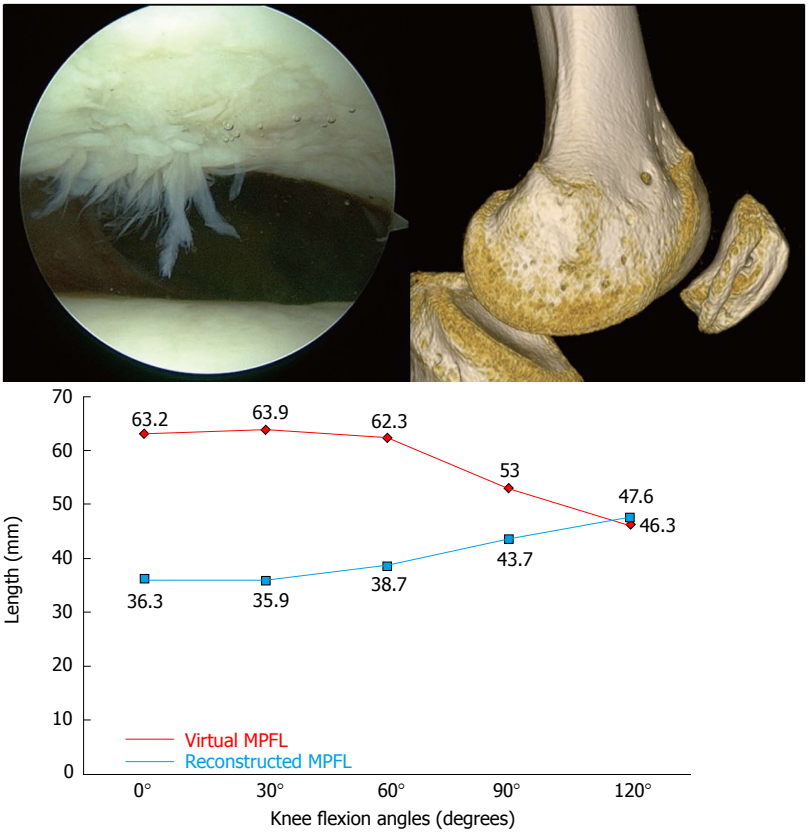

Figure 4 Patient of 19 years of age with severe anterior knee pain and lateral patellar instability. Three years ago, he had a MPFL reconstruction with a single bundle semitendinosus tendon graft. During the physical examination, there was no disorder in patellofemoral tracking. With the patient under general anesthesia, the patella could not be dislocated beyond 40° of knee flexion. We note that the femoral tunnel of the MPFL reconstruction is too anterior, which is a serious mistake. There is also severe chondropathy of the articular surface of the patella. We can see that the distance between the patellar fixation point and the femoral fixation point increases with knee flexion. Clinically, this causes an increase in patellofemoral pressure during knee flexion that could justify the severe patellar chondropathy the patient has. The anatomic MPFL reconstruction, using the contralateral semitendinosus tendon with a double bundle technique, led to the resolution of all the patient's symptoms. MPFL: Medial patellofemoral ligament.

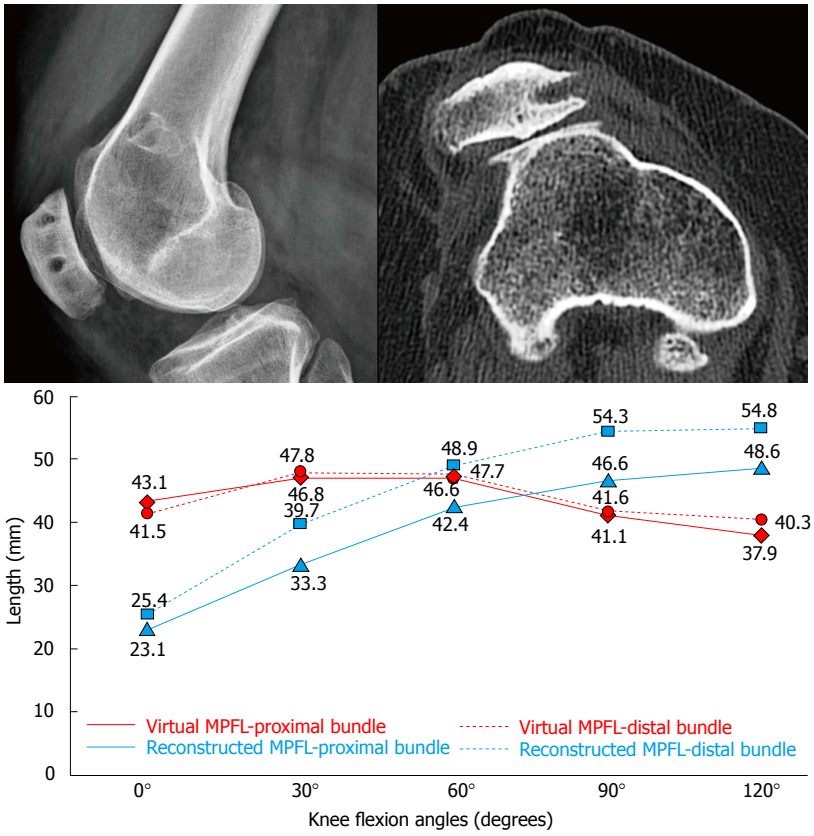

Figure 5 Patient 28-year-old, with very severe anterior knee pain and lateral patellar instability. During the physical examination, we saw a clear patellofemoral mal-tracking and we were able to dislocate the patella laterally beyond 60° of knee flexion. She has been operated on several times over the last 8 years: A lateral retinacular release, proximal realignment, an ostetotomy for medialization of the tibial tubercle and MPFL reconstruction. We note that the femoral tunnel is too proximal and anterior. The distance between the patellar fixation point and the femoral fixation point increases significantly with knee flexion. Clinically, this increases patellofemoral pressure significantly during knee flexion, which could explain the severe patellofemoral osteoarthritis the patient has. In this specific case the pain disappeared after a sulcus deepening trochleoplasty. We performed an anatomic double bundle MPFL reconstruction with a semitendinosus tendon graft and the lateral patellar instability also disappeared completely. MPFL: Medial patellofemoral ligament.

How to avoid excessive tension on the graft?

Use the trochlea to reduce the patella when the graft is fixed by having the patella fully engaged in the trochlea at this point - 30° of knee flexion is generally sufficient to accomplish it[8]. Do not pull the graft tight at the time of fixation. If the other knee is asymptomatic, the aim is to reproduce the degree of patellar mobility of the contralateral healthy knee. We must note that tighter is

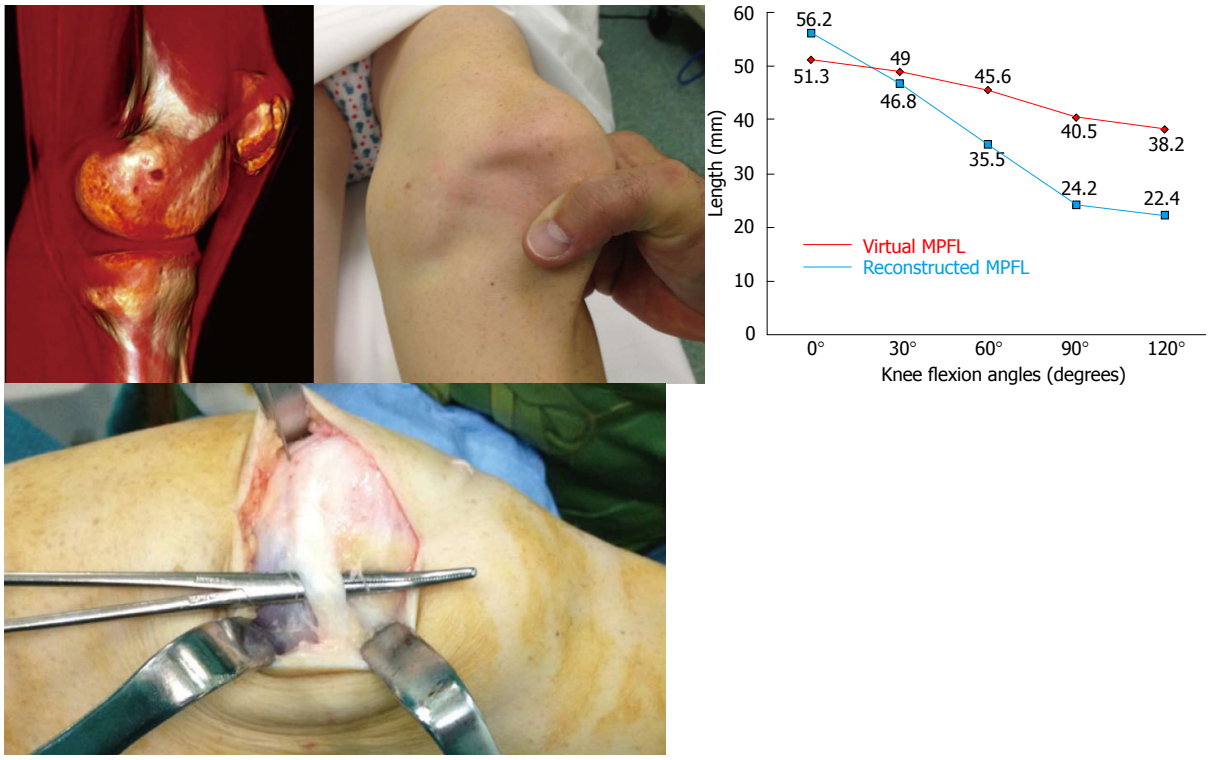

Figure 6 Very severe left anterior knee pain in a female patient of 30 years of age who had a medial patellofemoral ligament reconstruction using partial thickness quadriceps tendon. Clinically, no patellofemoral tracking disorders were found. With the patient under general anesthesia, the patella could be dislocated laterally despite an intact MPFL. In this specific case, the instability is due to an inadequate graft length change pattern during knee flexion and extension. After an anatomic double bundle MPFL reconstruction, using a semitendinosus tendon graft, the lateral patellar instability as well as the pain were completely resolved. MPFL: Medial patellofemoral ligament.

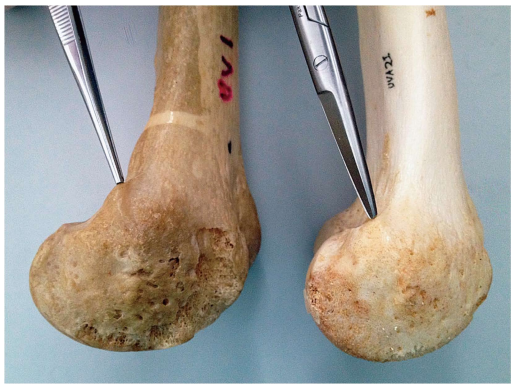

Figure 7 The anatomic variability of the adductor tubercle may explain the anatomic variability of the medial patellofemoral ligament femoral fixation point.

never better in this operation.

Case example

In Figure 8, you can see a failed MPFL reconstruction due to poor positioning of the femoral fixation point. The value of this particular clinical case is threefold. First, there are no confusion variables that can influence the result as the most important factors predisposing to instability were normal (no patellar tilt, no patella alta, normal TT-TG distance, and no trochlear dysplasia). Secondly, the contralateral knee was operated on with an excellent result, and therefore we were able to compare the femoral fixation point of the failed operated knee with the successfully treated contralateral knee. In the third place, the patient was a professional athlete with high demand on her knees and therefore the surgical precision had even a greater role. While minor surgical malpositioning of the femoral tunnel might be well tolerated in non-athlete patients, it is not the case in an athlete. The only differentiating factor between both knees was the position of the femoral fixation point, with maximum physical demand of both knees.

Figure 8 shows the case of a 20-year-old female, a professional classical and contemporary ballet dancer, operated on for lateral patellar instability in both knees, secondary to an obvious trauma during sport practice. She had had two clear dislocation episodes in each knee, one of which required a reduction in the emergency department. A double bundle semitendinosus reconstruction was performed in her left knee with an excellent result at 10 years after surgery. A single bundle partial thickness quadriceps tendon reconstruction was performed in the right knee. One year and a half after surgery, she complained of severe disability while practicing sports with pain and instability. She had AKP that caused her to develop defense mechanisms during physical activities to mitigate the pain. They included avoiding full knee extension while doing splits, avoiding performing full squats and squatting with the upper

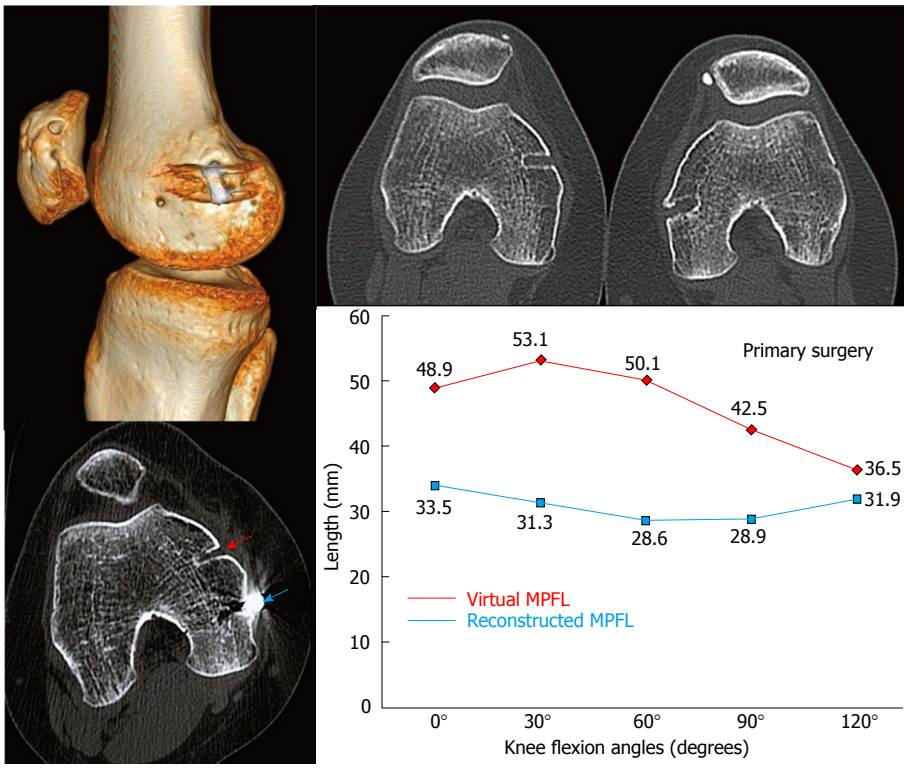

Figure 8 This patient had a bilateral medial patellofemoral ligament reconstruction for lateral patellar instability with no anatomical predisposing factors. The left knee has an anatomic femoral tunnel with an excellent clinical result. However, the right knee has a femoral tunnel that is too anterior and this fact is responsible for the non-physiological behavior of the graft. It is isometric from 0° to 120° of knee flexion. After anatomic MPFL reconstruction, the symptoms disappeared completely (Reproduced with permission from Springer). MPFL: Medial patellofemoral ligament.

body flexed forward in order to reduce patellofemoral compression force and therefore the pain. She also showed a very severe patellofemoral crepitus and pain with knee flexion. She also had instability and apprehension. To perform "spiral twists" in her classical ballet activity, she avoided knee flexion from 0 to 30 degrees because of the fear that the patella "would slip laterally". So, she also developed a defense mechanism against instability. She was then operated on again on the right knee. A semitendinosus double bundle graft was performed with an anatomic femoral fixation point. Four years after surgery, the clinical outcome was excellent. She was pain- and instability-free and was involved in high-level competitive sports with no limitations. Additionally, the previous severe painful crepitus completely disappeared.

How should we plan a revision surgery?

When we consider a revision surgery in a patient with a failed MPFL reconstruction, a dynamic 3D - Computed Tomography (CT) study at 0°, 30°, 60°, 90° and 120° of knee flexion to evaluate the kinematic behavior of the graft *in vivo*[5,8] should be performed. In the left knee of the patient in Figure 8, the length change behavior of the graft, although non-anatomic, was similar to that of a graft fixed anatomically in the femur, which is isometric from 0° to 30° of knee flexion. However, the first surgery performed on the right knee with a non-anatomic technique showed an isometric behavior between 0° to 120° of knee flexion, clearly different to the native anatomic MPFL. Therefore, a non-anatomic femoral fixation point is not necessarily associated with a failed reconstruction. In other words, if a patient with a reconstruction with a non-anatomic femoral fixation point which behaves physiologically has pain and instability, we must rule out other causes than the MPFL femoral fixation point as responsible for the pain and/or instability[8].

After performing an anatomic femoral fixation point during the revision surgery in the right knee the result was excellent, with the resolution of pain, crepitus, and instability. Therefore, we can conclude that the technical error in placing the femoral tunnel too anteriorly was the cause of the failed surgery in the right knee. On the other side, the left knee operated on with a non-anatomic femoral fixation point showed excellent outcome at ten years of follow-up. This gives rise the following question: Is the anatomic femoral tunnel position so relevant in MPFL reconstruction?

Femoral tunnel malposition does not always lead to a poor outcome[8,14]. In our experience, those ligaments with a non-anatomic femoral fixation point that behave kinematically as an anatomic MPFL, as occurs in the left knee of our "case example", are those with an excellent clinical outcome at long-term follow-up[8,14,15]. However those non-anatomic grafts that do not have a physiologic kinematic behavior, as in the right knee, are those that have a poor clinical outcome[8]. Therefore, what should we do? We believe every MPFL graft should be placed anatomically, because an anatomic femoral tunnel position maximizes outcomes and provides the best chance of excellent short-term and long-term success. In summary, an anatomic MPFL reconstruction of the MPFL is a fast and reproducible way to achieve an MPFL that is long enough to act as an isometric "leash" from 0° to 30° and becoming loose after 30° of knee flexion. In

conclusion, to avoid complications, the relevant anatomy and biomechanics must be identified and restored.

FAILED MPFL RECONSTRUCTION DUE TO AN INCORRECT ASSESSMENT OF THE CONCOMITANT RISK FACTORS FOR INSTABILITY

Instability occurs between 0° and 30° range of knee flexion in about 85% of the cases of CLPI. In these degrees of range of motion, patellar stability against the lateral displacing forces of the patella relies mainly on the MPFL[5]. Beyond 30° of knee flexion, the stability of the patella mainly depends on the bony anatomy of the femoral trochlea. While an isolated MPFL reconstruction it is sufficient in most cases in the former group of patients, this might fail to control the instability in the second group. Surgical failure in MPFL reconstructions are due to incorrect diagnosis where non-treatment of additional lateral patellar instability risk factors such as trochlear dysplasia are not addressed. Apprehension that is relieved at 30° of knee flexion suggests a good clinical result with an isolated MPFL reconstruction. An apprehension beyond 60° of knee flexion suggests a severe trochlear dysplasia, or a significant patella alta or both.

The surgical treatment of a patient with lateral patellar instability should be an individualized treatment as the Lyon School advocates. Awareness of the major risk factors for the development of CLPI (trochlear dysplasia, patella alta, TT-TG distance greater than 20 mm and patellar tilt greater than 20°) is required[16]. Among all these factors, the most relevant is trochlear dysplasia. Interestingly, Nelitz *et al*[17] observed that severe trochlear dysplasia (Dejour type B-D) was significantly more frequent in the surgical failure group (89%) than in the non-surgical failure group (21%) in an analysis of failed surgery for patellar instability. However, they did not find differences relative to the patellar height ratio (Insall-Salvati index) and the TT-TG distance between the two groups. Considering that trochlear dysplasia seems to be a major risk factor for failure of operative stabilization of CLPI, reconstruction of the MPFL as well as trochleoplasty should be considered in such cases. Wagner *et al*[18] also found that high degrees of trochlear dysplasia correlate with poor clinical outcome because the MPFL graft might be overloaded given that there is more instability in dysplastic situations. They conclude that trochleoplasty must be considered in cases with high degrees of trochlear dysplasia. However, this conclusion was only based on one case series study (level of evidence Ⅳ). Similarly, Kita *et al*[19] reported that severe trochlear dysplasia is the most important predictor of residual patellofemoral instability after isolated MPFL reconstruction. They have shown that a combination of severe trochlear dysplasia with an increased TT-TG distance was more likely to affect the outcomes of MPFL reconstruction[19]. They also suggested that additional stabilization procedures should be performed in the surgical treatment of such patients. Matsushita *et al*[20] demonstrated that isolated MPFL reconstructions performed in CLPI with a TT-TG distance greater than 20 yielded similar clinical outcomes to those performed with a TT-TG under 20. Moreover, there were no re-dislocations in either group. They concluded that a TT-TG distance greater than 20 mm may not be an absolute indication for medialization of the tibial tubercle.

Surgical pearl

The trochleoplasty procedure not only corrects the trochlear dysplasia, but also the increased TT-TG distance.

Dejour *et al*[21] have shown that the sulcus-deepening trochleoplasty is an acceptable revision option for the surgical treatment of patients with persisting patellar dislocation and high-grade trochlear dysplasia. According to Fucentese *et al*[22] trochleoplasty is a useful and reliable surgical technique to improve patellofemoral instability in patients with a dysplastic trochlea. However, while improved stability is predictable, pain is less predictable and may even increase following surgery. Interestingly, Schöttle *et al*[23] have shown that the risk for cartilage damage after trochleoplasty is low. Be that as it may, overall results are directly dependent on the type of the dysplasia, with a significantly better clinical outcome in type B and D[22]. In conclusion, severe trochlear dysplasia can be successfully treated with a trochleoplasty.

Case example

In Figure 9, a 25-year-old male patient complained of persistent instability after 2 surgical procedures for CLPI of his left knee. After the first procedure performed 2 years earlier with a single-bundle semitendinosus MPFL reconstruction, he had countless episodes of lateral patellar dislocation. In one of them, he had a patellar osteochondral fracture that was not diagnosed initially, and that brought on locking episodes. A second surgeon had recommended an arthroscopy to remove the intraarticular loose body and to perform an Insall proximal realignment surgery (overlapping of the VMO and a lateral retinaculum release). The patient did not accept this later technique. An isolated arthroscopic loose body removal and a lateral retinaculum release (LRR) were finally performed. Logically, while the locking symptoms were resolved, the instability got even worse. During physical examination, the patella could be dislocated laterally within the whole range of motion of the knee. Imaging studies showed a grade D trochlear dysplasia, a patella alta (Caton-Deschamps of 1.24), a TT-TG distance of 26 mm, and a patellar tilt of 38°. Thus, all the four major risk factors were concomitantly present.

The 3D-CT study revealed a non-anatomical femoral fixation point. However, the *in vivo* kinematic study of the MPFL using 3D-CT showed a graft similar in length to a native virtual ligament and an isometry from 0° to 30° similar to the native healthy ligament. We must note again that a non-anatomic MPFL reconstruction

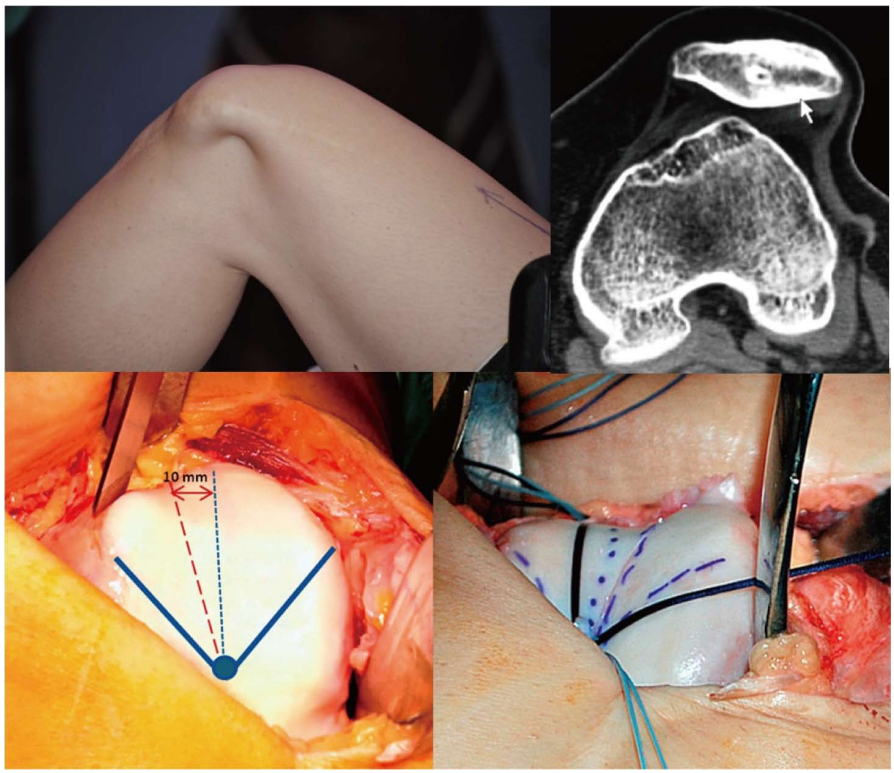

Figure 9 Chronic lateral patellar instability in a patient with grade D trochlear dysplasia. We note that the patella dislocates beyond 40° of knee flexion. Lateral patellar instability resolved after a MPFL reconstruction associated with a sulcus deepening trochleoplasty. MPFL: Medial patellofemoral ligament.

may be able to achieve an adequate change of length pattern of the graft and an optimal isometry from 0° to 30° that leads to excellent long-term clinical result[8]. Hence, the persistent pain and instability could not be attributed to this non-anatomic femoral fixation point. Thus, causes of graft failure other than the choice of the femoral fixation point should be highlighted. Type D trochlear dysplasia justified the instability at high degrees of knee flexion and might also explain the failure of the MPFL reconstruction.

Since a LRR was performed in the second surgery, medial patellar stability was also tested during the dynamic CT study. This study showed no pathological findings. Extensive LRR might lead to iatrogenic medial patellar instability or a patellar multidirectional instability that would require a reconstruction of the lateral patellar retinaculum[24-26].

Surgical pearl

Reconstruction of the deep bundle of the lateral patellar retinaculum in cases where the LRR performed in a previous surgery was too extensive should be considered.

A double bundle semitendinosus MPFL anatomic reconstruction associated with a sulcus deepening trochleoplasty was finally performed. After 4 years of follow up, the outcome was excellent.

Trochleoplasty should be only performed when the patella dislocates at high degrees of knee flexion, mostly in revision surgeries.

In this type of trochleoplasty, TT-TG distance and patellar tilt are secondarily corrected to normal physiological values. No tibial tubercle medialization or lengthening of the lateral retinaculum is needed. The remaining major instability factor, patella alta, is not addressed. However, the threshold from where the patella must be lowered remains unclear[7]. Moreover, we must note that isolated MPFL reconstruction can decrease patellar height[27]. Therefore, an isolated MPFL reconstruction may normalize patellar height in patients with CLPI and a borderline patella alta. Furthermore, we must be cautions when performing a distalization of the tibial tubercle because it always implies a certain degree of medialization (a decrease in the TT-TG distance)[28].

As to the timing of the surgical techniques, patellofemoral mal-tracking correction is needed initially. The trochleoplasty procedure fulfills the goal of neutralizing the lateral displacing forces.

Selective epidural analgesia in selected cases can help to evaluate the active patellar excursion after realignment surgery.

Once the patellofemoral joint is realigned, the second step is to stabilize the joint, which means restoring the passive restraining structures. In this second step, we perform an MPFL reconstruction.

In some infrequent cases and once the MPFL has been reconstructed, patellar tilt may still show an abnormal condition. In this scenario, a third surgical step in the lateral patellar retinaculum may be necessary to achieve a good patellofemoral balance. The decision to operate or not on the lateral patellar retinaculum is an intraoperative decision, based on the patella tilt test[29].

The patella tilt test is crucial to determine the necessity for surgery on the lateral retinaculum. To do this test, a transverse K wire is placed on the proximal patella, from medial to lateral. With the knee in full extension and at 20° of flexion, the K wire should be parallel to the surgery

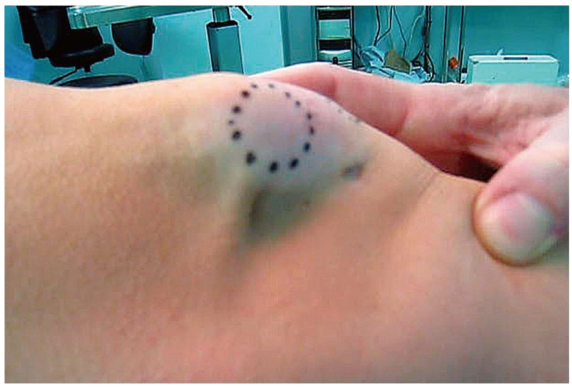

Figure 10 Notice how the medial patellofemoral ligament tightens with the patella's passive medial displacement. In this case, the MPFL can be visualized very well because the patient is slender and has subcutaneous tissue atrophy due to multiple cortisone injections. This finding confirms the fact that the MPFL is not only a stabilizer for patellar lateral displacement but also for medial displacement. MPFL: Medial patellofemoral ligament.

table. If the K wire is tilted (positive test) within this range of motion, a lateral patellar retinaculum lengthening is needed. Lateral retinaculum release is only performed when lengthening is not feasibly.

Also in cases where an extensive LRR had been performed, a reconstruction of this lateral retinaculum would be necessary[26]. This surgery should only be performed after a detailed radiological assessment of medial patellar instability. Always this technique is performed after the MPFL reconstruction, since this sometimes also stabilize the patella medially (Figure 10).

To guide the patella towards the trochlear sulcus during the first degrees of knee flexion, the MPFL and the lateral retinaculum must interact in a harmonious way. Both ligaments behave similarly to a horse's reins. The rider must hold the reins loosely, without too much tension. If not, the bit (equivalent to the patella) would press into the tongue (equivalent to the femoral trochlea), hurting the horse. However, both reins must have some degree of tension. Otherwise, it would not be possible to lead the horse to the right path.

IS RADIOLOGICAL ASSESSMENT HELPFUL IN DECISION MAKING WHEN OTHER INSTABILITY RISK FACTORS ARE PRESENT? WHAT ARE ITS LIMITATIONS?

In this section, the three anatomical factors most closely related to CLPI from an imaging point of view are analyzed.

Trochlear dysplasia

Although lateral conventional radiography allows the evaluation of the typical signs of trochlear dysplasia[16,30], it tends to underestimate the degree of dysplasia in comparison to CT and magnetic resonance imaging (MRI)[31]. It also requires a true lateral view of the knee to avoid misinterpretation[32].

CT and MRI also provide a more accurate assessment of trochlear dysplasia. The qualitative analysis is crucial and determines the severity of the dysplasia using the classification described by D. Dejour. In addition, different quantitative measurements have been proposed to determine the depth and inclination of the trochlea in CT and MRI[33-35]. However, diagnosis of the degree of trochlear dysplasia with CT and MRI is still a challenge. Firstly, a recent study has shown that only low-grade (type A) or high-grade trochlear dysplasia (types B-D) can be reliably distinguished using Dejour's classification, whereas the four-grade classification shows fair intraobserver and interobserver agreements[31]. Secondly, quantitative measurements of the femoral trochlea are not correlated with the Dejour's classification of trochlear dysplasia and there are no reproducible methods for quantifying types B, C and D severe dysplasia[36]. And finally, some studies have revealed differences in the surface geometry of the cartilage and subchondral osseous contours with an exacerbated dysplasia due to the overlying cartilaginous morphology[37-39]. This highlights the importance of evaluating the femoral trochlea with MRI, which provides direct visualization of the cartilage and functional information of articular congruence.

Patellar height

Patellar height has classically been evaluated in standard radiography with the use of different indexes, such as the Caton-Deschamps, the Insall-Salvati, the modified Insall-Salvati and the Blackburne-Peel. However, these methods have many limitations. They have poor agreement and the patellar height classification relies heavily on the chosen ratio[40]. In addition, they refer to the position of the patella relative to the tibia and are based on bone contours and not on cartilaginous landmarks. Patellar height may be normal when measured on one index and abnormal when measured on another index.

Some authors have studied the "functional engagement" between the articular surfaces of the femur and tibia in sagittal MRI, which is more clinically relevant in patellofemoral disorders. Biedert and Albrecht introduced the patellotrochlear index[41]. Dejour described the sagittal patellofemoral engagement index in two distinctive sagittal slices, allowing measurements in patients with patellar dislocation who have different positions of the patella in the axial plane[42]. Some studies have demonstrated the absence of correlation between these functional engagement indexes and the other ratios for patella alta[42-44]. Nowadays, the evaluation of the functional engagement of the patella with MRI is recommended as a supplementary tool to the existing radiographic methods[42,44].

TT-TG distance

The TT-TG distance is the distance between the deepest aspect of the trochlear groove (TG) and the most anterior

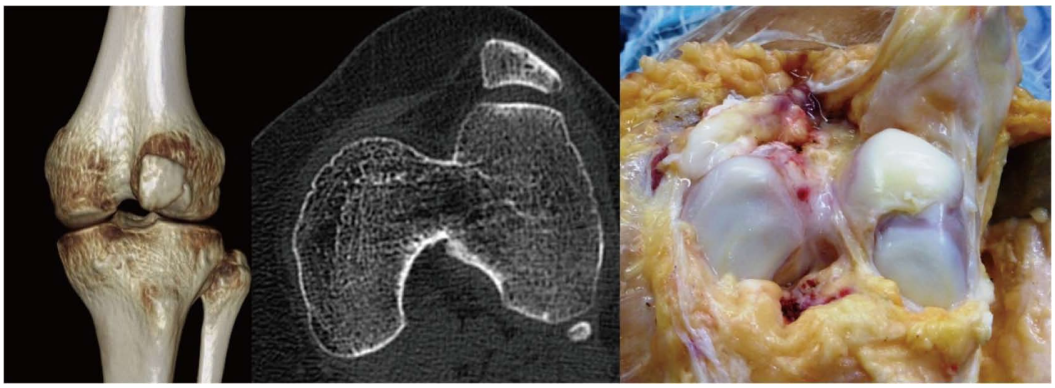

Figure 11 The TT-TG distance is not measurable in this particular case because of the severe and peculiar trochlear dysplasia. On the 3D model, the TT looks quite lateralized in comparison with the TT-TG distance calculated by the radiologist: 15 mm. We suggest a TT-PCL measurement when the TT-TG is not measurable.

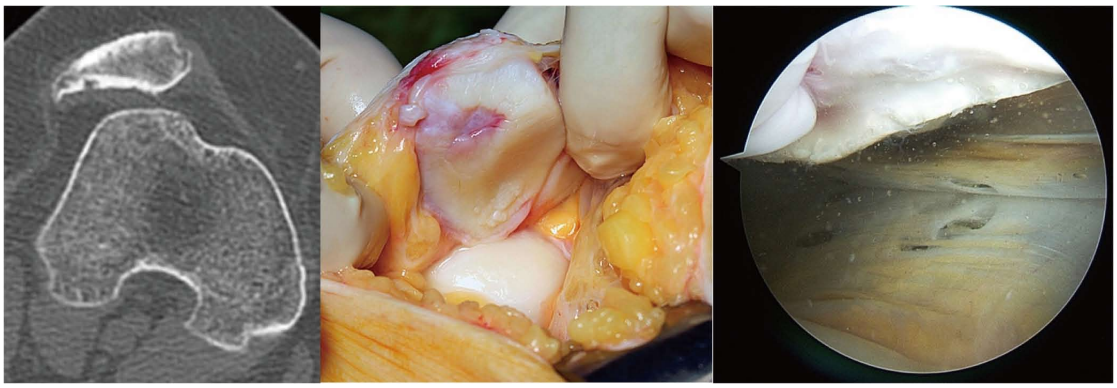

Figure 12 When we consider a surgical procedure to correct patellofemoral maltracking, we have to take not only the TT-TG distance (abnormal if > 20 mm) into consideration but also the existence of chondral lesions and their location in the patella. In this case, a possible candidate for a Fulkerson osteotomy, the location of the chondral lesion would worsen the prognosis.

aspect of the proximal tibial tubercle (TT) in the center of the patellar tendon insertion, measured on axial CT and MRI views. They are routinely measured with the patient in the supine position, knees at 0° of flexion, feet at 15° of external rotation and the quadriceps muscle relaxed. A threshold of 20 mm is widely considered pathological.

Some factors significantly influence this measurement. The TT-TG distance is sensitive to knee rotation, small changes in femoral alignment and axial CT or MRI scan orientation[45,46]. In addition, low reproducibility of the measurement has been described, with an error of about 3-4 mm depending on the slices selected and the landmarks chosen by the radiologist[47]. Therefore, it should be interpreted with caution if the examination procedure and the measurement method have not been standardized.

The tibial tubercle-posterior cruciate ligament (TT-PCL) distance has been recently introduced as a measurement not influenced by the rotation of the knee or the shape of the trochlea (Figure 11)[45]. Similarly, the new TT-TG index allows for correlation of the distance with individual joint size, which is especially important in cases of marginal TT-TG distance[48]. These additional methods for determining the position of the tibial tubercle are currently recommended to facilitate the therapeutic approach.

High quality clinical studies are needed to determine the specific role of the TT-TG measurement in surgical decision-making for the treatment of CLPI.

A pathologic index, as an isolated number, is insufficient to consider an associated surgical technique to the MPFL reconstruction. Other factors must be considered, such as maltracking, chondropathy location (Figure 12), type of dislocation (traumatic *vs* atraumatic), bilaterality, activity level, and patient expectations. Much more controversies exist about osteotomy indications. According to Robert Teitge (personal communication) we may consider an osteotomy in cases with torsion greater than 20° above normal (femoral anteversion > 35° and tibial external torsion > 45°) that have failed after a MPFL reconstruction while pain, instead of instability, is the main symptom, and there is no osteoarthritis.

MPFL RECONSTRUCTION WITHOUT BONE TUNNELS IN COMPLEX REVISION CASES

In patients who have been operated on several times, multiple tunnels and implants both in the patellar inser-

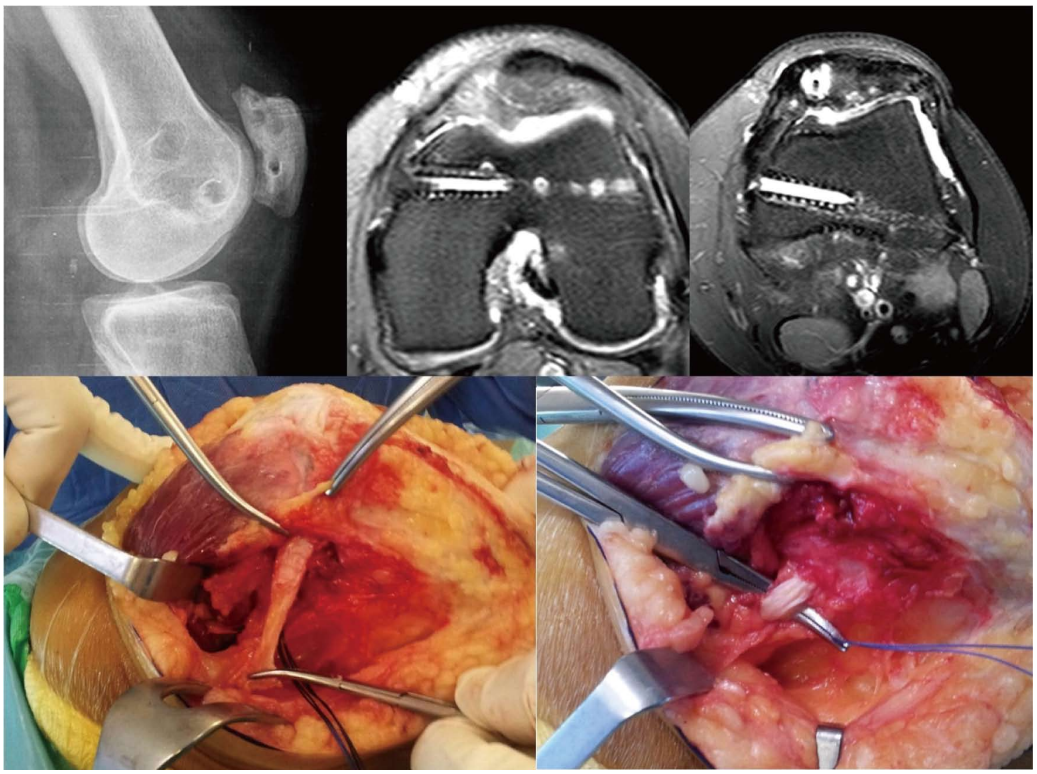

Figure 13 This patient has had two operations on his medial patellofemoral ligament. We can observe the different tunnels in the patella and distal femur. In this case, a MPFL reconstruction was performed without bone tunnels using the adductor magnus tendon as a post and a partial thickness medial quadriceps tendon as a graft (reproduced with permission from AOTT Journal, The Turkish Society of Orthopaedics and Traumatology). MPFL: Medial patellofemoral ligament.

tion area as well as in the femoral insertion area are usually seen. This situation makes revision surgery a real challenge (Figure 13), increasing the risk of patellar fractures either during or after surgery. Moreover, if we drill another tunnel in the patella or in the femur we can cause tunnel collisions that might compromise the implant fixation. This may sometimes call for a two-stage surgery as occasionally occurs in ACL revision surgery. Alternatively, we could consider a ligament reconstruction using methods that do not require anchoring bone tunnels. One option would be the use of an autologous quadriceps tendon graft which is anchored in the proximal 1/3 of the patella, maintaining its native patellar insertion site and using the AMT as a post (Figures 13 and 14). It has been reported that the AMT is a suitable point of insertion for MPFL reconstruction because the kinematic behavior exhibited by the reconstructed MPFL using either the anatomical femoral footprint of the MPFL and the AMT is similar[15]. In addition, this *quasi*-anatomic reconstruction using the AMT as the femoral fixation point has been shown to be safe and suitable for the treatment of CLPI and has good clinical results[14]. The advantages of this surgical technique are that there is no need to implants, no need for bone drilling and no need for allografts. These eliminate the necessity of a two-stage procedure.

The quasi-anatomical MPFL reconstruction using the adductor magnus tendon as the femoral fixation point is a good solution to deal with challenging cases in our daily practice.

Surgical technique

The quadriceps tendon graft is harvested in its medial aspect, obtaining 1 cm width and the superficial anterior half in its complete length (Figure 14). However, the most important thing to keep in mind is to make a good estimation of the length of the graft. It should be large enough to allow for the correct isometric properties of the graft. In this regard, an extra 2 cm in the graft length to the distance between the quadriceps tendon insertion and the AMT is recommended. This will allow the graft to flip around the AMT. When the graft is harvested, dissecting the plane between the VMO and the joint capsule is a must (Figure 14). Once the graft is passed on this plane, a loop is created with its end around the AMT. Then, the attachment of the quadriceps tendon graft into the medial rim of the patella (superior third) is fixed with sutures. This prevents the graft rupturing during posterior steps and also places the graft insertion in a more anatomical position. Finally, the quadriceps tendon graft is sutured to itself in an end-to-side fashion at 30 degrees of knee flexion (Figure 14).

CONCLUSION

Complications after MPFL reconstruction can be more disabling than the primary CLPI. Some patients who have experienced more than one patellar dislocation are still highly functional and may not need surgery. Only when patients are significantly limited in their activities of daily

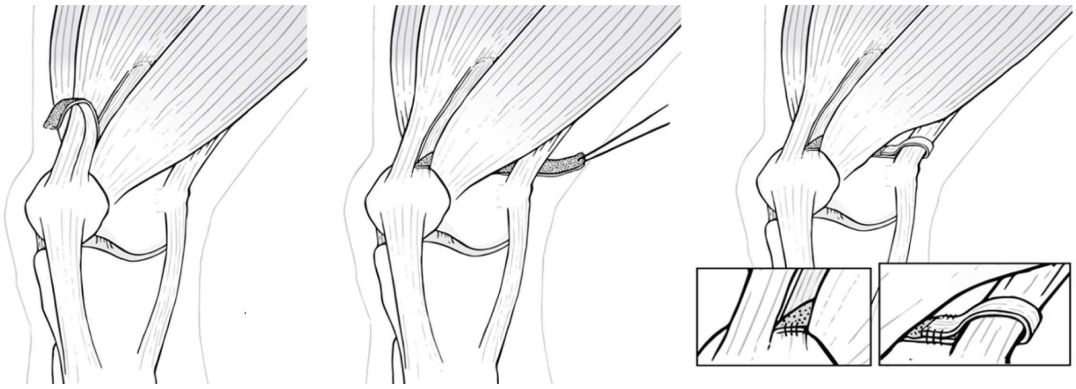

Figure 14 Diagram of a medial patellofemoral ligament reconstruction without bone tunnels using a partial thickness graft of the medial area of the quadriceps tendon (reproduced with permission from AOTT Journal, The Turkish Society of Orthopaedics and Traumatology).

living or with more demanding activities should surgical treatment such as MPFL reconstruction be considered. We, as a professional group, need to be extremely careful recommending this procedure to patients who must be clearly informed about the complications and secondary procedures. Even though, most failed MPFL reconstructions are a result of factors that the surgeon can control. Understanding of the anatomy and biomechanics, cautiousness with the imaging techniques while favoring clinical over radiological findings and common sense to determine the adequate surgical technique for each particular case are critical steps in minimizing potential complications.

Unfortunately, while there are several national registries collecting data on anterior cruciate ligament (ACL) reconstructions, there is a lack of such registries on MPFL reconstructions. Hopefully, the same interest will be given to the MPFL surgery in the future. These registries, along with evidence based medicine promotion, and planning higher levels of evidence studies than those available today, obviously including clinical trials, will provide tools to improve the surgical indications mostly in more the challenging cases of patellofemoral instability. Given the fact that MPFL injuries are much less frequent than ACL injuries and that there are many more factors favoring patellofemoral instability, some of them acting as confounding factors, multicentric studies should be promoted.

REFERENCES

1 **Sanchis-Alfonso V**, Montesinos-Berry E, Baydal-Bertomeu JM, Garrido-Jaen D. Are kinematic and kinetic analyses useful to evaluate patellofemoral disorders in clinical practice? *J Biomed Eng Med Devic* 2016; **1**: 105 [DOI: 10.4172/jbemd. 1000105]

2 **Shah JN**, Howard JS, Flanigan DC, Brophy RH, Carey JL, Lattermann C. A systematic review of complications and failures associated with medial patellofemoral ligament reconstruction for recurrent patellar dislocation. *Am J Sports Med* 2012; **40**: 1916-1923 [PMID: 22679297 DOI: 10.1177/0363546512442330]

3 **Parikh SN**, Nathan ST, Wall EJ, Eismann EA. Complications of medial patellofemoral ligament reconstruction in young patients. *Am J Sports Med* 2013; **41**: 1030-1038 [PMID: 23539043 DOI: 10.1177/0363546513482085]

4 **Schneider DK**, Grawe B, Magnussen RA, Ceasar A, Parikh SN, Wall EJ, Colosimo AJ, Kaeding CC, Myer GD. Outcomes After Isolated Medial Patellofemoral Ligament Reconstruction for the Treatment of Recurrent Lateral Patellar Dislocations: A Systematic Review and Meta-analysis. *Am J Sports Med* 2016; **44**: 2993-3005 [PMID: 26872895 DOI: 10.1177/0363546515624673]

5 **Sanchis-Alfonso V**. Guidelines for medial patellofemoral ligament reconstruction in chronic lateral patellar instability. *J Am Acad Orthop Surg* 2014; **22**: 175-182 [PMID: 24603827 DOI: 10.5435/JAAOS-22-03-175]

6 **Weinberger JM**, Fabricant PD, Taylor SA, Mei JY, Jones KJ. Influence of graft source and configuration on revision rate and patient-reported outcomes after MPFL reconstruction: a systematic review and meta-analysis. *Knee Surg Sports Traumatol Arthrosc* 2016; Epub ahead of print [PMID: 26856314 DOI: 10.1007/s00167-016-4006-4]

7 **Sanchis-Alfonso V**. How to Deal With Chronic Patellar Instability: What Does the Literature Tell Us? *Sports Health* 2016; **8**: 86-90 [PMID: 26733595 DOI: 10.1177/1941738115604156]

8 **Sanchis-Alfonso V**, Ramirez-Fuentes C, Montesinos-Berry E, Domenech J, Martí-Bonmatí L. Femoral insertion site of the graft used to replace the medial patellofemoral ligament influences the ligament dynamic changes during knee flexion and the clinical outcome. *Knee Surg Sports Traumatol Arthrosc* 2015; Epub ahead of print [PMID: 26658569 DOI: 10.1007/s00167-015-3905-0]

9 **Schöttle PB**, Schmeling A, Rosenstiel N, Weiler A. Radiographic landmarks for femoral tunnel placement in medial patellofemoral ligament reconstruction. *Am J Sports Med* 2007; **35**: 801-804 [PMID: 17267773 DOI: 10.1177/0363546506296415]

10 **Sanchis-Alfonso V**, Ramirez-Fuentes C, Montesinos-Berry E, Aparisi-Rodriguez F, Martí-Bonmatí L. Does radiographic location ensure precise anatomic location of the femoral fixation site in medial patellofemoral ligament surgery? *Knee Surg Sports Traumatol Arthrosc* 2016; **24**: 2838-2844 [PMID: 25634578]

11 **Ziegler CG**, Fulkerson JP, Edgar C. Radiographic Reference Points Are Inaccurate With and Without a True Lateral Radiograph: The Importance of Anatomy in Medial Patellofemoral Ligament Reconstruction. *Am J Sports Med* 2016; **44**: 133-142 [PMID: 26561652 DOI: 10.1177/0363546515611652]

12 **Fujino K**, Tajima G, Yan J, Kamei Y, Maruyama M, Takeda S, Kikuchi S, Shimamura T. Morphology of the femoral insertion site of the medial patellofemoral ligament. *Knee Surg Sports Traumatol Arthrosc* 2015; **23**: 998-1003 [PMID: 24296991 DOI: 10.1007/s00167-013-2797-0]

13 **Kikuchi S**, Tajima G, Yan J, Kamei Y, Maruyama M, Sugawara A, Fujino K, Takeda S, Doita M. Morphology of insertion sites on patellar side of medial patellofemoral ligament. *Knee Surg Sports Traumatol Arthrosc* 2016; Epub ahead of print [PMID: 26744281 DOI: 10.1007/s00167-015-3973-1]

14 **Monllau JC**, Masferrer-Pino À, Ginovart G, Pérez-Prieto D, Gelber PE, Sanchis-Alfonso V. Clinical and radiological outcomes after a quasi-anatomical reconstruction of medial patellofemoral ligament with gracilis tendon autograft. *Knee Surg Sports Traumatol Arthrosc* 2015;

26704788 [PMID: 26704788 DOI: 10.1007/s00167-015-3934-8]
15 **Pérez-Prieto D**, Capurro B, Gelber PE, Ginovart G, Reina F, Sanchis-Alfonso V, Monllau JC. The anatomy and isometry of a quasi-anatomical reconstruction of the medial patellofemoral ligament. *Knee Surg Sports Traumatol Arthrosc* 2015; 26581363 [PMID: 26581363 DOI: 10.1007/s00167-015-3865-4]
16 **Dejour H**, Walch G, Nove-Josserand L, Guier C. Factors of patellar instability: an anatomic radiographic study. *Knee Surg Sports Traumatol Arthrosc* 1994; **2**: 19-26 [PMID: 7584171 DOI: 10.1007/BF01552649]
17 **Nelitz M**, Theile M, Dornacher D, Wölfle J, Reichel H, Lippacher S. Analysis of failed surgery for patellar instability in children with open growth plates. *Knee Surg Sports Traumatol Arthrosc* 2012; **20**: 822-828 [PMID: 21732056 DOI: 10.1007/s00167-011-1599-5]
18 **Wagner D**, Pfalzer F, Hingelbaum S, Huth J, Mauch F, Bauer G. The influence of risk factors on clinical outcomes following anatomical medial patellofemoral ligament (MPFL) reconstruction using the gracilis tendon. *Knee Surg Sports Traumatol Arthrosc* 2013; **21**: 318-324 [PMID: 22538501 DOI: 10.1007/s00167-012-2015-5]
19 **Kita K**, Tanaka Y, Toritsuka Y, Amano H, Uchida R, Takao R, Horibe S. Factors Affecting the Outcomes of Double-Bundle Medial Patellofemoral Ligament Reconstruction for Recurrent Patellar Dislocations Evaluated by Multivariate Analysis. *Am J Sports Med* 2015; **43**: 2988-2996 [PMID: 26435448 DOI: 10.1177/0363546515606102]
20 **Matsushita T**, Kuroda R, Oka S, Matsumoto T, Takayama K, Kurosaka M. Clinical outcomes of medial patellofemoral ligament reconstruction in patients with an increased tibial tuberosity-trochlear groove distance. *Knee Surg Sports Traumatol Arthrosc* 2014; **22**: 2438-2444 [PMID: 24584694 DOI: 10.1007/s00167-014-2919-3]
21 **Dejour D**, Byn P, Ntagiopoulos PG. The Lyon's sulcus-deepening trochleoplasty in previous unsuccessful patellofemoral surgery. *Int Orthop* 2013; **37**: 433-439 [PMID: 23275080 DOI: 10.1007/s00264-012-1746-8]
22 **Fucentese SF**, Zingg PO, Schmitt J, Pfirrmann CW, Meyer DC, Koch PP. Classification of trochlear dysplasia as predictor of clinical outcome after trochleoplasty. *Knee Surg Sports Traumatol Arthrosc* 2011; **19**: 1655-1661 [PMID: 21302049 DOI: 10.1007/s00167-011-1410-7]
23 **Schöttle PB**, Schell H, Duda G, Weiler A. Cartilage viability after trochleoplasty. *Knee Surg Sports Traumatol Arthrosc* 2007; **15**: 161-167 [PMID: 16951977 DOI: 10.1007/s00167-006-0148-0]
24 **Sanchis-Alfonso V**, Montesinos-Berry E, Monllau JC, Merchant AC. Results of isolated lateral retinacular reconstruction for iatrogenic medial patellar instability. *Arthroscopy* 2015; **31**: 422-427 [PMID: 25450418 DOI: 10.1016/j.arthro.2014.09.005]
25 **Sanchis-Alfonso V**, Merchant AC. Iatrogenic Medial Patellar Instability: An Avoidable Injury. *Arthroscopy* 2015; **31**: 1628-1632 [PMID: 25823671 DOI: 10.1016/j.arthro.2015.01.028]
26 **Sanchis-Alfonso V**, Montesinos-Berry E, Monllau JC, Andrish J. Deep Transverse Lateral Retinaculum Reconstruction for Medial Patellar Instability. *Arthrosc Tech* 2015; **4**: e245-e249 [PMID: 26258038 DOI: 10.1016/j.eats.2015.02.003]
27 **Fabricant PD**, Ladenhauf HN, Salvati EA, Green DW. Medial patellofemoral ligament (MPFL) reconstruction improves radiographic measures of patella alta in children. *Knee* 2014; **21**: 1180-1184 [PMID: 25257777 DOI: 10.1016/j.knee.2014.07.023]
28 **Servien E**, Verdonk PC, Neyret P. Tibial tuberosity transfer for episodic patellar dislocation. *Sports Med Arthrosc* 2007; **15**: 61-67 [PMID: 17505319 DOI: 10.1097/JSA.0b013e3180479464]
29 **Arendt EA**. Lateral-sided surgery with MPFL reconstruction: When is this needed? La Patella, Sauramps Medical, Montpellier, 2012: 119-123
30 **Malghem J**, Maldague B. Depth insufficiency of the proximal trochlear groove on lateral radiographs of the knee: relation to patellar dislocation. *Radiology* 1989; **170**: 507-510 [PMID: 2911676 DOI: 10.1148/radiology.170.2.2911676]
31 **Lippacher S**, Dejour D, Elsharkawi M, Dornacher D, Ring C, Dreyhaupt J, Reichel H, Nelitz M. Observer agreement on the Dejour trochlear dysplasia classification: a comparison of true lateral radiographs and axial magnetic resonance images. *Am J Sports Med* 2012; **40**: 837-843 [PMID: 22238057 DOI: 10.1177/0363546511433028]
32 **Koëter S**, Bongers EM, de Rooij J, van Kampen A. Minimal rotation aberrations cause radiographic misdiagnosis of trochlear dysplasia. *Knee Surg Sports Traumatol Arthrosc* 2006; **14**: 713-717 [PMID: 16395562 DOI: 10.1007/s00167-005-0031-4]
33 **Biedert RM**, Bachmann M. Anterior-posterior trochlear measurements of normal and dysplastic trochlea by axial magnetic resonance imaging. *Knee Surg Sports Traumatol Arthrosc* 2009; **17**: 1225-1230 [PMID: 19495725 DOI: 10.1007/s00167-009-0824-y]
34 **Pfirrmann CW**, Zanetti M, Romero J, Hodler J. Femoral trochlear dysplasia: MR findings. *Radiology* 2000; **216**: 858-864 [PMID: 10966723 DOI: 10.1148/radiology.216.3.r00se38858]
35 **Carrillon Y**, Abidi H, Dejour D, Fantino O, Moyen B, Tran-Minh VA. Patellar instability: assessment on MR images by measuring the lateral trochlear inclination-initial experience. *Radiology* 2000; **216**: 582-585 [PMID: 10924589 DOI: 10.1148/radiology.216.2.r00au07582]
36 **Nelitz M**, Lippacher S, Reichel H, Dornacher D. Evaluation of trochlear dysplasia using MRI: correlation between the classification system of Dejour and objective parameters of trochlear dysplasia. *Knee Surg Sports Traumatol Arthrosc* 2014; **22**: 120-127 [PMID: 23196644 DOI: 10.1007/s00167-012-2321-y]
37 **Stäubli HU**, Dürrenmatt U, Porcellini B, Rauschning W. Anatomy and surface geometry of the patellofemoral joint in the axial plane. *J Bone Joint Surg Br* 1999; **81**: 452-458 [PMID: 10872365 DOI: 10.1302/0301-620X.81B3.8758]
38 **Shih YF**, Bull AM, Amis AA. The cartilaginous and osseous geometry of the femoral trochlear groove. *Knee Surg Sports Traumatol Arthrosc* 2004; **12**: 300-306 [PMID: 14530849 DOI: 10.1007/s00167-003-0414-3]
39 **van Huyssteen AL**, Hendrix MR, Barnett AJ, Wakeley CJ, Eldridge JD. Cartilage-bone mismatch in the dysplastic trochlea. An MRI study. *J Bone Joint Surg Br* 2006; **88**: 688-691 [PMID: 16645122 DOI: 10.1302/0301-620X.88B5.16866]
40 **Seil R**, Müller B, Georg T, Kohn D, Rupp S. Reliability and interobserver variability in radiological patellar height ratios. *Knee Surg Sports Traumatol Arthrosc* 2000; **8**: 231-236 [PMID: 10975264 DOI: 10.1007/s001670000121]
41 **Biedert RM**, Albrecht S. The patellotrochlear index: a new index for assessing patellar height. *Knee Surg Sports Traumatol Arthrosc* 2006; **14**: 707-712 [PMID: 16496126 DOI: 10.1007/s00167-005-0015-4]
42 **Dejour D**, Ferrua P, Ntagiopoulos PG, Radier C, Hulet C, Rémy F, Chouteau J, Chotel F, Boisrenoult P, Sebilo A, Guilbert S, Bertin D, Ehkirch FP, Chassaing V. The introduction of a new MRI index to evaluate sagittal patellofemoral engagement. *Orthop Traumatol Surg Res* 2013; **99**: S391-S398 [PMID: 24246663 DOI: 10.1016/j.otsr.2013.10.008]
43 **Ali SA**, Helmer R, Terk MR. Patella alta: lack of correlation between patellotrochlear cartilage congruence and commonly used patellar height ratios. *AJR Am J Roentgenol* 2009; **193**: 1361-1366 [PMID: 19843754 DOI: 10.2214/AJR.09.2729]
44 **Barnett AJ**, Prentice M, Mandalia V, Wakeley CJ, Eldridge JD. Patellar height measurement in trochlear dysplasia. *Knee Surg Sports Traumatol Arthrosc* 2009; **17**: 1412-1415 [PMID: 19421740 DOI: 10.1007/s00167-009-0801-5]
45 **Seitlinger G**, Scheurecker G, Högler R, Labey L, Innocenti B, Hofmann S. Tibial tubercle-posterior cruciate ligament distance: a new measurement to define the position of the tibial tubercle in patients with patellar dislocation. *Am J Sports Med* 2012; **40**: 1119-1125 [PMID: 22415209 DOI: 10.1177/0363546512438762]
46 **Yao L**, Gai N, Boutin RD. Axial scan orientation and the tibial tubercle-trochlear groove distance: error analysis and correction. *AJR Am J Roentgenol* 2014; **202**: 1291-1296 [PMID: 24848827 DOI: 10.2214/AJR.13.11488]
47 **Lustig S**, Servien E, Aït Si Selmi T, Neyret P. [Factors affecting reliability of TT-TG measurements before and after medialization: A CT-scan study]. *Rev Chir Orthop Reparatrice Appar Mot* 2006; **92**: 429-436 [PMID: 17088736 DOI: 10.1016/S0035-1040(06)75829-9]

48 **Hingelbaum S**, Best R, Huth J, Wagner D, Bauer G, Mauch F. The TT-TG Index: a new knee size adjusted measure method to determine the TT-TG distance. *Knee Surg Sports Traumatol Arthrosc* 2014; **22**: 2388-2395 [PMID: 25085528 DOI: 10.1007/s00167-014-3204-1]

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ORIGINAL ARTICLE

Basic Study

Evaluation of a chitosan-polyethylene glycol paste as a local antibiotic delivery device

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Abstract

AIM

To investigate the efficacy of a chitosan/polyethylene glycol blended paste as a local antibiotic delivery device, particularly in musculoskeletal wounds.

METHODS

Acidic (A) chitosan sponges and neutralized (N) chitosan/polyethylene glycol (PEG) blended sponges were combined in ratios of 3A:2N, 1A:1N, and 2A:3N; then hydrated with phosphate buffered saline to form a chitosan/PEG paste (CPP). Both *in vitro* and *in vivo* studies were conducted to determine the potential CPP has as a local antibiotic

delivery device. *In vitro* biocompatibility was assessed by the cytotoxic response of fibroblast cells exposed to the experimental groups. Degradation rate was measured as the change in dry mass due to lysozyme based degradation over a 10-d period. The antibiotic elution profiles and eluate activity of CPP were evaluated over a 72-h period. To assess the *in vivo* antimicrobial efficacy of the CPP, antibiotic-loaded paste samples were exposed to subcutaneously implanted murine catheters inoculated with *Staphylococcus aureus*. Material properties of the experimental paste groups were evaluated by testing the ejection force from a syringe, as well as the adhesion to representative musculoskeletal tissue samples.

RESULTS

The highly acidic CPP group, 3A:2N, displayed significantly lower cell viability than the control sponge group. The equally distributed group, 1A:1N, and the highly neutral group, 2A:3N, displayed similar cell viability to the control sponge group and are deemed biocompatible. The degradation studies revealed CPP is more readily degradable than the chitosan sponge control group. The antibiotic activity studies indicated the CPP groups released antibiotics at a constant rate and remained above the minimum inhibitory concentrations of the respective test bacteria for a longer time period than the control chitosan sponges, as well as displaying a minimized burst release. The *in vivo* functional model resulted in complete bacterial infection prevention in all catheters treated with the antibiotic loaded CPP samples. All experimental paste groups exhibited injectability and adhesive qualities that could be advantageous material properties for drug delivery to musculoskeletal injuries.

CONCLUSION

CPP is an injectable, bioadhesive, biodegradable, and biocompatible material with potential to allow variable antibiotic loading and active, local antibiotic release to prevent bacterial contamination.

Key words: Chitosan; Polyethylene glycol; Paste; Local antibiotic delivery; Biofilm; Bacterial infection

Core tip: The study investigates the efficacy of a chitosan-polyethylene glycol paste as a local antibiotic delivery device to prevent bacterial infection, particularly in high risk, severe musculoskeletal wounds complex in shape and experiencing decreased vascularity. Research focusing on three different paste formulations categorized by the ratio of acidic to neutral components involved *in vitro* evaluation of the paste cytotoxicity, degradation, antibiotic elution, as well as an *in vivo* functional infection model evaluating the antimicrobial efficacy of the paste. Preliminary study outcomes demonstrate the potential of a chitosan-polyethylene glycol paste as a local antibiotic delivery device capable of infection prevention.

Rhodes CS, Alexander CM, Berretta JM, Courtney HS, Beenken KE, Smeltzer MS, Bumgardner JD, Haggard WO, Jennings JA. Evaluation of a chitosan-polyethylene glycol paste as a local antibiotic delivery device. *World J Orthop* 2017; 8(2): 130-141 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i2/130.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i2.130

INTRODUCTION

Musculoskeletal wounds are among the most prevalent types of injuries in the United States, accounting for over 60% of unintentional injuries per year[1], and are among the leading causes of death in all age groups[2]. Systemic antibiotic therapy is standard prophylactic treatment[3], but compromised vasculature in some complex musculoskeletal wounds reduces systemic distribution allowing for proliferation of contaminating bacteria and establishment of infection[4,5]. A complex musculoskeletal wound has an estimated 20% chance of becoming infected in a civilian[1,5,6] and 65% chance for soldiers suffering an open fracture in battlefield conditions[6,7]. Musculoskeletal infections severely impair wound healing[1] and can be complicated even further when antibiotic resistant and/or biofilm-forming bacterial strains are present, such as *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*)[6,8,9], resulting in the need for higher concentrations of systemic antibiotics[10]. Increased systemic antibiotics can help clear infection, but may lead to adverse side effects[4]. Even with systemic antibiotics delivered in a clinical setting, patients still develop infections, reported by Mlynek *et al*[11]. Antibiotics present at levels below the minimum inhibitory concentration (MIC) in a *S. aureus* infection can lead to the development of more biofilm and a resistance to the antibiotic. One could rationally associate the peaks and troughs of antibiotic bioavailability seen in systemic delivery with the development of antibiotic resistant bacterial strains and biofilm. A local antibiotic delivery system could increase antibiotic levels at the musculoskeletal wound without increasing risk to the patient[10].

Vancomycin and amikacin are both optimal for local delivery to musculoskeletal trauma, and were used for all studies involving antibiotics. Vancomycin is effective against *S. aureus* which can evolve into methicillin resistant *S. aureus*, a difficult to treat strain of bacteria attracted to open and avascular musculoskeletal wounds. Amikacin has a broad spectrum of efficacy including against Gram negative bacteria, such as the biofilm forming *P. aeruginosa*. Both antibiotics are considered reliable because they're capable of sustained activity over an extended elution time, storage time, or variable environmental conditions such as a low pH.

Biomaterials currently used as local antibiotic delivery devices, including polymethylmethacrylate and calcium sulfate, increase the local antibiotic levels within the tissue

surrounding a wound; which could enhance treatment outcome for contaminated wounds. However, the current options present limitations such as surgical removal after a period of time[12,13], rapid degradation[14], or a limited choice of antibiotics utilized at the time of application[15]. These limitations, among others, drive the need for the development of novel local drug delivery devices in order to provide enhanced treatment over current devices; particularly in complex trauma wounds or patients with infection risk factors (*i.e.*, diabetes, positive skin cultures, history of infection)[16-20]. The study objective is to develop a biocompatible, local drug delivery device capable of being loaded with physician-selected antimicrobials at the time of surgical intervention, presenting extended drug release profiles, and degrading *in vivo*.

Chitosan has been shown to be effective as a drug delivery system in several forms (*i.e.*, films, sponges), capable of releasing antibiotics at a predictable rate with *in vivo* degradation[16,21-24]. Additionally, when blended with polyethylene glycol (PEG), chitosan sponges have demonstrated improved biocompatibility, biodegradability, and antibiotic release profiles compared to chitosan alone[17,18]. Chitosan devices have been approved by the Food and Drug Administration to be used clinically as a hemostatic wound dressing. Starting in 2003, HemCon wound dressings were used widespread by the United States military in combat operations in Iraq and Afghanistan to effectively control hemorrhaging injuries[25]. Results of previous studies investigating the antimicrobial drug delivery characteristics of sponges consisting of a chitosan/PEG blend as well as sponges made from chitosan alone support their use as local antibiotic delivery device[16-20]. However, chitosan sponges have shortcomings, including incomplete wound coverage and some implant migration[19,26]. A chitosan paste developed from sponges and modified with PEG was evaluated to address the shortcomings of sponges[17,18]. For this body of work, acidic chitosan and neutral PEG blended chitosan sponges were fabricated and combined in various ratios to form a chitosan/PEG paste (CPP).

The aim of the current study is to determine the feasibility of the CPP as a local drug delivery device for the prevention of bacterial wound infections by evaluating the following aspects: Biocompatibility, degradation, antibiotic elution, efficacy in preventing a biofilm-based bacterial infection, the ease of injection, and adhesion to musculoskeletal tissue.

MATERIALS AND METHODS

Fabrication

All materials purchased from Fisher Scientific (Pittsburgh, PA) unless otherwise noted. Chitosan and PEG-blended chitosan products were prepared as previously reported using chitosan powder (Chitinor AS, Tromsø, Norway) and 6000g/mol PEG (Sigma Aldrich, St. Louis, MO)[17,18]. Chitosan and PEG were dissolved in a 1% acetic acid solution (v/v) containing 0.5% chitosan and 0.5% PEG (w/v), the PEG must first be dissolved then the chitosan added after. Control chitosan only solution was also made using a 1% acetic acid solution, but instead containing 1% chitosan (w/v). Chitosan/PEG and chitosan solutions (333 mL) were cast, frozen overnight (-80 ℃), and lyophilized in a LabConco FreeZone 4.5 Liter Benchtop Freeze Dry System (Kansas City, MO) to create slightly acidic, dehydrated sponges. After lyophilization, the control chitosan sponges and the chitosan/PEG sponges were neutralized *via* submersion in NaOH solution. The chitosan/PEG sponges were submerged in 0.25 mol/L NaOH for 15 min and the control chitosan sponges were in 0.6 mol/L NaOH for 20 min, followed by rinsing cycles with distilled water until a neutral pH was reached. Finally, neutralized sponges were again frozen and lyophilized. Neutral chitosan sponges were used as the control for all experiments, excluding paste injectability evaluations. Acidic and neutral chitosan/PEG sponges were ground separately into a powder, with flake sizes $\leqslant$ 0.5 mm in diameter, using a blade grinder. Three different combinations of CPP were made by varying the mass ratios of acidic (A) chitosan to neutral (N) chitosan/PEG powder: 3A:2N, 1A:1N, and 2A:3N. Phosphate buffered saline (PBS) solution was used to hydrate the chitosan/PEG powder with a ratio of PBS volume to dry paste mass of 7.5. Dry CPP components used for biological testing and the infection prevention model were sterilized with ethylene oxide gas (EtO) prior to hydration, and PBS was sterile filtered.

Biocompatibility

In vitro cytocompatibility was assessed using a modified protocol[18] (Figure 1A). Normal human dermal fibroblast (NHDF) cells (Lonza, Walkersville, MD) were seeded at 1.0 × 10^4 cells/cm^2 in 12-well tissue culture plates in 1.5 mL of Dulbecco's Modified Eagle's Medium solution supplemented with 10% fetal bovine serum and 1 × antibiotic-antimycotic solution (100 units/mL Penicillin G, 100 μg/mL streptomycin sulfate, 0.25 μg/mL amphotericin B, Corning Inc., Manassas, VA). Twenty-four hours after cell seeding, hydrated paste samples (0.5 mL) and control sponge samples (8 mm diameter) were added to cell culture inserts (8 μm pore membrane, Corning Inc., Manassas, VA) (n = 5/group at each time point), and placed into wells containing NHDF cells and media. To asses NHDF viability, at 24 and 72 h post-exposure a Cell Titer-Glo® assay (Promega, Madison, WI) was used to measure cell viability using a BioTek Synergy H1 plate reader (Winooski, VT). Tissue culture plastic controls from each time point were used to calibrate luminescence values to a cell viability relative to the tissue culture plastic.

Degradation

In vitro degradation was assessed by weight reduction over time based on a previous method[18] (Figure 1B). Sample weights were recorded before hydration (n = 5), and 5 mL paste samples or 22 mm × 23 mm sponges were placed in metal, hemispherical containers (Norpro,

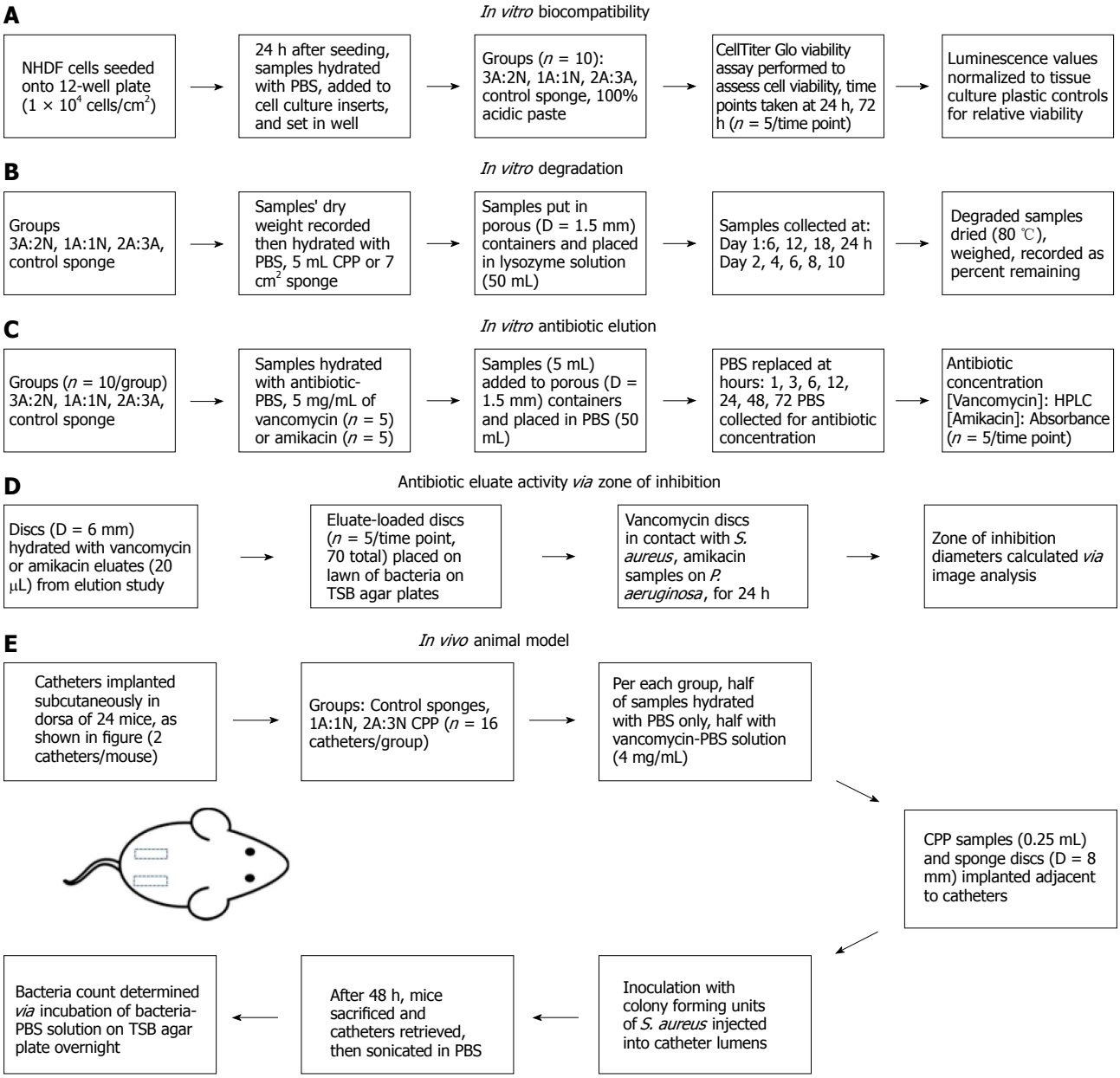

Figure 1 Experimental design flowchart detailing methods for the following studies. A: Biocompatibility; B: Degradation; C: Antibiotic elution; D: Antibiotic eluate activity; E: *In vivo* functional model. NHDF: Normal human dermal fibroblast; PBS: Phosphate buffered saline; CPP: Chitosan/polyethylene glycol paste; TSB: Trypticase soy broth.

Everett, WA) with 1.5 mm diameter holes. Container openings were covered with para-film with appropriate lower holes occluded, in order to prevent leakage of CPP and still allow the transfer of media across the sample surface. The porous vessels containing the samples were placed inside plastic containers, para-film side down, in 50 mL of lysozyme solution (1 mg/mL Lysozyme Type Ⅵ, MP Biomedicals, Santa Ana, CA), and placed in an incubator on a shaker. Lysozyme is a naturally occurring enzyme found in human macrophages, among many other tissues and bodily fluid; used for its natural degradation of chitosan, as described by Varum *et al*[27]. Samples were gently shaken at 37 ℃ for the duration of the study. Time points were taken every 6 h through day 1, 24 h later at day 2, and subsequently every 48 h through day 10. Lysozyme solution was completely replaced every 6 h over the entire 10 d degradation period. Degraded samples were dried (80 ℃), weighed, and percent CPP remaining was calculated.

Elution

The *in vitro* concentration release profile of vancomycin and amikacin was determined over 72 h by high performance liquid chromatography (HPLC) (Figure 1C). Seventy-two hours was selected as the average period of time between the debridement and irrigation of a complex musculoskeletal wound in a clinical setting[28]. Contrary to the degradation study, samples were hydrated with an antibiotic loaded PBS (5 mg/mL of amikacin or vancomycin, *n* = 5, separate groups per

antibiotic type), and the porous hemispheres were placed in 50 mL of PBS, instead of a lysozyme solution. Samples were gently shaken at 37 ℃ for the duration of the study.

Samples used for the HPLC and antibiotic activity from the elution solution, were collected at 1, 3, 6, 12, 24, 48 and 72 h with complete elution solution replacement at each time point with 50 mL of PBS; thereby implementing infinite sink conditions. Using a modified HPLC protocol[29,30], vancomycin concentrations were measured utilizing a reversed-phase C18 column with mobile phase containing 35% acetonitrile and 65% phosphate buffer at 0.1 mol/L and 3 pH. Vancomycin had a 2.5 min retention time (1.0 mL/min flow rate, 250 nm UV detection). Vancomycin absorbance readings were normalized to corresponding concentration values *via* a standard curve made form serial dilutions of vancomycin.

Concentration of amikacin in eluates was determined *via* a spectrofluorometric method[31]. Amikacin eluate samples were reacted with acetylacetone and formaldehyde in a buffer solution containing a combination of boric, acetic, and phosphoric acid at a pH of 2.7. Closed sample vials were heated in an oven at 100 ℃ for 20 min. Absorbance of the reacted product was measured at 450 nm with a BioTek Synergy H1 plate reader (Winooski, VT). Absorbance values were normalized to concentrations *via* a standard curve of known amikacin concentrations.

Antibiotic eluate activity

Antibiotic activity of vancomycin and amikacin eluted from samples obtained in the elution study was determined using zone of inhibition (ZOI) as described by[32] (Figure 1D). On trypticase soy broth (TSB) agar plates, blank discs (6 mm diameter) hydrated with vancomycin or amikacin eluates (20 μL) were placed on lawns of *S. aureus* (ATCC 12598) or *P. aeruginosa* (ATCC 27317), respectively. *S. aureus* and *P. aeruginosa* were chosen as the representative bacterial strains because they are found in infected musculoskeletal wounds and are known to be capable of forming biofilm[33]. The sample size for each test group was n = 5. TSB agar plates were incubated (37 ℃) and removed after 24 h for photography and measurement of ZOI diameters, excluding discs.

Functional animal model

Animal care and use statement: Study protocols were approved by the University of Arkansas for Medical Sciences IACUC and all appropriate measures were taken to minimize pain and discomfort.

Following an established mouse model protocol[17,34,35] (Figure 1E) approved by the University of Arkansas for Medical Sciences IACUC (protocol #3608), 24 mice were used to assess *in vivo* prevention of biofilm-forming *S. aureus* (ATCC 49230) growth. The functional evaluation was used to determine the *in vivo* infection prevention efficacy of the CPPs. The more acidic CPP group (3A:2N) was not tested due to the results of the cytocompatibility study indicating its cytotoxic qualities.

Incisions 0.3 cm in length were made on the left and right dorsal surface of the hip and two polytetrafluoroethylene catheters, 1 cm length, were implanted subcutaneously into each mouse. Simultaneously, control 1% chitosan sponges, 1A:1N CPP, and 2A:3N CPP samples were hydrated with either a PBS-vancomycin solution, containing 4 mg/mL vancomycin, or PBS alone. There were six test groups with four animals (8 catheters) in each group. Paste samples (0.25 mL) were injected adjacent to each catheter using a U-100 insulin syringe (BD, Franklin Lakes, NJ) with needle removed. Control chitosan sponge discs (D = 8 mm) were also placed adjacent to each catheter *via* tweezers. Incisions were closed with surgical glue. *S. aureus* (UAMS-1) was injected into the catheter lumens at a concentration of 1×10^5 colony forming units (CFUs) in 2 μL of solution. Mice were sacrificed after 48 h and catheters were surgically removed and placed in a sterile saline solution and sonicated to remove biofilm. The resultant bacterial PBS solutions were serially diluted, plated on TSB agar, and incubated at 37 ℃ overnight in order to quantify the CFUs of *S. aureus* attached to each catheter.

Injection

Injectability was assessed by ejecting paste from a standard 25 mL repeater pipette syringe (Eppendorf; Hamburg, Germany) with 3.25 mm diameter tips (n = 3). Syringes were loaded with 6 mL of paste and fixed in an Instron 33R Universal Testing Machine model 4465 (Instron, Norwood, MA) with 5kN load cell, automated by Instron's Bluehill 2 (v2.13) software, compressing the plunger 1 mm/s to fully eject paste. Injectability was also visually assessed by ejecting 0.5 mL of paste from modified repeater pipette syringes (n = 5).

Adhesion

To determine the quality of adhesion of CPP to a representative musculoskeletal tissue, porcine cervical vertebrae were used (Kroger, Memphis, TN) coated in fetal bovine serum simulating blood-like components. Adhesion was visually assessed by adhering 5 mL of paste or 22 mm × 23 mm sponge to FBS-coated tissue and timing adherence for a minimum of 1 min (n = 3). Samples were then doused with 10 mL of PBS, to partially simulate wound fluid exudate from the representative tissues, to determine if samples would dislodge.

Statistical analysis

The statistical methods for this study were reviewed by Dr. Amber Jennings, professor of Biostatistics in the department of Biomedical Engineering at the University of Memphis. For all applicable data, normality was determined *via* the Shapiro-Wilk test. Data from the *in vitro* degradation, biocompatibility, antibiotic elution, and antibiotic activity studies was analyzed using a two-way Analysis of Variance (ANOVA), and further analyzed *via* Holm-Sidak post hoc tests. Injectability and remaining CFUs from the *in vivo* model were analyzed using Kruskal-Wallis one-way ANOVA on ranks followed by Tukey post hoc tests. An *a priori* power analysis was performed using results from previous studies[35] by assuming

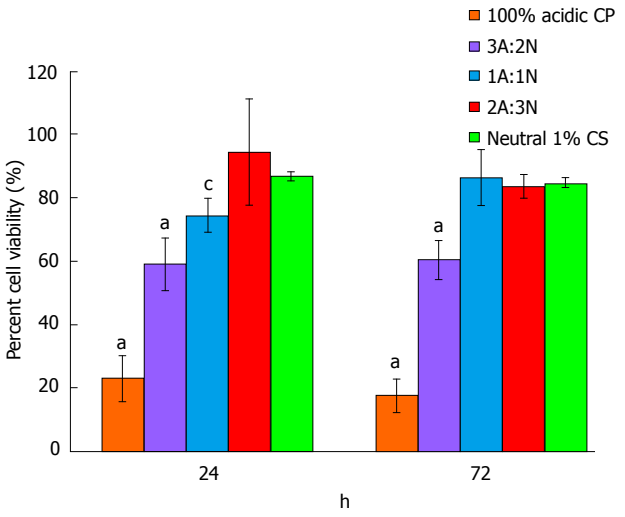

Figure 2 ***In vitro*** **direct contact biocompatibility normalized to tissue culture plastic control reported as the average ± standard deviation of percent cell viability for 100% acidic chitosan paste, 3A:2N, 1A:1N, and 2A:3N chitosan/polyethylene glycol paste variations, and neutral 1% chitosan sponges after 24 and 72 h (*n* = 5).** ($^{a}P < 0.05$ *vs* all at respective time point, $^{c}P < 0.05$ *vs* 2A:3N CPP and neutral 1% CS at respective time point). CPP: Chitosan/polyethylene glycol paste.

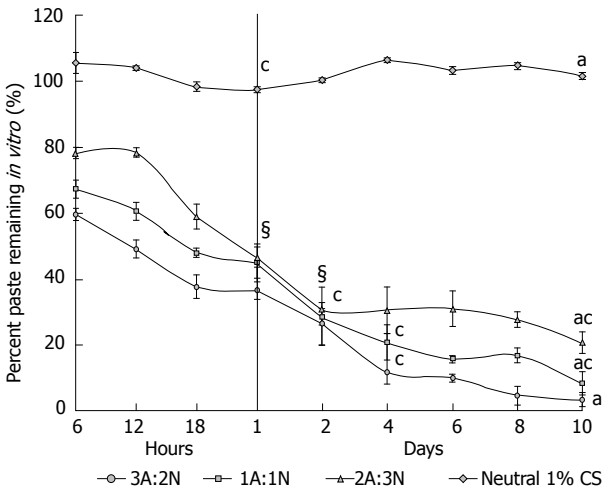

Figure 3 ***In vitro*** **enzymatic degradation reported as the average ± standard deviation of weight percent remaining of the sample for 3A:2N, 1A:1N, and 2A:3N chitosan/ polyethylene glycol paste variations and neutral 1% chitosan sponges over 10 d (*n* = 5).** $^{a}P < 0.05$ *vs* each other at all time points except § for all pastes at day 2 and 2A:3N and 1A:1N at day 1; $^{c}P < 0.05$ showing significant degradation through marked time points.

standard deviation of 0.9 log-CFUs to determine eight catheters per group were required for 87% power to detect a mean difference of 1.85 log-CFUs between control and experimental groups at significance level $P < 0.05$. All results, excluding percent clearance of bacteria, are presented as average ± standard deviation (SD). SigmaPlot 12.5 (Systat Software Inc, San Jose, CA) was used for analysis. Statistical significance level was set at $\alpha = 5\%$.

RESULTS

Biocompatibility

Lower cell viability at both time points (approximately 60%) was observed for 3A:2N CPP compared with all other samples ($P \leqslant 0.006$), excluding 100% acidic paste ($P < 0.001$; negative control) (Figure 2). 1A:1N CPP exhibited lower viability than 2A:3N CPP and neutral sponge (positive control) after 24 h ($P \leqslant 0.025$). However, after 72 h the groups displayed similar viability ($P \geqslant 0.800$). From microscopic observations, no evidence was found of cellular malformation, sloughing, or lysis for any samples except the 100% acidic paste.

Degradation

After undergoing lysozyme mass-based degradation, the pastes displayed a greater degradation rate for the first 24 to 48 h than the control sponge group. After approximately 48 h, steady degradation was shown for the 3A:2N and 1A:1N CPP groups at a higher rate than the 2A:3N group (Figure 3). The control group of 1% chitosan sponges remained at a constant mass through day 10. 3A:2N, 1A:1N, and 2A:3N CPP variations displayed significantly greater percentage loss of mass compared to control sponges ($P \leqslant 0.001$), 98%, 93% and 81%, respectively.

In vitro antibiotic elution

All paste variations steadily released vancomycin over 72 h. The control chitosan sponges released an initial, high burst with minimal to no release after 6 h. Vancomycin released from the CPP groups remained above the MIC for *S. aureus* of 2 μg/mL[36] through 72 h while sponges released vancomycin concentrations above the MIC through 6 h (Figure 4A). Percent vancomycin released from CPP was lower after 6 h and the initial burst release effect ($P \leqslant 0.001$), but the vancomycin concentrations increased, in part due to the degradation of the paste, through 48 h and was again significantly lower at 72 h ($P \leqslant 0.001$). Similarly to the vancomycin elution profile, all CPP groups released amikacin at a concentration above the MIC for *P. aeruginosa* of 4-25 μg/mL[16,37] for 48 h. The control chitosan sponges initially released amikacin at a very high concentration for 3 h then minimal elution after (Figure 4B).

Antibiotic eluate activity

Vancomycin eluates from the paste samples remained active against *S. aureus* through 72 h. The eluates from sponges only remained active through 6 h. Amikacin eluates from the CPP groups were active against *P. aeruginosa* through 24 h, while eluates from the control sponge group were active for 3 h (Table 1). Vancomycin eluates from sponges exhibited similar ZOI diameters to 2A:3N CPP at 1 h ($P = 0.252$) but significantly smaller than CPP at all other time points ($P \leqslant 0.001$). Although vancomycin eluates from the CPP groups exhibited significantly lower ZOI diameters at 72 h ($P \leqslant 0.001$), activity of *S. aureus* was still inhibited. Amikacin eluates

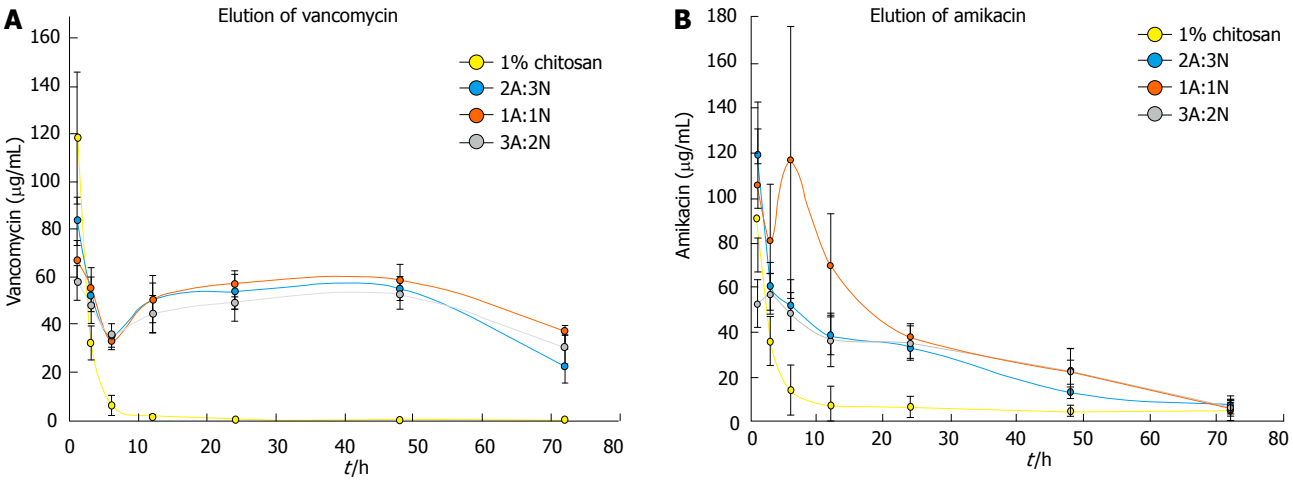

Figure 4 ***In vitro*** **release of antibiotics, vancomycin elution group (A), and Amikacin elution group (B), from 3A:2N, 1A:1N, and 2A:3N chitosan/polyethylene glycol paste variations and neutral 1% chitosan sponges over 72 h reported as the average ± standard deviation in concentration of antibiotic in sample retrieved.**

Table 1 Zone of inhibition of antibacterial activity results reported as the average ± standard deviation of the inhibited growth diameter using vancomycin antibiotic eluates against *Staphylococcus aureus* and amikacin antibiotic eluates against *Pseudomonas aeruginosa* from 3A:2N, 1A:1N, and 2A:3N chitosan/polyethylene glycol paste variations and neutral 1% chitosan sponges after 24 h of direct contact (*n* = 5)

Group	Antibiotic eluate time points (h)						
	1	3	6	12	24	48	72
Staphylococcus aureus zone of inhibition diameter (mm, *n* = 5) of vancomycin eluates							
3A:2N CPP	13 ± 1.1	11 ± 0.5[a]	10 ± 0.4[a]	12 ± 0.4	12 ± 0.4	12 ± 0.5	10 ± 0.8
1A:1N CPP	13 ± 0.5	13 ± 1.1	11 ± 0.0[a]	12 ± 0.4	11 ± 0.4[a]	13 ± 0.4	10 ± 0.8
2A:3N CPP	12 ± 0.4	11 ± 1.1	11 ± 0.5	11 ± 0.5	11 ± 0.5	12 ± 0.0	8 ± 0.9
Neut 1% CS	12 ± 0.7[c]	7 ± 0.5	1 ± 3.1	0	0	0	0
Pseudomonas aeruginosa zone of inhibition diameter (mm, *n* = 5) of amikacin eluates							
3A:2N CPP	10 ± 0.9	9 ± 2.3	10 ± 2.2	8 ± 1.5	8 ± 1.8	2 ± 3.8	0
1A:1N CPP	13 ± 2.2	10 ± 2.1	9 ± 1.1[a]	5 ± 3.2[a]	4 ± 3.8[a]	0	0
2A:3N CPP	11 ± 1.6	9 ± 1.3	8 ± 0.7[a]	9 ± 1.6	5 ± 3.2[a]	0	0
Neut 1% CS	10 ± 1.9[c]	5 ± 3.2	0	0	0	0	0

[a]$P < 0.05$ *vs* hour 1 value; [c]$P < 0.05$ *vs* all other time points.

from sponges also displayed similar ZOI diameters to the CPP groups at 1 h ($P \geqslant 0.288$), but the diameters quickly decreased to minimal levels by 6 h. All CPP sample eluates exhibited a significantly lower diameter at 48 and 72 h ($P \leqslant 0.001$), with only 3A:2N remaining active against *P. aeruginosa* through 48 h.

In vivo functional model

CPP and sponges proved effective in preventing *S. aureus* from contaminating implanted catheters. Vancomycin-loaded CPP resulted in 100% clearance rate of bacterial contamination on the catheters, while vancomycin-loaded sponges cleared bacteria from seven of eight catheters (88%) (Figure 5A). Additionally, PBS-only paste samples were ineffective in preventing bacterial contamination in all catheters; containing CFU levels between 10^3 and 10^4 ($P < 0.001$) (Figure 5B).

Injectability

Average ejection forces for all CPP variations were less than or around 150N, and easily injectable with a handheld repeater pipette (Figure 6). It can be concluded the ratio of acidic to neutral components of the CPP may lead to a significant difference in the ejection force. It can also be concluded that acidity of paste components is inversely related to ejection force.

Adhesion

Adhesion tests illustrated that all variations of CPP and the control chitosan sponges were capable of adhering to both soft and hard tissue long enough to allow proper wound closure and prevent the paste from moving in order to elute antibiotics at the intended location. The completely acidic chitosan paste proved incapable of adhering to either type of tissue for a significant amount

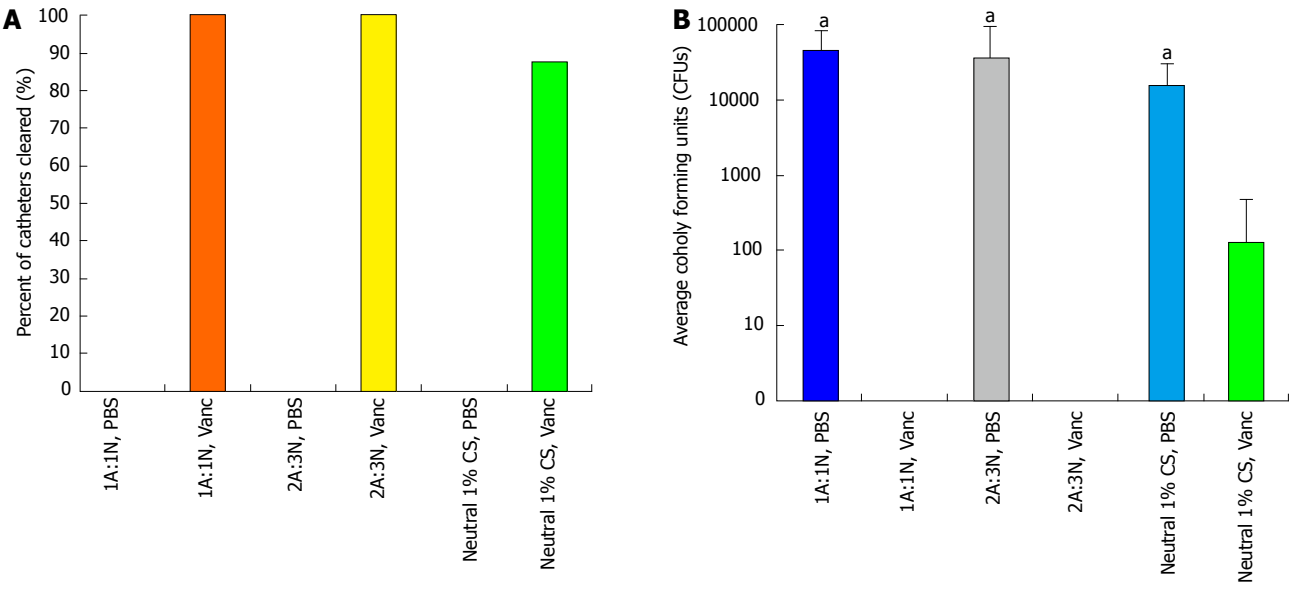

Figure 5 Percentage of catheters cleared (A) and average Staphylococcus aureus colony (B) forming units per catheter for those retrieved from mice treated with 1A:1N and 2A:3N chitosan/polyethylene glycol paste variations and neutral 1% chitosan sponges over 48 h (*n* = 8, 2 catheters per mouse). All samples were loaded with either PBS alone or 4 mg/mL of vancomycin. [a]*P* < 0.05 *vs* all vancomycin samples. PBS: Phosphate buffered saline; CPP: Chitosan/polyethylene glycol paste.

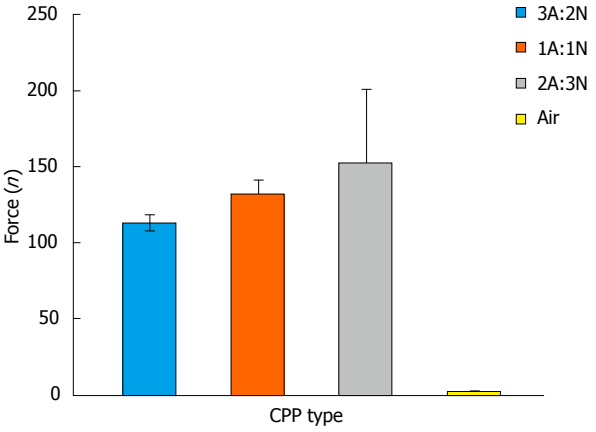

Figure 6 Ejection results represented as the average ± standard deviation of force required to eject air and 3A:2N, 1A:1N, and 2A:3N chitosan/polyethylene glycol paste variations from a syringe (*n* = 3). CPP: Chitosan/polyethylene glycol paste.

of time.

DISCUSSION

Complex musculoskeletal wound infections, especially those complicated by biofilm-forming bacteria, increase treatment duration, surgeries, total cost, and patient morbidity[1,6,8,9]. Systemic antibiotic therapy efficacy is substantially reduced at musculoskeletal wound sites with reduced bacteria-clearing ability. Delivery of very high dosages of antibiotics are effective but there is potential of causing adverse effects[4,5]. The clinical need for local drug delivery devices that effectively eliminate contaminating bacteria while also being biocompatible, biodegradable, and capable of antibiotic application at the time of surgical intervention resulted in chitosan and chitosan/PEG sponge development[16-20]. Paste development from these sponges was a modification designed to address device migration and wound coverage while maintaining the beneficial degradability, biocompatibility, and drug elution qualities[19,26]. The research evaluated whether chitosan/PEG blended sponges fabricated into an injectable form could result in a local antibiotic delivery device that will satisfy clinical needs. The preliminary study evaluates if chitosan/PEG in a paste form can perform as an effective localized delivery device of antibiotics with needed biocompatibility, degradability, antibiotic elution, and the functional *in vivo* antibacterial properties.

There are limitations of this preliminary study that should be noted. Primarily, the *in vivo* animal study of antibiotic activity did not investigate CPP loaded with amikacin against the bacterial contamination prevention of *P. aeruginosa* or polymicrobial infections. Second, the timeline of the *in vitro* drug delivery qualities of the CPP (*i.e.*, degradation, antibiotic elution, biocompatibility) could be lengthened, which would further support the biocompatibility and degradation qualities of CPP. Third, the interaction of CPP with complex musculoskeletal wounds or orthopedic hardware is needed for a more accurate representation of a large, complex, and infected clinical musculoskeletal wound. The results of the *in vitro* and screening model for biofilm formation warrant further investigation into local delivery of antibiotics adjunctive to systemic delivery to prevent infection, especially in at-risk patients. In past studies using the murine catheter model, antibiotics administered systemically were only partially effective in preventing biofilm formation[35]. Therefore, to avoid confounding effects and also reduce

animal number, systemic delivery of antibiotics was avoided in the present functional model. Since a portion of the CPP variations are acidic, degradation of the acidic components will inevitably lower the pH of the surrounding environment. There is potential for the lowered pH to affect the efficacy of vancomycin and amikacin. However, the *in vitro* antibiotic activity tests revealed there was not a significant effect on the efficacy of the antibiotics in question, suggesting that CPP has the potential to prevent and treat polymicrobial infections in musculoskeletal injuries.

Studies investigating local antibiotic delivery in gels and paste, other than chitosan derivatives, have reported similar results. Overstreet *et al*[38] investigated the local delivery of gentamicin from a hydrogel composed of polyN-isopropylacrylamide-co-dimethyl-γ-butyrolactone acrylate-co-Jeffamine® M-1000 acrylamide (PNDJ). It was discovered the gentamicin loaded PNDJ hydrogel was capable of releasing effective levels of gentamicin over 7 d and preventing infection in an *in vivo* model for up to 4 wk. However, there was no significant *in vivo* degradation, meaning the hydrogel may have to be surgically removed after a period of time. Additionally, renal dysfunction was observed at higher doses of applied gentamicin[38]. Pritchard *et al*[39] investigated the efficacy of a silk-fibroin based hydrogel as a local antibiotic delivery device, specifically, for use in avascular wounds. *In vitro* elution profiles of silk hydrogels loaded with ampicillin and penicillin produced eluates active against *S. aureus* for up to 72 h and 48 h, respectively. The *in vivo* efficacy of the ampicillin loaded silk hydrogel was tested on a *S. aureus* infected murine model over 24 h. Results indicated effective infection prevention from the silk hydrogel compared to the control. However, there was no significant difference from local injection of ampicillin alone due to the short test time period. Additionally, the study did not directly test the degradation qualities of the silk hydrogel. It was also noted antibiotics with low water solubility were difficult to conventionally load onto the silk hydrogel[39].

Studies have been published highlighting the drug delivery qualities of chitosan/PEG blended biomaterial. One study investigated a thermosensitive chitosan/PEG hydrogel drug delivery device administered as a nasal spray[40]; another developed an injectable chitosan-PEG-tyramine hydrogel to be used as tissue adhesives for wound healing[41]; while others have explored injectable PEG-grafted-chitosan thermosensitive hydrogels for sustained protein release[42] and drug delivery[43]. Many of the researched studies did not explicitly examine injectability. The devices were characterized as *in situ* forming hydrogels injectable from a needle, but the CPP would be injected through a larger cannula device due to higher viscosity. A study found a hydrogel made from tyramine modified polyethylene glycol grafted onto the backbone of a chitosan molecule exhibited similar adhesion to porcine skins as CPP did to porcine vertebral tissue[41]. Karn *et al*[44] determined the cationic nature of chitosan at pH below 6.5-7 is responsible for its mucoadhesion, the strong charge attraction between chitosan and mucins, negatively charged glycosylated proteins highly concentrated on tissue surfaces such as pulmonary, corneal, intestinal, and gastric mucosal tissues. Sogias *et al*[45] reported the mucoadhesive qualities of chitosan can be linked to the electrostatic attraction of the primary amino groups to the negatively charged mucins, as well as the attractive forces caused by hydrogen bonding between the chitosan and the mucosal membranes. Chitosan can adhere to a musculoskeletal wound *via* negatively charged molecules in the tissue such as the proteoglycans in connective tissue.

There are studies addressing degradation of chitosan/PEG hydrogel. Parker *et al*[18] developed neutral chitosan/PEG sponges for drug delivery utilizing 6000 g/mol PEG. *In vitro* degradation studies reported 55%-75% sponge remaining after 10 d of mass-based degradation, significantly higher than CPP with 0%-24% remaining, and 99%-100% of their neutral chitosan sponge remaining after 10 d, comparable to the neutral sponge (100% remaining). Acidic variations of chitosan, compared to neutralized, contain a protonated amine group. In aqueous solution, the proton dissociates from the amine group to join the water molecules; facilitating the solubilization of the chitosan molecules. Therefore, the lower degradation rates of neutral chitosan, compared to acidic, can be attributed to the lack of protonation with the surrounding environment[46]. Based on previous *in vivo* results[18,47] and the rapid *in vitro* degradation experienced by CPP, rapid degradation of CPP should be expected *in vivo*. Sample degradation was not measured in the *in vivo* studies due to the short time course of the subcutaneous catheter infection model, but ongoing evaluations will characterize time course of *in vivo* degradation. In previous *in vitro* studies, multiple chitosan/PEG hydrogels were reported to be biocompatible without eliciting significant cytotoxicity[40,43,48] along with various chitosan hydrogels[47,49] and chitosan/PEG sponges[17,18]. Biocompatibility studies involving indirect exposure of CPP to cell culture models demonstrated similar cell viability to control sponges, comparable to results of other *in vitro* studies[40,43,48]. Based on previously reported *in vivo* biocompatibility for other chitosan/PEG devices, a minimal[40,41,47] to moderate[18,43] inflammatory response is expected, which is comparable to other implanted devices[50].

Other chitosan/PEG hydrogels were successful in releasing bovine serum albumin and cyclosporin A[42,48]. Although *in vitro* release or activity of antibiotics was not investigated in the studies, the release profiles characterized by PEG content are still relevant. Bhattarai *et al*[42] concluded that a hydrogel with a PEG weight percentage of at least 40% demonstrated a burst release of albumin within the first 5 h followed by a steady linear release for approximately 70 h. Tsao *et al*[48] reported the grafting of a methoxy-poly(ethylene glycol) onto the hydrophobic chitosan results in a hydrophilic composite material. The hydrophobic-hydrophilic balance among the components instills a multi-stimuli-responsive property into the hydrogel. The degradation of the hydrogel can

be controlled by stimuli involving salt concentration, solute concentration, temperature, and pH. Jiang *et al*[43] investigated the release of cyclosporin A from a PEG/chitosan hydrogel; reporting an absence of any significant burst effect and a sustained release at an effective concentration for three weeks *in vitro* and more than five weeks *in vivo*. Parker *et al*[17] reported an initial burst release of vancomycin from neutral chitosan/PEG and chitosan sponges after 1 h, with significant decrease in eluted antibiotic thereafter. Noel *et al*[16] investigated *in vitro* release of vancomycin from chitosan sponges made with lactic and acetic acid, showing an initial burst release after 1 h with 98% of the loaded vancomycin released after 72 h. The chitosan sponges used as controls in the present study experienced a similar initial burst release of vancomycin after 1 h with a sharp decrease to minimal levels thereafter. The CPP samples displayed a more extended release through 72 h, eluting 35% of the total loaded vancomycin after 72 h. While vancomycin concentrations measured by Parker *et al*[17] from chitosan/PEG blend sponges were above the MIC through 24 h, eluates utilized for turbidity testing only remained active against *S. aureus* through 6 h. Noel *et al*[16] found levels of vancomycin remained above the MIC and eluates remained active through 72 h, similar to findings with CPP. Noel *et al*[16] also reported amikacin eluates from chitosan sponges remaining active through 48 h while amikacin eluates from CPP remained active through 24 h. The PEG/chitosan sponges may not absorb as much solution as the sponges made of chitosan alone. The studies by Parker *et al*[17] and Noel *et al*[16] did not report the amount of antibiotics absorbed by the sponges while soaking in excess solution; highlighting the limitations of varying elution protocols as well as the need for confirmation of *in vitro* antibiotic elution results in functional animal models. The difference between the elution profiles of vancomycin compared to amikacin within chitosan drug delivery systems may be due to differences in antibiotic structure or charge. It is possible that vancomycin may associate with the chitosan/PEG leading to a more extended release.

Other chitosan/PEG hydrogels were successful in *in vivo* delivery of insulin[40] and cyclosporin A at effective levels[43], but none tested the *in vivo* activity of these therapeutic devices. Our control sponge cleared bacteria from 87.5% of catheters, while Parker *et al*[17] only reported a 50% clearance rate; however, the number of remaining viable CFUs in both studies was reduced compared to controls. All groups of vancomycin-loaded CPP displayed 100% bacterial clearance of catheter. Longer durations of study are necessary to determine the long-term infection prevention efficacy, as although bacterial counts may be reduced by local delivery of antibiotics, remaining viable bacteria could rebound and lead to infection.

In conclusion, CPP is an injectable, bioadhesive, biodegradable, and biocompatible material with potential to allow variable antibiotic loading at the time of surgical intervention, and active, local antibiotic release to prevent bacterial contamination. *In vitro* studies confirm CPP is more readily degradable, and displays similar cytocompatibility compared to other chitosan and chitosan/PEG drug delivery devices. CPP also demonstrated a uniform and extended antibiotic release over the course of 72 h. Antibiotic loaded CPP proved to be more effective than chitosan sponges in preventing biofilm formation in a murine catheter model. CPP, unlike other chitosan/PEG hydrogels that form *in situ*[40,43], must be injected through a larger cannula device, and exhibited adhesion to representative musculoskeletal tissues. The CPP formulations were found to have comparable antimicrobial effects to the control chitosan sponge devices and also infection prevention devices studied in previous studies. Future studies will modify the formulation to improve material properties, such as injectability, and to further evaluate the drug delivery devices in expanded preclinical models of complex extremity trauma, both with and without implanted hardware.

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COMMENTS

Background

Complex musculoskeletal wounds are highly susceptible to polymicrobial infections; severely impairing the healing process and threatening patient health. Systemic delivery of antibiotics can be ineffective in preventing bacterial infection due to the lack of vascularity surrounding a severe complex musculoskeletal wounds. Therefore, a method of locally delivering antibiotics to the wound could prove effective in the prevention of a bacterial infection. Utilizing previously developed chitosan sponges, a polyethylene glycol-chitosan blended paste was investigated as a local delivery device. Chitosan/PEG paste (CPP) was evaluated as an injectable, adhesive device to determine biodegradability, biocompatibility, antibiotic elution and activity, and *in vivo* efficacy.

Research frontiers

Chitosan is being researched as a drug delivery device because it is biocompatible, degradable by enzymes found in the body such as lysozyme, and adhesive to mucins on the surface of visceral tissues. It can be loaded with different types of drugs and applied directly to a wound as a paste, hydrogel, or wound dressing to locally deliver the designated drugs to the surrounding injured tissue. The diversity of drugs chitosan is capable of delivering make it a versatile component to be used in drug delivery devices. The addition of polyethylene glycol to chitosan increases the rate of degradation and also improves the drug releasing ability of the drug delivery device.

Innovations and breakthroughs

The local delivery of antibiotics provides an effective concentration of infection preventing molecules sustained at a more steady concentration over an extended amount of time compared to the peaks and troughs associated systemic delivery. The decrease in bioavailability of antibiotics during breaks

from systemic delivery leaves the wound vulnerable to a bacterial infection. The bacterial population can become resistant to a particular antibiotic if it is being exposed to levels below the minimum inhibitory concentration. Antibiotic loaded CPP has shown to be capable of locally releasing antibiotics while maintaining biocompatibility and being completely biodegradable; qualities that are advantages compared to common methods of local drug delivery such as calcium sulfate and polymethylmethacrylate beads.

Applications

In vitro test results suggest CPP is capable of being loaded with amikacin and successfully inhibiting the growth of *Pseudomonas aeruginosa* (*P. aeruginosa*), a representative Gram negative bacteria. Both *in vitro* studies and *in vivo* functional models proved the bacterial prevention efficacy of vancomycin-loaded CPP against *Staphylococcus aureus* (*S. aureus*), a representative Gram positive bacteria. Therefore, the CPP is being researched as an adjunctive method of bacterial contamination prevention in wounds; particularly in complex musculoskeletal wounds that are inherently at a higher risk of becoming infected.

Terminology

Chitosan is the deacetylated form chitin, the most abundant naturally occurring amino-polysaccharide found in arthropod exoskeletons. Polyethylene glycol is a hydrophilic polyether compound; blended with chitosan to increase the dissociation rate of the paste in an aqueous environment. Biofilm forms when bacteria or other microorganisms attach to a surface, such as a metal implant or damaged tissue, and causes infection that is highly resistant to antibiotics or immune system clearance. *S. aureus* and *P. aeruginosa* are among the common pathogens that cause infections in the musculoskeletal system with the formation of biofilm.

Peer-review

The paper is of interest and well-organized. The aims and objectives are clear, the hypothesis is sound and the data are well presented.

REFERENCES

1 **Andersson GB**, Bouchard J, Bozic KJ. The burden of musculoskeletal diseases in the United States: Prevalence, societal and economic cost. Rosemont, IL: American Academy of Orthopaedic Surgeons, 2008
2 **Bernstein J**. Musculoskeletal Medicine. Rosemont, IL: American Academy of Orthopaedic Surgeons, 2003
3 **Park H**, Copeland C, Henry S, Barbul A. Complex wounds and their management. *Surg Clin North Am* 2010; **90**: 1181-1194 [PMID: 21074035 DOI: 10.1016/j.suc.2010.08.001]
4 **Hanssen AD**. Local antibiotic delivery vehicles in the treatment of musculoskeletal infection. *Clin Orthop Relat Res* 2005; **(437)**: 91-96 [PMID: 16056032]
5 **Skinner HB**. Current diagnosis and treatment in orthopedics. New York: Lange Medical Books/McGraw-Hill Medical Pub. Div., 2006
6 **Esterhai JL**, Gristina AG, Poss R. Musculoskeletal infection. Park Ridge, IL: American Academy of Orthopaedic Surgeons, 1992
7 **Zalavras CG**, Patzakis MJ, Holtom PD, Sherman R. Management of open fractures. *Infect Dis Clin North Am* 2005; **19**: 915-929 [PMID: 16297739 DOI: 10.1016/j.idc.2005.08.001]
8 **Davis JS**. Management of bone and joint infections due to Staphylococcus aureus. *Intern Med J* 2005; **35** Suppl 2: S79-S96 [PMID: 16271064 DOI: 10.1111/j.1444-0903.2005.00982.x]
9 **Brady RA**, Leid JG, Calhoun JH, Costerton JW, Shirtliff ME. Osteomyelitis and the role of biofilms in chronic infection. *FEMS Immunol Med Microbiol* 2008; **52**: 13-22 [PMID: 18081847 DOI: 10.1111/j.1574-695X.2007.00357.x]
10 **Diefenbeck M**, Mückley T, Hofmann GO. Prophylaxis and treatment of implant-related infections by local application of antibiotics. *Injury* 2006; **37** Suppl 2: S95-104 [PMID: 16651078 DOI: 10.1016/j.injury.2006.04.015]
11 **Mlynek KD**, Callahan MT, Shimkevitch AV, Farmer JT, Endres JL, Marchand M, Bayles KW, Horswill AR, Kaplan JB. Effects of Low-Dose Amoxicillin on Staphylococcus aureus USA300 Biofilms. *Antimicrob Agents Chemother* 2016; **60**: 2639-2651 [PMID: 26856828 DOI: 10.1128/AAC.02070-15]
12 **Gitelis S**, Brebach GT. The treatment of chronic osteomyelitis with a biodegradable antibiotic-impregnated implant. *J Orthop Surg* (Hong Kong) 2002; **10**: 53-60 [PMID: 12401922]
13 **McLaren AC**. Alternative materials to acrylic bone cement for delivery of depot antibiotics in orthopaedic infections. *Clin Orthop Relat Res* 2004; **(427)**: 101-106 [PMID: 15552144]
14 **Robinson D**, Alk D, Sandbank J, Farber R, Halperin N. Inflammatory reactions associated with a calcium sulfate bone substitute. *Ann Transplant* 1999; **4**: 91-97 [PMID: 10853791]
15 **Bronzino JD**. The biomedical engineering handbook. Boca Raton: CRC Press, 1995
16 **Noel SP**, Courtney HS, Bumgardner JD, Haggard WO. Chitosan sponges to locally deliver amikacin and vancomycin: a pilot in vitro evaluation. *Clin Orthop Relat Res* 2010; **468**: 2074-2080 [PMID: 20352389 DOI: 10.1007/s11999-010-1324-6]
17 **Parker AC**, Beenken KE, Jennings JA, Hittle L, Shirtliff ME, Bumgardner JD, Smeltzer MS, Haggard WO. Characterization of local delivery with amphotericin B and vancomycin from modified chitosan sponges and functional biofilm prevention evaluation. *J Orthop Res* 2015; **33**: 439-447 [PMID: 25408519 DOI: 10.1002/jor.22760]
18 **Parker AC**, Rhodes C, Jennings JA, Hittle L, Shirtliff M, Bumgardner JD, Haggard WO. Preliminary evaluation of local drug delivery of amphotericin B and in vivo degradation of chitosan and polyethylene glycol blended sponges. *J Biomed Mater Res B Appl Biomater* 2016; **104**: 78-87 [PMID: 25615516 DOI: 10.1002/jbm.b.33356]
19 **Stinner DJ**, Noel SP, Haggard WO, Watson JT, Wenke JC. Local antibiotic delivery using tailorable chitosan sponges: the future of infection control? *J Orthop Trauma* 2010; **24**: 592-597 [PMID: 20736801 DOI: 10.1097/BOT.0b013e3181ed296c]
20 **Parker AC**, Jennings JA, Bumgardner JD, Courtney HS, Lindner E, Haggard WO. Preliminary investigation of crosslinked chitosan sponges for tailorable drug delivery and infection control. *J Biomed Mater Res B Appl Biomater* 2013; **101**: 110-123 [PMID: 22997172 DOI: 10.1002/jbm.b.32822]
21 **Dash M**, Chiellini F, Ottenbrite RM, Chiellini E. Chitosan - A versatile semi-synthetic polymer in biomedical applications. *Prog Polym Sci* 2011; **36**: 981-1014 [DOI: 10.1016/j.progpolymsci.2011.02.001]
22 **Noel SP**, Courtney H, Bumgardner JD, Haggard WO. Chitosan films: a potential local drug delivery system for antibiotics. *Clin Orthop Relat Res* 2008; **466**: 1377-1382 [PMID: 18421540 DOI: 10.1007/s11999-008-0228-1]
23 **Smith JK**, Moshref AR, Jennings JA, Courtney HS, Haggard WO. Chitosan sponges for local synergistic infection therapy: a pilot study. *Clin Orthop Relat Res* 2013; **471**: 3158-3164 [PMID: 23604649 DOI: 10.1007/s11999-013-2988-5]
24 **Phaechamud T**, Charoenteeraboon J. Antibacterial activity and drug release of chitosan sponge containing doxycycline hyclate. *AAPS PharmSciTech* 2008; **9**: 829-835 [PMID: 18626774 DOI: 10.1208/s12249-008-9117-x]
25 **Wedmore I**, McManus JG, Pusateri AE, Holcomb JB. A special report on the chitosan-based hemostatic dressing: experience in current combat operations. *J Trauma* 2006; **60**: 655-658 [PMID: 16531872 DOI: 10.1097/01.ta.0000199392.91772.44]
26 **Jones LC**, Frondoza C, Hungerford DS. Effect of PMMA particles and movement on an implant interface in a canine model. *J Bone Joint Surg Br* 2001; **83**: 448-458 [PMID: 11341436]
27 **Vårum KM**, Myhr MM, Hjerde RJ, Smidsrød O. In vitro degradation rates of partially N-acetylated chitosans in human serum. *Carbohydr Res* 1997; **299**: 99-101 [PMID: 9129298]
28 **Owens BD**, White DW, Wenke JC. Comparison of irrigation solutions and devices in a contaminated musculoskeletal wound survival model. *J Bone Joint Surg Am* 2009; **91**: 92-98 [PMID: 19122083 DOI: 10.2106/JBJS.G.01566]
29 **Sattur AP**, Lee JH, Song KB, Panda T, Kim CH, Rhee SK, Gokul B.

Analytical techniques for vancomycin - A review. *Biotechnol Bioproc E* 2000; **5**: 153-158 [DOI: 10.1007/BF02936586]
30 **McClain JB**, Bongiovanni R, Brown S. Vancomycin quantitation by high-performance liquid chromatography in human serum. *J Chromatogr* 1982; **231**: 463-466 [PMID: 7130325]
31 **Omar MA**, Ahmed HM, Hammad MA, Derayea SM. Validated spectrofluorimetric method for determination of selected aminoglycosides. *Spectrochim Acta A Mol Biomol Spectrosc* 2015; **135**: 472-478 [PMID: 25113735 DOI: 10.1016/j.saa.2014.07.020]
32 **Ericsson H**, Tunevall G, Wickman K. The paper disc method for determination of bacterial sensitivity to antibiotics. Relationship between the diameter of the zone of inhibition and the minimum inhibitory concentration. *Scand J Clin Lab Invest* 1960; **12**: 414-422 [PMID: 13697132 DOI: 10.3109/00365516009065406]
33 **Costerton JW**, Lewandowski Z, Caldwell DE, Korber DR, Lappin-Scott HM. Microbial biofilms. *Annu Rev Microbiol* 1995; **49**: 711-745 [PMID: 8561477 DOI: 10.1146/annurev.mi.49.100195.003431]
34 **Beenken KE**, Dunman PM, McAleese F, Macapagal D, Murphy E, Projan SJ, Blevins JS, Smeltzer MS. Global gene expression in Staphylococcus aureus biofilms. *J Bacteriol* 2004; **186**: 4665-4684 [PMID: 15231800 DOI: 10.1128/JB.186.14.4665-4684.2004]
35 **Weiss EC**, Zielinska A, Beenken KE, Spencer HJ, Daily SJ, Smeltzer MS. Impact of sarA on daptomycin susceptibility of Staphylococcus aureus biofilms in vivo. *Antimicrob Agents Chemother* 2009; **53**: 4096-4102 [PMID: 19651914 DOI: 10.1128/AAC.00484-09]
36 **van Hal SJ**, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in Staphylococcus aureus infections: a systematic review and meta-analysis. *Clin Infect Dis* 2012; **54**: 755-771 [PMID: 22302374 DOI: 10.1093/cid/cir935]
37 **Nakamura A**, Hosoda M, Kato T, Yamada Y, Itoh M, Kanazawa K, Nouda H. Combined effects of meropenem and aminoglycosides on Pseudomonas aeruginosa in vitro. *J Antimicrob Chemother* 2000; **46**: 901-904 [PMID: 11102407]
38 **Overstreet D**, McLaren A, Calara F, Vernon B, McLemore R. Local gentamicin delivery from resorbable viscous hydrogels is therapeutically effective. *Clin Orthop Relat Res* 2015; **473**: 337-347 [PMID: 25227556 DOI: 10.1007/s11999-014-3935-9]
39 **Pritchard EM**, Valentin T, Panilaitis B, Omenetto F, Kaplan DL. Antibiotic-Releasing Silk Biomaterials for Infection Prevention and Treatment. *Adv Funct Mater* 2013; **23**: 854-861 [PMID: 23483738 DOI: 10.1002/adfm.201201636]
40 **Wu J**, Wei W, Wang LY, Su ZG, Ma GH. A thermosensitive hydrogel based on quaternized chitosan and poly(ethylene glycol) for nasal drug delivery system. *Biomaterials* 2007; **28**: 2220-2232 [PMID: 17291582]
41 **Lih E**, Lee JS, Park KM, Park KD. Rapidly curable chitosan-PEG hydrogels as tissue adhesives for hemostasis and wound healing. *Acta Biomater* 2012; **8**: 3261-3269 [PMID: 22617740 DOI: 10.1016/j.actbio.2012.05.001]
42 **Bhattarai N**, Ramay HR, Gunn J, Matsen FA, Zhang M. PEG-grafted chitosan as an injectable thermosensitive hydrogel for sustained protein release. *J Control Release* 2005; **103**: 609-624 [PMID: 15820408 DOI: 10.1016/j.jconrel.2004.12.019]
43 **Jiang G**, Sun J, Ding F. PEG-g-chitosan thermosensitive hydrogel for implant drug delivery: cytotoxicity, in vivo degradation and drug release. *J Biomater Sci Polym Ed* 2014; **25**: 241-256 [PMID: 24160458 DOI: 10.1080/09205063.2013.851542]
44 **Karn PR**, Vanić Z, Pepić I, Skalko-Basnet N. Mucoadhesive liposomal delivery systems: the choice of coating material. *Drug Dev Ind Pharm* 2011; **37**: 482-488 [PMID: 20961263 DOI: 10.3109/03639045.2010.523425]
45 **Sogias IA**, Williams AC, Khutoryanskiy VV. Why is chitosan mucoadhesive? *Biomacromolecules* 2008; **9**: 1837-1842 [PMID: 18540644 DOI: 10.1021/bm800276d]
46 **Rinaudo M**. Chitin and chitosan: Properties and applications. *Prog Polym Sci* 2006; **31**: 603-632 [DOI: 10.1016/j.progpolymsci.2006.06.001]
47 **De Souza R**, Zahedi P, Allen CJ, Piquette-Miller M. Biocompatibility of injectable chitosan-phospholipid implant systems. *Biomaterials* 2009; **30**: 3818-3824 [PMID: 19394688 DOI: 10.1016/j.biomaterials.2009.04.003]
48 **Tsao CT**, Hsiao MH, Zhang MY, Levengood SL, Zhang M. Chitosan-PEG hydrogel with sol-gel transition triggerable by multiple external stimuli. *Macromol Rapid Commun* 2015; **36**: 332-338 [PMID: 25522283 DOI: 10.1002/marc.201400586]
49 **Tan H**, Chu CR, Payne KA, Marra KG. Injectable in situ forming biodegradable chitosan-hyaluronic acid based hydrogels for cartilage tissue engineering. *Biomaterials* 2009; **30**: 2499-2506 [PMID: 19167750 DOI: 10.1016/j.biomaterials.2008.12.080]
50 **Anderson JM**. Inflammatory response to implants. *ASAIO Trans* 1988; **34**: 101-107 [PMID: 3285869]

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ORIGINAL ARTICLE

Basic Study

Neuromuscular trunk activation patterns in back pain patients during one-handed lifting

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Author contributions: Mueller J, Mayer F and Mueller S designed the research; Mueller J, Engel T and Kopinski S assessed and analyzed the data; Mueller J, Mayer F and Mueller S interpreted the results; Mueller J and Mueller S wrote the paper; all authors revised the paper.

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Abstract

AIM

To analyze neuromuscular activity patterns of the trunk in healthy controls (H) and back pain patients (BPP) during one-handed lifting of light to heavy loads.

METHODS

After assessment of back pain (graded chronic pain scale according to von Korff) all subjects (n = 43) performed a warm-up (treadmill walking). Next, subjects were instructed to lift 3 × a 20 kg weight placed in front of them (with both hand) onto a table (height: 0.75 m). Subsequently, all subjects lifted with one hand (left-side, 3 repetitions) a weight of 1 kg (light), 10 kg (middle) and 20 kg (heavy) in random order from the ground up onto the table left of them. Trunk muscle activity was assessed with a 12-lead EMG (6 ventral/6 dorsal muscles; 4000 Hz). EMG-RMS (%) was averaged over the 3 repetitions and analyzed for the whole one-handed lifting cycle, then normalized to RMS of the two-handed lifting. Additionally, the mean (normalized) EMG-RMS of four trunk areas [right/left ventral area (VR/VL); right/left dorsal area (DR/DL)] was calculated. Data were analyzed descriptively (mean ± SD) followed by student's t-test comparing H and BPP (α = 0.05). With respect to the unequal distribution of subjects in H and BPP, a matched-group analysis was conducted. Seven healthy controls were gender- and age-

matched (group $H_{matched}$) to the 7 BPP. In addition, task failure was calculated and compared between H/$H_{matched}$ *vs* BPP using χ^2.

RESULTS

Seven subjects (3m/4f; 32 ± 7 years; 171 ± 7 cm; 65 ± 11 kg) were assigned to BPP (pain grade $\geqslant$ 2) and 36 (13m/23f; 28 ± 8 years; 174 ± 10 cm; 71 ± 12 kg) to H (pain grade $\leqslant$ 1). H and BPP did not differ significantly in anthropometrics ($P > 0.05$). All subjects were able to lift the light and middle loads, but 57% of BPP and 22% of H were not able to lift the heavy load (all women). χ^2 analysis revealed statistically significant differences in task failure between H *vs* BPP ($P = 0.03$). EMG-RMS ranged from 33% ± 10%/30% ± 9% (DL, 1 kg) to 356% ± 148%/283% ± 80% (VR, 20 kg) in H/BPP with no statistical difference between groups regardless of load ($P > 0.05$). However, the EMG-RMS of the VR was greatest in all lifting tasks for both groups and increased with heavier loads.

CONCLUSION

Heavier loading leads to an increase (2- to 3-fold) in trunk muscle activity with comparable patterns. Heavy loading (20 kg) leads to task failure, especially in women with back pain.

Key words: Lifting; Core; Trunk; EMG; MISPEX

Core tip: The aim of this study was to analyze neuromuscular activity patterns of the trunk in healthy controls (H) and back pain patients (BPP) during one-handed lifting of light to heavy loads. Neuromuscular trunk compensation strategies for expected loading with different weights did not differ between BPP and H, and showed a similar muscular activation pattern with the highest activity found in the contralateral abdominal muscles (VR). Heavier loading leads to an increase (2- to 3-fold) in trunk muscle activity with comparable patterns between groups. Heavy loading (20 kg) may lead to task failure, especially in women with back pain.

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INTRODUCTION

Back pain places a large burden on the societies and healthcare systems of western industrialized nations with high direct (*e.g.*, therapy measures) and indirect costs (*e.g.*, loss of working hours)[1-3]. Hence, research to develop approaches for the prevention and/or rehabilitation of back pain is extremely interesting and could have a very beneficial effect. Consequently, the investigation of differences in trunk function between people with and without back pain is of primary interest in order to define adequate therapy and/or prevention strategies.

In etiology, repetitive micro-trauma, as well as insufficiency of the muscle-tendon complex based on inadequate postural and neuromuscular control, reduced maximum trunk strength capacity and trunk muscle fatigue during dynamic loading, have been supposed[4,5]. Thus, an altered neuromuscular activity of the trunk muscles is already evident in back pain patients (BPP)[6-12]. Longer response times[6,12], altered recruiting or activation patterns[8,11,12], extended activation times[7] and increased co-contractions[10,11] have been described in affected patients[13]. However, these differences are only valid in situations where the load is applied rapidly or suddenly either directly to the trunk or to the upper/lower limbs. Nevertheless, these situations are often limited in representing daily life activities which is highly comprised of lifting tasks. Since lifting tasks are omnipresent in daily life and correspond with an automated movement pattern, they seem expedient for the comparison of trunk muscle activity pattern between H and BPP.

In terms of lifting tasks, McGill *et al*[14] investigated the influence of different loads (5, 10, 15, 20, 30 kg) and carrying conditions (one-handed *vs* two-handed) on low back load. One-handed carrying led to greater low back loads compared to two-handed carrying of the same weight due to an increased shear stress on the spine. Therefore, one-handed lifting proposes a more challenging situation compared to two-handed lifting. Moreover, different loads might provoke different muscular activation patterns of the trunk and its regions as part of the compensation strategy of the trunk, even in healthy controls.

Nevertheless, it is ultimately unclear whether BPP suffer from altered trunk neuromuscular activity during expected, continuous loading, while lifting different loads. Therefore, the aim of this study is to analyze neuromuscular activity patterns of the trunk in healthy controls (H) and BPP during one-handed lifting with different loads. It is hypothesized that both healthy controls (H) and BPP will show increased trunk muscle activity with heavier loads, especially for muscles opposite the lifting hand. In addition, BPP might show increased activity and an altered activation pattern compared to healthy controls to compensate for pain. Consequently, this trunk muscle activation analysis could help define adequate therapy and/or prevention strategies for back pain.

MATERIALS AND METHODS

Subjects

Forty-eight subjects were initially recruited and explained the procedures by the study coordinator. Forty-three (16m/27f; 29 ± 7 years; 174 ± 10 cm; 70 ± 12 kg)

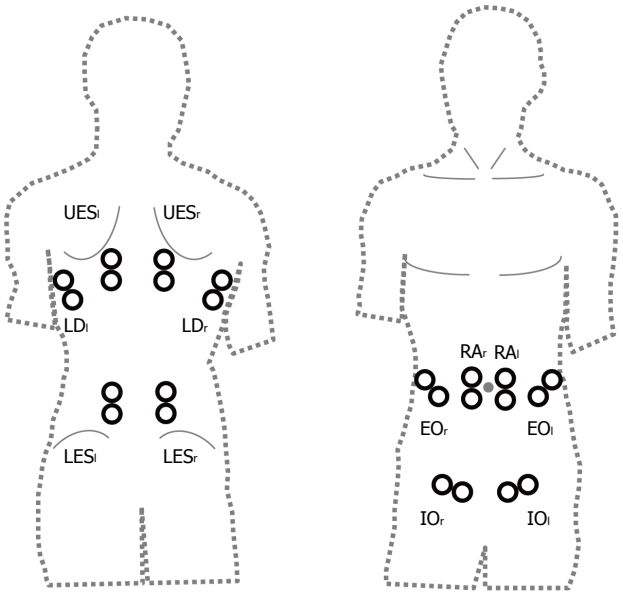

Figure 1 12-lead EMG trunk-setup. Single muscles: $RA^{ri/le}$: M. rec. abd. right/left; $EO_{ri/le}$: M. obl. ext. abd. right/left; $IO_{ri/le}$: M. obl. int. abd. right/left; $LD_{ri/le}$: M. latis. dorsi right/left; $UES_{ri/le}$: M. erec. spinae thoracic (T9) right/left; $LES_{ri/le}$: M. erec. spinae lumbar (L3) right/left.

subjects agreed to participate and formally gave written informed consent before voluntary participation. The University's Ethical Commission approved the study.

With respect to the unequal distribution of subjects included in H and BPP, an additional matched-group analysis was conducted. Therefore, an equal number of healthy controls were gender-, age- and anthropometrically matched (group $H_{matched}$) to the number of BPP.

Measurement protocol

Initially, all participants answered an online-based (Pro WebDB, Germany) version of a back-pain questionnaire (von Korff) determining the presence of back pain[15]. Next, subjects were prepared for electromyographic measurements of the trunk. Before the lifting tasks, every subject performed a 5-min warm-up (treadmill walking). Subsequently, the lifting protocol started with a two-handed task, used as reference for EMG-normalization. Therefore, subjects lifted a 20 kg weight from the ground up and onto a table (height: 0.75 m) being positioned in front of them three times. Afterwards, all subject performed exclusively one-sided left-handed liftings. In random order, three times each, subjects lifted a light (1 kg), a middle (10 kg) and a heavy (20 kg) load with the left hand from the ground up and onto a table (height: 0.75 m). The table was positioned on the left side of the subjects. Subjects began all lifting tasks in an identical neutral position (hip-width bipedal upright stance) and were instructed to lift the load with a self-selected moderate speed, starting with slight bending of the knees and the trunk. Each lifting task was first demonstrated by the examiner, then subjects performed one test trial before starting the measurement.

Back pain questionnaire

The back pain questionnaire consisted of 7 items, including pain intensity and disability (acute and last 3 mo)[15]. Six out of seven items are analyzed by a numeric rating scale ranging from 0 (no pain/disability) to 10 (highest pain/disability). Based on the grading score of the questionnaire, subjects were assigned to the healthy control group (H; Korff grades 0 and 1) or back pain patient group (BPP; Korff grades 2-4). Back pain prevalence was calculated based on this group assignment.

EMG analysis

Trunk muscle activity was assessed by means of a 12-lead surface EMG[12] including six ventral [Mm rectus abdominis (RA), obliquus externus abdominis (EO), obliquus internus abdominis (IO) of left and right side] and six dorsal [Mm erector spinae thoracic (T9; UES)/lumbar (L3; LES), latissimus dorsi (LD) of left and right side] muscles (Figure 1). Muscular activity was analyzed using bilateral, bipolar surface EMG (bandpass filter: 5-500 Hz; sampling frequency: 4000 Hz, amplification: overall gain: 1000; myon, Switzerland). Before electrodes were applied (AMBU Medicotest, Denmark, Type N-00-S, inter-electrode distance: 2 cm), the skin was shaved, slightly exfoliated to remove surface epithelial layers and finally disinfected. In addition, skin resistance was measured and controlled to be less than 5 kΩ. The longitudinal axes of the electrodes were aligned with the presumed direction of the underlying muscle fibers.

The mean amplitude of the whole lifting cycle (average of 3 repetitions) was calculated for all lifting loads (1, 10, 20 kg). As a main outcome measurement, the one-handed lifting root mean square [EMG-RMS; (%)] normalized to EMG-RMS of the two-handed lifting task (with 20 kg) was calculated. In addition, the mean (normalized) EMG-RMS for muscle groups was calculated and therefore averaged of the EMG-RMS of the three single muscles per group: right ventral area ((VR: RA, EO, IO of right side), left ventral area (VL: RA, EO, IO of left side), right dorsal area (DR: UES, LES, LD of right side) and left dorsal area (DL: UES, LES, LD of left side)[12].

Statistical analysis

All non-digital data were documented in a paper and pencil-based case report form (CRF) and transferred to a statistical database (JMP Statistical Software Package 9, SAS Institute®). After plausibility checks, data was analyzed descriptively (means, SD) for all given outcome measures followed by student's *t*-tests to investigate for differences between H and BPP. The level of significance was set $\alpha = 0.05$. In addition, task failure was calculated and compared between H ($H_{matched}$) *vs* BPP using χ^2. Multiple testing was controlled *via* Bonferroni adjustment (*e.g.*, 4 muscle groups: $P = 0.01$; 12 single muscles: $P = 0.004$). In addition, the statistical review of the study was performed by a

Table 1 Anthropometrics and back pain status of healthy controls (H; $H_{matched}$) and back pain group

Group	*n*	Gender (f/m)	Age (yr)	Body weight (kg)	Body height (cm)	Pain Intensity score[b,d]	Disability score[b,d]	Korff grade
H	36	23/13	28 ± 8	71 ± 12	174 ± 10	16 ± 11	7 ± 12	0.9 ± 0.3
BPP	7	4/3	32 ± 7	65 ± 11	171 ± 7	50 ± 17	43 ± 10	2.6 ± 0.8
$H_{matched}$	7	4/3	30 ± 7	64 ± 6	170 ± 9	15 ± 9	6 ± 9	1.0 ± 0.0

[b]Significant differences between H and BPP ($P < 0.001$); [d]Significant differences between $H_{matched}$ and BPP ($P < 0.001$). BPP: Back pain patients.

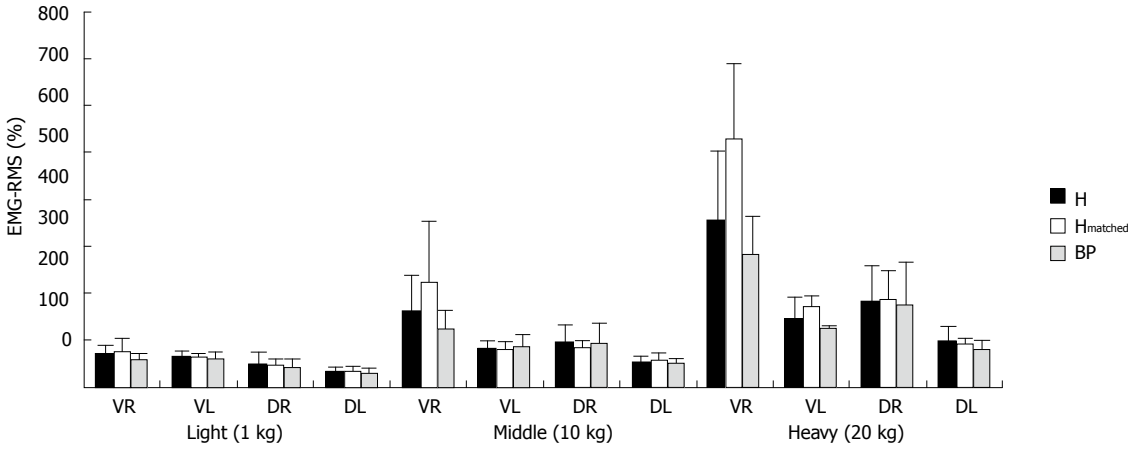

Figure 2 Neuromuscular activity (EMG-RMS; %) of trunk areas for healthy controls (H; $H_{matched}$) and back pain patients for the lifting tasks with 1, 10 and 20 kg (VR/VL: RA, EO, $IO_{ri/le}$; DR/DL: LD, UES, $LES_{ri/le}$). BPP: Back pain patients; VR/VL: Right/left ventral area; DR/DL: Right/left dorsal area.

biomedical statistician.

RESULTS

Back pain prevalence

Thirty-six subjects were allocated as healthy controls (H) and seven as BPP. This represents a back pain prevalence of 16% in the cohort analyzed. Anthropometrics and pain subscores (pain intensity/disability score) of both groups are presented in Table 1. Statistically significant differences between H and BPP were present in the pain subscores ($P < 0.001$), but not in anthropometrics.

Regarding matched-group analysis, seven healthy subjects were age- and gender-matched (group $H_{matched}$) to the seven BPP. Again, statistically significant differences between $H_{matched}$ and BPP were present in the pain subscores ($P < 0.001$), but not in anthropometrics.

Task failure

All subjects were able to lift the light (1 kg) and middle (10 kg) loads. However, 57% ($n = 4$) of BPP and 22% ($n = 8$) of H/29% of $H_{matched}$ ($n = 2$) were unable to lift the heavy (20 kg) load. All of them were female. χ^2 analysis revealed significant differences here between H and BPP ($P = 0.03$), but not for $H_{matched}$ *vs* BPP ($P = 0.06$).

Trunk muscle activity during lifting

In EMG-RMS analysis, no statistically significant group differences (BPP *vs* H; BPP *vs* $H_{matched}$) were found ($P > 0.05$) (Figure 2). However, H showed higher mean EMG-RMS compared to BPP in all four trunk areas analyzed ($P > 0.05$) (Figure 2).

EMG-RMS during lifting of the light load (1 kg) ranged between 33% ± 10% (DL) to 71% ± 18% (VR) for H, between 33% ± 9% (DL) to 76% ± 27% (VR) in $H_{matched}$ and between 30% ± 9% (DL) to 59% ± 11% (VR) in BPP. During lifting of the middle load (10 kg), EMG-RMS varied between 52% ± 12% (DL) to 161% ± 76% (VR) for H, between 58% ± 15% (DL) to 224% ± 129% (VR) in $H_{matched}$ and between 50% ± 11% (DL) to 124% ± 39% (VR) in BPP. Regarding high loading (20 kg), EMG-RMS ranged between 97% ± 30% (DL) to 356% ± 148% (VR) for H, between 92% ± 10% (DL) to 530% ± 157% (VR) in $H_{matched}$ and between 80% ± 19% (DL) to 283% ± 80% (VR) in BPP. Regardless of load, no significant differences in trunk muscle activity could be found between groups ($P > 0.05$).

Regardless, VR produced the greatest EMG-RMS during all lifting tasks in both groups. In addition, EMG-RMS increased in all four trunk areas with heavier loading, especially VR and DR muscle groups. The polar plot (Figure 3) shows the activation pattern of all 12 muscles comparing H ($H_{matched}$) and BPP.

In addition, matched group analysis did not show any significant differences between groups with regards to loading tasks ($P > 0.05$; BPP *vs* $H_{matched}$) (Figures 2 and 3).

DISCUSSION

The main purpose of this study was to analyze neuromuscular activity patterns of the trunk in healthy con-

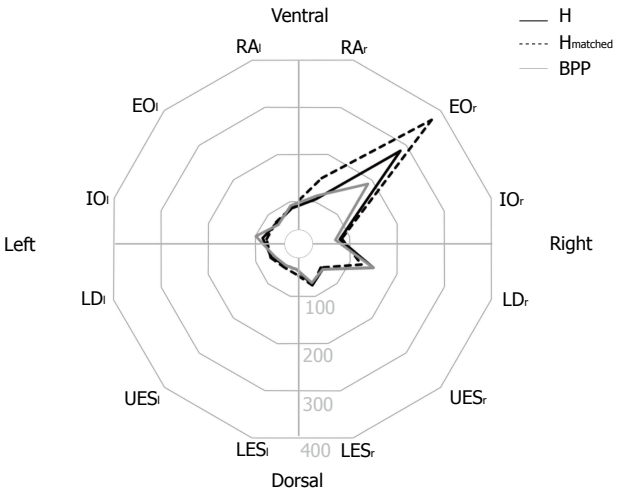

Figure 3 Polarplot of neuromuscular activity (EMG-RMS; %) of the 12 trunk muscles in healthy controls (H/$H_{matched}$) and back pain patients for lifting of middle load (10 kg).

trols (H) and BPP during one-handed lifting of different loads. This study demonstrates that BPP do not show an altered neuromuscular activity pattern, in terms of EMG amplitude, of the trunk during one-handed lifting of three different loads compared to healthy controls. Nevertheless, a significantly greater rate of task failure, while lifting heavy loads (20 kg), could be shown in BPP.

In contrast to the known alterations of the neuromuscular activation pattern of the trunk during suddenly applied loads[12,16], no significant differences in trunk muscle amplitudes could be shown between BPP and H ($H_{matched}$) during one-handed lifting of expected loads. This can be discussed in the context of the experimental task: lifting *vs* quick-release experiments. The used lifting task correlates to an expected, continuous loading of the trunk. It could be discussed that due to the knowledge of the task, as well as the low (1 kg) and middle (10 kg) lifting weight, BPP are able to use an adequate - comparable to healthy controls - activation strategy to perform the task despite pain. In contrast, frequently used quick-release experiments apply a sudden, unexpected load to either the trunk or the limbs[12,13,17]. In these studies, patients could not prepare themselves for the high loading and therefore showed altered neuromuscular activity pattern. However, lifting tasks are omnipresent in daily life, thus adequately represent functional movements. It could be speculated that the lifting pattern is an automated movement pattern, comparable to the human gait, and therefore BPP are able to reproduce an adequate neuromuscular activation pattern showing no difference to healthy controls. However, the presented EMG-RMS differences between H ($H_{matched}$) and BPP showed no statistical significance, but could be interpreted as clinically relevant with differences up to 250% between groups [*e.g.*, 530% ± 157% ($H_{matched}$) *vs* 283% ± 80% (BPP)]. Due to a high inter-individual variability and the small sample size, especially the low number of BPP, statistically significant differences would have been difficult to yield. Additionally, it should be mentioned that the acute pain level of the BPP group was actually quite low. In detail, it ranged between 0 and 8 on the numeric rating scale (0-10) (mean ± SD: 2.9 ± 2.5).

Despite finding no effect of back pain on neuromuscular activity patterns, lifting of a heavy load (20 kg) led to a significant increase in task failure in the BPP group, especially in women. The frequently observed trunk strength deficits in BPP could be a cause for the task failure at high loads (20 kg)[18]. In addition, task failure in women could correspond to the higher prevalence of back pain and reduced trunk stability in females documented by Schneider *et al*[19]. As a consequence, back pain therapy, especially in females, should focus on the preparation of adequate compensation of high loading (expected, continuous). Moreover, the results imply that an overall reduced performance capacity in BPP leads to task failure. Therefore, additional diagnostics are recommended, *e.g.*, strength assessment, to deliver individual therapy regimes.

Although BPP neuromuscular activity levels did not differ, both groups revealed a specific neuromuscular activity pattern of the trunk with muscle activity becoming more pronounced with rising load (20 kg). With increased loading, neuromuscular activity level also increased in all trunk muscles. In addition, the ventral muscle group (VR) ipsilateral to the side of the applied load (left hand) revealed the greatest activity during all loading conditions (1, 10, 20 kg). Therefore, a task-specific compensation strategy could be assumed in healthy controls and in BPP during continuous lifting of (expected) weights.

Certain limitations of the study, however, have to be considered. During the experiment, all participants lifted the same defined weights (1, 10, 20 kg) regardless of their body weight. In addition, a standardized table height (0.75 m) was used regardless of individual body height. These methods were chosen for comparability to certain daily life tasks, *e.g.*, carrying a crate full of bottles. Therefore, no individual adaptations were made. Additionally, giving instructions to the subjects as to how to lift the objects could have influenced results. Therefore, with respect to standardization and demands in daily life, a consistent test situation for all subjects was favored[20]. Except for sample size, there were no baseline (anthropometric) differences between groups. The added matched group analysis (BPP *vs* $H_{matched}$) did not change results of trunk EMG pattern analysis.

Conclusion

Neuromuscular trunk compensation strategies during one-handed lifting of different loads did not differ between H and BPP. Heavier loads led to an increase in trunk muscle activity (2- to 3-fold) with comparable patterns between groups. In both groups, the greatest activity was found in the contralateral abdominal muscles (VR). Heavy loading (20 kg) led to task failure, especially in women with back pain, implying reduced performance

for these subjects. Consequently, the application of additional diagnostics are recommended, *e.g.*, strength assessment. Moreover, rehabilitation and prevention of back pain should focus on the preparation and compensation of high loading.

ACKNOWLEDGMENTS

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COMMENTS

Background

Back pain places a large burden on the healthcare systems of western industrialized nations. Research to develop approaches for the prevention of back pain could have a very beneficial effect. Therefore, the investigation of differences in trunk function between people with and without back pain is of primary interest in order to define adequate therapy and prevention strategies.

Research frontiers

An altered neuromuscular activity of the trunk muscles in back pain patients (BPP) is evident: Longer response times, altered recruiting patterns, extended activation times and increased co-contractions. Besides, these differences are only valid in situations where the load is applied suddenly either directly to the trunk or to the limbs. These situations are often limited in representing daily life activities which is highly comprised of lifting tasks. Since lifting tasks are omnipresent in daily life and correspond with an automated movement pattern, they seem expedient for the comparison of trunk muscle activity pattern between H and BPP. In terms of lifting tasks, one-handed carrying led to greater low back loads compared to two-handed carrying of the same weight due to an increased shear stress on the spine. Therefore, one-handed lifting proposes a more challenging situation compared to two-handed lifting.

Innovation and breakthroughs

This study demonstrates that BPP do not show an altered neuromuscular activity pattern, in terms of EMG amplitude, of the trunk during one-handed lifting of three different loads compared to healthy controls. Nevertheless, a significantly greater rate of task failure, while lifting heavy loads (20 kg), could be shown in BPP.

Applications

Neuromuscular trunk compensation strategies during one-handed lifting of different loads did not differ between healthy controls and BPP. Heavier loads led to an increase in trunk muscle activity (2- to 3-fold) with comparable patterns between groups. In both groups, the greatest activity was found in the contralateral abdominal muscles (VR). Heavy loading (20 kg) led to task failure, especially in women with back pain, implying reduced performance for these subjects. Consequently, the application of additional diagnostics are recommended, *e.g.*, strength assessment. Moreover, rehabilitation and prevention of back pain should focus on the preparation and compensation of high loading.

Peer-review

The authors investigated EMG of back muscles of people with or without back pain when they underwent one handed lift task. The methods were clear, and the results were easy to imagine and understand.

REFERENCES

1 **Balagué F**, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. *Lancet* 2012; **379**: 482-491 [PMID: 21982256 DOI: 10.1016/S0140-6736(11)60610-7]

2 **Choi BK**, Verbeek JH, Tam WW, Jiang JY. Exercises for prevention of recurrences of low-back pain. *Occup Environ Med* 2010; **67**: 795-796 [PMID: 20959397 DOI: 10.1002/14651858.CD006555.pub2]

3 **Mannion AF**, Caporaso F, Pulkovski N, Sprott H. Spine stabilisation exercises in the treatment of chronic low back pain: a good clinical outcome is not associated with improved abdominal muscle function. *Eur Spine J* 2012; **21**: 1301-1310 [PMID: 22270245 DOI: 10.1007/s00586-012-2155-9]

4 **Bono CM**. Low-back pain in athletes. *J Bone Joint Surg Am* 2004; **86-A**: 382-396 [PMID: 14960688 DOI: 10.2106/00004623-200402000-00027]

5 **Trainor TJ**, Trainor MA. Etiology of low back pain in athletes. *Curr Sports Med Rep* 2004; **3**: 41-46 [PMID: 14728913 DOI: 10.1249/00149619-200402000-00008]

6 **Cholewicki J**, Simons AP, Radebold A. Effects of external trunk loads on lumbar spine stability. *J Biomech* 2000; **33**: 1377-1385 [PMID: 10940396 DOI: 10.1016/S0021-9290(00)00118-4]

7 **Ferguson SA**, Marras WS, Burr DL, Davis KG, Gupta P. Differences in motor recruitment and resulting kinematics between low back pain patients and asymptomatic participants during lifting exertions. *Clin Biomech* (Bristol, Avon) 2004; **19**: 992-999 [PMID: 15531048 DOI: 10.1016/j.clinbiomech.2004.08.007]

8 **Hanada EY**, Johnson M, Hubley-Kozey C. A comparison of trunk muscle activation amplitudes during gait in older adults with and without chronic low back pain. *PM R* 2011; **3**: 920-928 [PMID: 22024323 DOI: 10.1016/j.pmrj.2011.06.002]

9 **Hodges PW**, Moseley GL. Pain and motor control of the lumbopelvic region: effect and possible mechanisms. *J Electromyogr Kinesiol* 2003; **13**: 361-370 [PMID: 12832166 DOI: 10.1016/S1050-6411(03)00042-7]

10 **Nelson-Wong E**, Callaghan JP. Is muscle co-activation a predisposing factor for low back pain development during standing? A multifactorial approach for early identification of at-risk individuals. *J Electromyogr Kinesiol* 2010; **20**: 256-263 [PMID: 19467607 DOI: 10.1016/j.jelekin.2009.04.009]

11 **Nelson-Wong E**, Alex B, Csepe D, Lancaster D, Callaghan JP. Altered muscle recruitment during extension from trunk flexion in low back pain developers. *Clin Biomech* (Bristol, Avon) 2012; **27**: 994-998 [PMID: 22877831 DOI: 10.1016/j.clinbiomech.2012.07.007]

12 **Radebold A**, Cholewicki J, Panjabi MM, Patel TC. Muscle response pattern to sudden trunk loading in healthy individuals and in patients with chronic low back pain. *Spine* (Phila Pa 1976) 2000; **25**: 947-954 [PMID: 10767807 DOI: 10.1097/00007632-200004150-00009]

13 **Maaswinkel E**, Griffioen M, Perez RS, van Dieën JH. Methods for assessment of trunk stabilization, a systematic review. *J Electromyogr Kinesiol* 2016; **26**: 18-35 [PMID: 26803526 DOI: 10.1016/j.jelekin.2015.12.010]

14 **McGill SM**, Marshall L, Andersen J. Low back loads while walking and carrying: comparing the load carried in one hand or in both hands. *Ergonomics* 2013; **56**: 293-302 [PMID: 23384188 DOI: 10.1080/00140139.2012.752528]

15 **Klasen BW**, Hallner D, Schaub C, Willburger R, Hasenbring M. Validation and reliability of the German version of the Chronic Pain Grade questionnaire in primary care back pain patients. *Psychosoc Med* 2004; **1**: Doc07 [PMID: 19742049]

16 **Radebold A**, Cholewicki J, Polzhofer GK, Greene HS. Impaired postural control of the lumbar spine is associated with delayed muscle response times in patients with chronic idiopathic low back pain. *Spine* (Phila Pa 1976) 2001; **26**: 724-730 [PMID: 11295888 DOI: 10.1097/00007632-200104010-00004]

17 **Müller J**, Müller S, Engel T, Reschke A, Baur H, Mayer F. Stumbling reactions during perturbed walking: Neuromuscular reflex activity and 3-D kinematics of the trunk - A pilot study. *J Biomech* 2016; **49**: 933-938 [PMID: 26518368 DOI: 10.1016/j.jbiomech.2015.09.041]

18 **Müller S**, Stoll J, Müller J, Mayer F. Validity of isokinetic trunk measurements with respect to healthy adults, athletes and low back pain patients. *Isokinet Exerc Sci* 2012; **20**: 255-266 [DOI: 10.3233/IES-2012-00482]

19 **Schneider S**, Lipinski S, Schiltenwolf M. Occupations associated with a high risk of self-reported back pain: representative outcomes of a back pain prevalence study in the Federal Republic of Germany. *Eur Spine J* 2006; **15**: 821-833 [PMID: 16432750 DOI: 10.1007/s00586-005-1015-2]

20 **Müller J**, Müller S, Stoll J, Rector M, Baur H, Mayer F. Influence of Load on Three-Dimensional Segmental Trunk Kinematics in One-Handed Lifting: A Pilot Study. *J Appl Biomech* 2016; **32**: 520-525 [PMID: 27341406 DOI: 10.1123/jab.2015-0227]

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ORIGINAL ARTICLE

Case Control Study

Interleukin-6 and ratio of plasma interleukin-6/ interleukin-10 as risk factors of symptomatic lumbar osteoarthritis

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Author contributions: Suyasa IK designed the research and collect material and clinical data from patients; Kawiyana IKS collect material and clinical data from patients; Bakta IM wrote the paper; Widiana IGR analyzed the data.

Institutional review board statement: The study was approved by the ethics committee of Sanglah General Hospital (Bali, Indonesia).

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Abstract

AIM

To determine the role of cartilage oligomeric matrix protein (COMP), interleukin (IL)-6, IL-10 and ratio of IL-6/ IL-10 as risk factors of symptomatic lumbar osteoarthritis (OA) in postmenopausal women with estrogen deficiency.

METHODS

Case-control study had been conducted in Sanglah General Hospital from October 2015 until March 2016. The blood samples were obtained and analyzed by enzyme-linked immunosorbent assay (ELISA).

RESULTS

From 44 pairs of samples which divided into 44 samples as case group and 44 samples as control group showed that high level of COMP in estrogen deficiency postmenopausal women were not at risk (OR = 0.7; 95%CI: 0.261-1.751; *P* = 0.393) for symptomatic lumbar OA (cut-off point 0.946). Estrogen deficiency in postmenopausal women with the high level of IL-6 had 2.7 times risk (OR = 2.7; 95%CI: 0.991-8.320; *P* = 0.033) for symptomatic lumbar OA from the low level of IL-6 (cut-off point 2.264). At lower level of IL-10, there was no risk for symptomatic lumbar OA (OR = 0.6; 95%CI: 0.209-1.798; *P* = 0.345) than with the higher level of IL-10 (cut-off point 6.049). While the high ratio of IL-6/IL-10 level in estrogen deficiency postmenopausal women gave 3.4 times risk (OR = 3.4; 95%CI: 1.204-11.787; *P* = 0.011)

for symptomatic lumbar OA than the low ratio of IL-6/IL-10 level (cut-off point 0.364).

CONCLUSION

High ratio of IL-6/IL-10 plasma level was the highest risk factor for causing symptomatic lumbar OA in post-menopausal women with estrogen deficiency.

Key words: Symptomatic lumbar osteoarthritis; Ratio of interleukin-6/interleukin-10; Interleukin-6; Interleukin-10; Cartilage oligomeric matrix protein

Core tip: High levels of cartilage oligomeric matrix protein in estrogen deficiency postmenopausal women were not at risk for symptomatic lumbar osteoarthritis (OA). Estrogen-deficient postmenopausal women with the high levels of interleukin (IL)-6 had higher risk for symptomatic lumbar OA from the low level of IL-6. At lower levels of IL-10, there was no risk for symptomatic lumbar OA than with the higher levels of IL-10. High ratio of IL-6/IL-10 levels in estrogen deficiency postmenopausal women produced higher risk for symptomatic lumbar OA.

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INTRODUCTION

Low back pain is a common symptom in elderly due to spine degeneration process which is termed as osteo-arthritis (OA) of the lumbar. The prevalence of OA both in men and women at 50 years are alike, while prevalence in over 50 years are increasing in women. However, the etiology remains unknown. Numerous factors are thought to be the cause of low back pain, such as estrogen changes that often occur in older women at post-menopause[1].

Low back pain in post-menopausal women is a clinical manifestation of degeneration process over the most mobile spine main areas/segments. Lumbar OA is the degeneration of cartilage which involves three joints complex that are characterized by narrowing of the lumbar intervertebral disc, vertebral osteophytes formation and occurrence of OA in the facet joints[2,3]. These pathological processes can be resulted from mechanical stress loads due to weight gain and aging that will lead to cartilage thinning, as well as inflammatory process.

Inflammatory process that occurs in the lumbar OA is a chronic inflammatory process which involve the role of cytokines, either proinflammatory cytokines such as interleukin (IL)-6, or antiinflammatory cytokines such as IL-1ra or IL-10. Production of IL-6 by human chondrocytes are also affected by estradiol, suggesting the possibility of a mechanism that affect the metabolism of cartilage[4]. Increased IL-6 will facilitate degeneration process and stimulates the formation of osteoclast precursors of granulocyte macrophage colony-forming units and incr-ease the number of osteoclasts *in vivo* which leads to increase bone resorption, contributes to the change in spondiloarthrosis[5]. IL-6 are also produced by fat cells. Inhibitors of IL-6 (including estrogen) are used for the treatment of osteoporosis in post-menopausal women[6].

IL-6 also plays an important role in bone metabolism *via* induction of osteoclastogenesis and stimulates osteoclast activity[7]. IL-6 increases the formation of osteoclasts, especially when estrogen levels decline[8]. IL-6 stimulates formation of osteoclast precursors of granulocyte macro-phage colony-forming units and increases the number of osteoclasts *in vivo*, leading to increased bone resorption, which contributes to spondiloarthrosis and degeneration of intervertebral discs[5]. Increasing amount of IL-6 in patients with aging and menopause are suspected that IL-6 is one of cytokine which plays an important role in the process of bone resorption, by affecting activity of osteoclasts, including the subkondral bone, followed by destruction of cartilage[5].

IL-10 is formerly known as cytokine synthesis inhibitory factor, plays an important role as an anti-inflammatory and immunosuppressive cytokines. IL-10 is produced from regulatory of T cells, also produced by a large number of other cells including macrophages[9]. IL-10 is very effective when suppressing macrophages to release tumor necrosis factor (TNF)-α[5].

Degradation of cartilage resulting in increasing level of cartilage oligomeric matrix protein (COMP) in synovial fluid and serum. The products of cartilage degradation will be fagocyted by the synovium and stimulate the inflammatory process. Synovium cells are activated and produce various catabolic, proinflammatory mediators and proteolytic enzymes which will cause cartilage damage[10]. Increased of COMP level indicates an increase in cartilage damage, as well as the IL-6 increasing the number of osteoclasts which leads to increased bone resorption including subchondral bone[11]. Estrogen deficiency will affect the metabolism of the chondrocytes.

In post-menopausal women with estrogen deficiency prone to have cartilage damage. It is supported by the study of the OA prevalence in post-menopausal women with and without hormone replacement therapy (HRT) showed strong evidence of the benefits of estrogen on OA. Identification over two estrogen receptors: ERα and ERβ proves that the cartilage chondrocytes sensitive to estrogen[1]. Several *in vivo* and *in vitro* studies showed that chondrocytes respond to estrogen and its mechanisms that affect the metabolism of the chondrocytes[3,12].

To date, it is still unclear whether high levels of COMP and IL-6 and low level of IL-10 in postmenopausal women with estrogen deficiency could be determined as risk factors for symptomatic lumbar OA. In this study, the

Table 1 Characteristic of symptomatic and asymptomatic lumbar osteoarthritis

Characteristic	Cases (n = 44) median (interquartile range)	Controls (n = 44) median (interquartile range)
Age (yr)	58 (54-61)	58 (53-60)
Length of menopause (yr)	7 (4-10)	8 (3-10)
Blood estrogen levels (pg/mL)	12.7 (9.00-20.87)	14.16 (9.51-19.23)
Body mass indexes (kg/m^2)	25.92 (23.27-28.06)	25.28 (22.86-27.37)

Table 2 Bivariate analysis of cartilage oligomeric matrix protein, interleukin-6, interleukin-10 and ratio of interleukin-6/interleukin-10 in symptomatic lumbar osteoarthritis

Variables	OR	P^a	95%CI
All subjects (44 pairs)			
COMP	0.7	0.393	0.261-1.751
IL-6	2.7	0.033	0.991-8.320
IL-10	0.6	0.345	0.209-1.798
Ratio IL-6/IL-10	3.4	0.011	1.204-11.787

[a]Significant at value < 0.05. COMP: Cartilage oligomeric matrix protein; IL: Interleukin.

authors aimed to prove that the COMP, IL-6 and IL-10 are risk factors for symptomatic lumbar OA in postmenopausal women with estrogen deficiency. By determining the role of COMP, IL-6 and IL-10 as risk factors for the occurrence of symptomatic lumbar OA in postmenopausal women estrogen deficiency, it is expected that early prediction, prevention and management can be recognized in the future.

MATERIALS AND METHODS

The study was conducted from October 2015 until March 2016 at Sanglah General Hospital, Denpasar, Bali. The aim of this study was to determine the role of COMP, IL-6, IL-10 and IL-6 to IL-10 ratio as risk factors of lumbar symptomatic OA in postmenopausal women with estrogen deficiency.

This was a case control study with consecutive sampling method. It started with identification for group of cases which was defined as postmenopausal women with estrogen deficiency and symptomatic lumbar OA. The pair of the cases was taken with control group, which was defined as postmenopausal women with estrogen deficiency and asymptomatic lumbar OA. The independent variables were measured retrospectively. The analysis continued with comparison of exposure probability to risk factors. The case group later compared with the control group to describe baseline characteristics and analyzed using two by two table to obtain odds ratio (OR). Odds ratio described as the risk effects, which result from exposure to the risk factors.

Forty four post-menopausal women from the population were identified and defined for both cases and controls and matched by age and body mass index. The blood sampling was performed to measure serum COMP levels and plasma cytokine levels consisting of IL-6 and IL-10 using ELISA. The obtained data were analyzed for normality and the characteristics of cases and controls equality were analyzed by comparing the mean length of menopause, age, BMI and estrogen levels. Analysis of risk factors for symptomatic lumbar OA performed with bivariate analysis (McNemar's Chi Square). The risk estimation was calculated with OR.

RESULTS

Subjects in this study were aged 57 years old in average, with BMI of 25.8 kg/m^2 and length of menopause about 6 years with the levels of estrogen approximately 15 pg/mL (Table 1).

By using the serum COMP levels of 0.946 as the cut-off point, the OR between symptomatic lumbar OA in postmenopausal women with estrogen deficiency and asymptomatic lumbar OA was 0.7 (95%CI: 0.261 to 1.751), and statistically not significant with P value of < 0.05 (P = 0.393) (Table 2). This suggests that postmenopausal women with estrogen deficiency and high levels of serum COMP is not a risk factor for symptomatic lumbar OA. Whereas, by using the plasma IL-6 levels of 2.264 as the cut-off point, the OR between symptomatic lumbar OA and asymptomatic lumbar OA in postmenopausal women with estrogen deficiency was 2.7 (95%CI: 0.991 to 8.320) with P < 0.05 (P = 0.033) (Table 2 and Figure 1). This suggest that postmenopausal women with estrogen deficiency who had high levels of plasma IL-6 were-associated with increased risk for symptomatic lumbar OA with calculated risk 2.7 times than those having low levels of plasma IL-6.

The risk difference was statistically significant with P < 0.05. By using the plasma IL-10 levels of 6.049 as the cut-off point, the OR between symptomatic lumbar OA and asymptomatic lumbar OA in postmenopausal women with estrogen deficiency was 0.6 (95%CI: 0.209 to 1.798) with P > 0.05 (P = 0.345). This suggests that low levels of plasma IL-10 in postmenopausal women with estrogen deficiency was not a risk factor for symptomatic lumbar OA (Table 2).

Using the ratio levels of plasma IL-6/IL-10 0.364 as the cut-off point, the OR between symptomatic lumbar OA in postmenopausal women with estrogen deficiency and asymptomatic lumbar OA was 3.4 (95%CI: 1.204 to 11.787) with P value of < 0.05 (P = 0.011) (Table 2 and Figure 2). This suggest that high ratio of plasma IL-6/IL-10 in postmenopausal women with estrogen deficiency had significantly higher risk for symptomatic lumbar OA with calculated risk 23.4 times than those having low ratio of plasma IL-6/IL-10.

DISCUSSION

Postmenopausal women who enrolled in the study were aged 58 years old in average, most of them had BMI

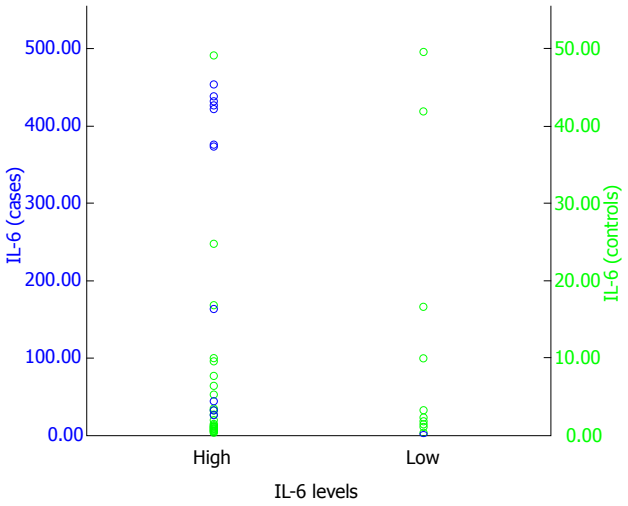

Figure 1 Distribution of interleukin-6 levels in cases and controls. IL: Interleukin.

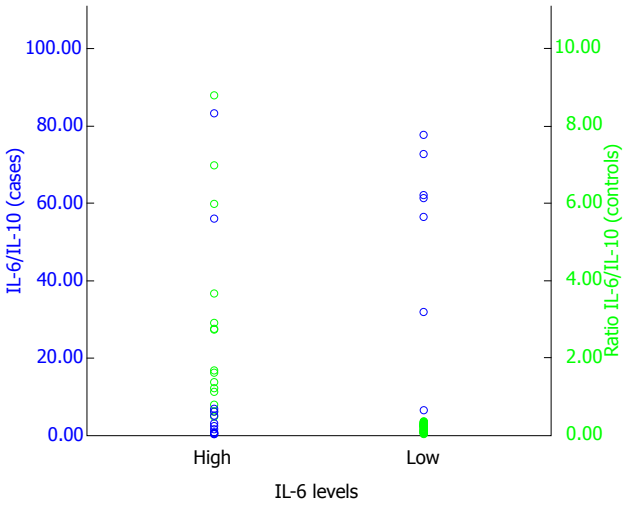

Figure 2 Distribution of ratio interleukin-6/interleukin-10 levels in cases and controls. IL: Interleukin.

category of overweight, length of menopause about 6 years and estrogen deficiency.

According to Richette *et al*[1] (2003), there is a relationship between estrogen decline and progression of OA, and it was found that its prevalence increases over age 50 years. Suyasa IK and Setiawan IGNY (2016) also found relationship of aging, BMI and estrogen deficiency with symptomatic lumbar OA[13]. The lumbar OA defined as a degeneration of cartilage which involves three joint complexes which characterized by narrowing of lumbar intervertebral disc, vertebral osteophytes formation and occurrence of OA in facet joints. These pathological conditions potentially caused by mechanical stress load due to aging, weight gain and hormonal changes that occur in joint cartilage thinning process[3].

Two estrogen receptors: ERα and ERβ, identified in chondrocytes and has proven sensitive to estrogen. *In vivo* animal studies showed that intra-articular injection of estrogen have a dose dependent; supraphysiological dose of 17β estradiol histologically induces OA histologically, on the other hand, it had no effect when given in low dose. In postmenopausal women, estrogen may decrease the speed of subchondral bone remodelling, which is a key factor in the pathophysiology of OA. Furthermore, estrogen receptor expression was shown in sinoviocytes, which are targets effect of estrogen on the joints[1,3,5].

Role of serum COMP levels in symptomatic lumbar OA

In this study, the levels of serum COMP was not significantly with different risk for symptomatic lumbar OA with OR of 0.7 (95%CI: 0.261 to 1.751; P = 0.393). These results are in contrast to recent research by Goode *et al*[11] (2012) regarding the relationship between narrowing of the intervertebral discs, COMP and low back pain. Among patients with low back pain, strong correlations between COMP and narrowing of the intervertebral discs was found with OR of 1.82 (95%CI: 1:02 to 3:27). These finding reflects the degeneration of the intervertebral disc which characterized by narrowing of the intervertebral discs and any other symptoms associated with degeneration process[11].

COMP is a non-collagen protein which originated from cartilage extracellular matrix, act as a prognostic marker for OA. The levels of COMP can be used to predict the severity of damage in large joints, in addition, it can also predict the narrowing gap of joints[14]. As a biomarker, the concentration of COMP in synovial fluid or serum can be used as an indicator of early abnormalities[15,16], thus, COMP is very sensitive to detect early occurrence of premature OA in patients whom genetically suffering from OA[17].

OA is characterized by the destruction of cartilage and subchondral bone. Similarly, in lumbar OA which involved three joint complex, those pathological changes will occur in the cartilage of facet joint. Cartilage damage can be induced by mechanical factors, in which antigen release by the joint cartilage occurred. This situation will stimulate immune system, causing immunological reaction such as release of inflammatory mediators and proteases that are destructive and can aggravate the cartilage damage[11]. Cartilage damage characterized by the increase levels of COMP. As a diagnosis indicator, COMP correlated with disease severity. It is proved by detection of COMP levels 10 times higher in the synovial fluid of patients with OA.

Degradation of cartilage resulted in increased levels of COMP in synovial fluid and serum. These cartilage degradation products will be fagocyted by the synovium and stimulate inflammatory process. Synovium cells are activated and produce various catabolic and proinflammatory mediators and proteolytic enzymes which will lead to cartilage damage[10].

However, serum COMP levels can not be stated as a specific indicator that reflects the facet joint cartilage damage because serum COMP levels generally increased as a result of damage to the cartilage in the various joints of the body. This is in correspond with research of Söderlin *et al*[18] (2004), which stated that

increase in serum COMP levels is a common finding in OA that indicate cartilage involvement. These are due to the narrow facet cartilage surface area and the serum COMP does not fully describe the extent of cartilage damage.

According to Neidhart *et al*[19] (1997), serum COMP levels constantly lower in the synovial fluid than cartilage matrix, so that taking samples from cartilage matrix might provide more accurate results. In addition, the concept of three joint complex in the lumbar OA involves only a small portion of cartilage in the facet joints, because 2/3 of load movement in one single functional unit is in the anterior unit[19].

The levels of serum COMP in this study gathered due to differences in OA stages of the subjects as well as differences in affinity or specificity of primary antibody used in the detection of COMP. Western blot analysis with the mAbs 12C4 showed higher affinity towards COMP fragments which had low molecular weight compared to mAbs 14G4[20]. According to Tseng *et al*[21] (2009), specificity of COMP against cartilage and specific reagent for degradation of COMP is still lacking. These conditions would limit its usefulness in determining the presence of OA as well as for the examination of dichotomous outcome in the population (normal *vs* abnormal)[21]. Another study by Lohmander *et al*[22] (1994) also stated that high concentration of COMP can be found only at the early stages of OA development and not at the advanced stage.

According to Mobasheri and Henrotin[23] (2011), COMP has the ability to mediate interaction between chondrocytes and cartilage extracellular matrix. COMP suppresses apoptosis in primary chondrocytes through activation of caspase-3 and induction of apoptosis inhibitor protein family (IAP) on survival proteins such as Baculoviral IAP Repeat Containing 3 and 5, X-linked IAP (BIRC3, BIRC5, XIAP). This is certainly in accordance with the study where investigated that COMP may be a protective factor against Symptomatic lumbar OA although not proven to be statistically significant.

The role of IL-6 plasma levels in symptomatic lumbar OA

In this study, IL-6 plasma levels were high (above median) in postmenopausal women with estrogen deficiency. This finding suggested that high levels of IL-6 plasma significantly act as a risk factor for symptomatic lumbar OA with OR of 2.7 (95%CI: 0.991 to 8.320; $P = 0.033$). This finding was in line with the study of Weber *et al*[24] (2016) and Valdes[25] (2010), that IL-6 was significantly higher in patients with low back pain (LBP), moreover, IL-6, BMI, duration of symptoms and age were significantly correlated with low back pain. IL-1, IL-6 and IL-10 that involved in the inflammatory process were also correlated with the risk of OA.

IL-6 is a cytokine that acts as an innate and acquired immunity, formed by many cells and affect multiple targets. The main sources of IL-6 are macrophages and lymphocytes in inflammatory area. IL-6 also plays an important role in enhancing the formation of osteoclasts, especially when estrogen levels are declining[8]. IL-6 stimulates formation of osteoclast precursors of granulocyte macrophage colony-forming units and increase the number of osteoclasts *in vivo*, leading to increased bone resorption, which contributed to spondiloarthrosis and degeneration of intervertebral discs[5]. While Ershler, Harman and Keller[7] (2002) found an increase in IL-6 on aging and menopausal women. The levels of IL-6 increased in older age[26] and significantly increased at the age of 70[27].

In OA, the production of IL-6 is mainly stimulated by increased catabolic cytokines that are IL-1 and TNF-α, and then IL-6 will potentiate the effect of IL-1. In the pathogenesis of OA, IL-6 has dual functions that are as a trigger of the inflammatory process and has the ability to down-regulate the factors involved catabolic role in the degeneration of cartilage[28]. In addition, IL-6 is also plays an important role in bone resorption including subchondral bone through the activity of osteoclasts.

The role of IL-6 plasma against symptomatic lumbar OA is through the activation of transducer glycoprotein 130 (gp130) on neurons due to the formation of complex IL-6/soluble IL-6R. Transducer glycoprotein 130 (gp130) is associated with sensitization taste buds of pain through activation of phosphoinositide 3-kinase, protein kinase C-delta and Janus kinase as well as the regulation of ion channel transient receptor potential cation channels vanilloid 1 (TRPV1)[29].

IL-6 is regarded as a key cytokine, which cause changes in the subchondral bone layer. The effect is largely based on the formation of osteoclasts resulting in bone resorption and also showed synergism with IL-1β and TNF[30].

Plasma levels of IL-10 in symptomatic lumbar OA

In this study, the plasma levels of IL-10 were not proven to be significant as a risk factor for symptomatic lumbar OA with OR of 0.6 (95%CI: 0.209 to 1.798; $P = 0.345$). This is in contrast with the study by John *et al*[31] (2007) and Wang *et al*[32] (2001) which found that IL-10 not only inhibits the synthesis of inflammatory cytokines, but also protect the chondrocytes directly to antagonize the role of IL-1. Immunoregulatory cytokine IL-10 modulates a series of apoptosis in TNF-α such as caspase activity in human articular chondrocytes.

IL-10, known as cytokine synthesis inhibitory factor, is an anti-inflammatory and immunosuppressive cytokine, produced by T-regulatory cells and macrophages. IL-10 is a cytokine that is highly effective on suppressing the release of TNF-α by macrophages. There are two main functions of IL-10 such as inhibit the production of several cytokines (TNF, IL-1, and the chemokine IL-12) and inhibit the function of macrophages and dendritic cells in the activation of T-cell, generally it has an immunosuppressive effect. Supression on macrophage function occurs because IL-10 suppressing the expression of MHC class Ⅱ molecules on macrophages, and reduce the expression of co-stimulatory (a.l. B7-1 and B7-2). The final impact of IL-10 activities is specific and non-specific supression

of inflammatory reactions which mediated by T-cells. According to those, IL-10 known as cytokine synthesis inhibitory factor and anti-inflammatory cytokines[9].

IL-10 also able to show chondroprotective effect in the course of OA. Chondrocytes express the cytokines IL-10 and IL-10R receptor. It has been proven that IL-10 is involved in stimulating the synthesis of collagen type II and aggrecan. After administration of IL-10 *in vitro*, the healthy articular cartilage over the course of OA showed increased in proteoglycan synthesis and its percentage in the extracellular matrix. IL-10 inhibits apoptosis of chondrocytes, which might be a result of stimulation on IL-1β antagonist synthesis, IL-1Ra, tissue inhibitor of metalloproteinase-1 (TIMP-1) and growth factors. IL-10 reduces the effect of TNF-α in synovial fibroblasts in patients with OA[16].

In lumbar OA, IL-10 alone can not be used as a risk factor, because the inflammatory process is chronic involving *via* complex interaction by various cytokines, both pro-inflammatory cytokines such as TNF-α and IL-6, as well as cytokines anti-inflammatory such as IL-1ra or IL-10. Increased levels of TNF-α and IL-6 will be responded by anti-inflammatory cytokines. IL-10 is very powerful suppressor for TNF-α released by macrophages. The low levels of IL-10 can be used as an indicator of failure in the process of TNF-α and IL-6 suppression.

The role of IL-10 plasma in symptomatic lumbar OA is a protective factor although not clearly proved. To determine the role of IL-10 levels as a risk factor, it can be evaluated on the expression of IL-10 ratio against other potential cytokines such as ratio of IL-6/IL-10[33].

The ratio of plasma levels IL-6 / IL-10 in symptomatic lumbar OA

In this study, the ratio levels of plasma IL-6/IL-10 were high (above median) in postmenopausal women estrogen deficiency. This finding showed that high ratio levels of plasma IL-6/IL-10 significantly acts as a risk factor for symptomatic lumbar OA with OR of 3.4 (95%CI: 1.204 to 11.787; P = 0.011). The results of this study showed the concept of balance between proinflammatory cytokines and anti-inflammatory cytokines. Until now, data and research on the ratio of IL-6/IL-10 in symptomatic lumbar OA in postmenopausal women with estrogen deficiency does not exist. And the role of inflammatory and anti-inflammatory cytokines in the pathogenesis of OA on inter and intracellular signaling pathways are still under study[30].

Based on the explanation, the levels of IL-6 or IL-10 alone did not reflect the existence of symptomatic lumbar OA in postmenopausal women with estrogen deficiency. The ratio of both IL-6 and IL-10 is required to obtain more accurate result and reflect incidence of symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

The role of the IL-6 to IL-10 ratio levels against symptomatic lumbar OA is through the interaction of pro-inflammatory cytokines with anti-inflammatory cytokines. Both of these cytokines potentially provide accurate information on the risk of symptomatic lumbar OA. IL-6 plasma has a function as a trigger of the inflammatory process and has the ability to down-regulation the catabolic factors that involved in cartilage degeneration, while IL-10 inhibits specific and non-specific inflammatory reactions as a response to the increase of cytokines TNF-α and IL-6.

From the data analysis that had been done in this study, it is concluded that the high ratio of IL-6/IL-10 plasma levels is the strongest risk factor of symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

Plasma COMP can not be considered as a biomarker of symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

COMMENTS

Background

Lumbar osteoarthritis (OA) is the degeneration of cartilage which involves three joint complex. Indeed, the inflammatory process, which is a chronic inflammatory process, influence this pathological process especially if alteration of estrogen levels occurs. Furthermore, degradation of cartilage lead to increased cartilage oligomeric matrix protein (COMP) levels. Either proinflammatory cytokines [interleukin (IL)-6] or anti-inflammatory cytokines (IL-1ra or IL-10) and COMP are thought to be relevant as risk factor for symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

Research frontiers

IL-6, IL-10, and COMP had been extensively studied in relation to inflammatory process and cartilage damage. Chronic inflammatory process occurs in individuals with lumbar OA and this inflammatory process related to estrogen levels. Thus, it is of interest whether IL-6, IL-10, and COMP are risk factors for symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

Innovations and breakthroughs

The authors confirm that high ratio of IL-6/IL-10 plasma level was the highest risk factor for causing symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

Applications

Determining ratio of IL-6/IL-10 could be used as risk factors for causing symptomatic lumbar OA in postmenopausal women with estrogen deficiency. It is expected that early prediction, prevention and management can be recognized.

Terminology

COMP: Cartilage oligomeric matrix protein; IL-6: Interleukin-6; IL-10: Interleukin-10; OA: Osteoarthritis.

Peer-review

This is an interesting paper.

REFERENCES

1 **Richette P**, Corvol M, Bardin T. Estrogens, cartilage, and osteoarthritis. *Joint Bone Spine* 2003; **70**: 257-262 [PMID: 12951307]

2 **Fujiwara A**, Lim TH, An HS, Tanaka N, Jeon CH, Andersson GB, Haughton VM. The effect of disc degeneration and facet joint osteoarthritis on the segmental flexibility of the lumbar spine. *Spine* (Phila Pa 1976) 2000; **25**: 3036-3044 [PMID: 11145815]

3 **Sniekers YH**, Weinans H, van Osch GJ, van Leeuwen JP. Oestrogen

is important for maintenance of cartilage and subchondral bone in a murine model of knee osteoarthritis. *Arthritis Res Ther* 2010; **12**: R182 [PMID: 20923566 DOI: 10.1186/ar3148]
4 **Wluka AE**, Cicuttini FM, Spector TD. Menopause, oestrogens and arthritis. *Maturitas* 2000; **35**: 183-199 [PMID: 10936736]
5 **Holm S**, Mackiewicz Z, Holm AK, Konttinen YT, Kouri VP, Indahl A, Salo J. Pro-inflammatory, pleiotropic, and anti-inflammatory TNF-alpha, IL-6, and IL-10 in experimental porcine intervertebral disk degeneration. *Vet Pathol* 2009; **46**: 1292-1300 [PMID: 19605905 DOI: 10.1354/vp.07-VP-0179-K-FL]
6 **Bastard JP**, Jardel C, Delattre J, Hainque B, Bruckert E, Oberlin F. Evidence for a link between adipose tissue interleukin-6 content and serum C-reactive protein concentrations in obese subjects. *Circulation* 1999; **99**: 2221-2222 [PMID: 10217702 DOI: 10.1161/01.CIR.99.16.2219.c]
7 **Keller ET**, Wanagat J, Ershler WB. Molecular and cellular biology of interleukin-6 and its receptor. *Front Biosci* 1996; **1**: d340-d357 [PMID: 9159238]
8 **Roitt I**, Brostoff J, Male D. Cell-mediated immune reactions. In: Immunology. 5th ed. London: Mosby, 1998: 121-123
9 **Kresno SB**. Imunologi: diagnosis dan prosedur laboratorium. 4th edition. Balai Penerbit Fakultas Kedokteran Universitas Indonesia, Jakarta, 2001: 63-68
10 **Yuan GH**, Masuko-Hongo K, Kato T, Nishioka K. Immunologic intervention in the pathogenesis of osteoarthritis. *Arthritis Rheum* 2003; **48**: 602-611 [PMID: 12632410 DOI: 10.1002/art.10768]
11 **Goode AP**, Carey TS, Jordan JM. Low back pain and lumbar spine osteoarthritis: how are they related? *Curr Rheumatol Rep* 2013; **15**: 305 [PMID: 23307577 DOI: 10.1007/s11926-012-0305-z]
12 **Ushiyama T**, Ueyama H, Inoue K, Ohkubo I, Hukuda S. Expression of genes for estrogen receptors alpha and beta in human articular chondrocytes. *Osteoarthritis Cartilage* 1999; **7**: 560-566 [PMID: 10558854 DOI: 10.1053/joca.19990260]
13 **Suyasa IK**, Setiawan IGNY. The role of aging, body mass index and estrogen on symptomatic lumbar osteoarthritis in post-menopausal women. *Int J Res Med Sci* 2016; **4**: 1-4 [DOI: 10.18203/2320-6012.ijrms20161003]
14 **Conrozier T**, Saxne T, Fan CS, Mathieu P, Tron AM, Heinegård D, Vignon E. Serum concentrations of cartilage oligomeric matrix protein and bone sialoprotein in hip osteoarthritis: a one year prospective study. *Ann Rheum Dis* 1998; **57**: 527-532 [PMID: 9849311 DOI: 10.1136/ard.57.9.527]
15 **Sharif M**, Kirwan JR, Elson CJ, Granell R, Clarke S. Suggestion of nonlinear or phasic progression of knee osteoarthritis based on measurements of serum cartilage oligomeric matrix protein levels over five years. *Arthritis Rheum* 2004; **50**: 2479-2488 [PMID: 15334461 DOI: 10.1002/art.20365]
16 **Dragomir AD**, Kraus VB, Renner JB, Luta G, Clark A, Vilim V, Hochberg MC, Helmick CG, Jordan JM. Serum cartilage oligomeric matrix protein and clinical signs and symptoms of potential pre-radiographic hip and knee pathology. *Osteoarthritis Cartilage* 2002; **10**: 687-691 [PMID: 12202121 DOI: 10.1053/joca.2002.0816]
17 **Bleasel JF**, Poole AR, Heinegård D, Saxne T, Holderbaum D, Ionescu M, Jones P, Moskowitz RW. Changes in serum cartilage marker levels indicate altered cartilage metabolism in families with the osteoarthritis-related type II collagen gene COL2A1 mutation. *Arthritis Rheum* 1999; **42**: 39-45 [PMID: 9920012 DOI: 10.1002/1529-0131(199901)42: 1<39: : AID-ANR5>3.0.CO; 2-Y]
18 **Söderlin MK**, Kastbom A, Kautiainen H, Leirisalo-Repo M, Strandberg G, Skogh T. Antibodies against cyclic citrullinated peptide (CCP) and levels of cartilage oligomeric matrix protein (COMP) in very early arthritis: relation to diagnosis and disease activity. *Scand J Rheumatol* 2004; **33**: 185-188 [PMID: 15228190 DOI: 10.1080/03009740310004856]
19 **Neidhart M**, Hauser N, Paulsson M, DiCesare PE, Michel BA, Häuselmann HJ. Small fragments of cartilage oligomeric matrix protein in synovial fluid and serum as markers for cartilage degradation. *Br J Rheumatol* 1997; **36**: 1151-1160 [PMID: 9402858 DOI: 10.1093/rheumatology/36.11.1151]
20 **Arai K**, Misumi K, Carter SD, Shinbara S, Fujiki M, Sakamoto H. Analysis of cartilage oligomeric matrix protein (COMP) degradation and synthesis in equine joint disease. *Equine Vet J* 2005; **37**: 31-36 [PMID: 15651731 DOI: 10.2746/0425164054406784]
21 **Tseng S**, Reddi AH, Di Cesare PE. Cartilage Oligomeric Matrix Protein (COMP): A Biomarker of Arthritis. *Biomark Insights* 2009; **4**: 33-44 [PMID: 19652761]
22 **Lohmander LS**, Saxne T, Heinegård DK. Release of cartilage oligomeric matrix protein (COMP) into joint fluid after knee injury and in osteoarthritis. *Ann Rheum Dis* 1994; **53**: 8-13 [PMID: 8311563 DOI: 10.1136/ard.53.1.8]
23 **Mobasheri A**, Henrotin Y. Biomarkers of osteoarthritis: a review of recent research progresson soluble biochemical markers, published patents and areas for future development. *Recent Patents on Biomarkers* 2011; **1**: 25-43 [DOI: 10.2174/2210310411101010025]
24 **Weber KT**, Alipui DO, Sison CP, Bloom O, Quraishi S, Overby MC, Levine M, Chahine NO. Serum levels of the proinflammatory cytokine interleukin-6 vary based on diagnoses in individuals with lumbar intervertebral disc diseases. *Arthritis Res Ther* 2016; **18**: 3 [PMID: 26743937 DOI: 10.1186/s13075-015-0887-8]
25 **Valdes AM**. Molecular pathogenesis and genetics of osteoarthritis: implications for personalized medicine. *Personalized Medicine* 2010; **7**: 49-63 [DOI: 10.2217/pme.09.68]
26 **Maggio M**, Guralnik JM, Longo DL, Ferrucci L. Interleukin-6 in aging and chronic disease: a magnificent pathway. *J Gerontol A Biol Sci Med Sci* 2006; **61**: 575-584 [PMID: 16799139 DOI: 10.1093/gerona/61.6.575]
27 **Giuliani N**, Sansoni P, Girasole G, Vescovini R, Passeri G, Passeri M, Pedrazzoni M. Serum interleukin-6, soluble interleukin-6 receptor and soluble gp130 exhibit different patterns of age- and menopause-related changes. *Exp Gerontol* 2001; **36**: 547-557 [PMID: 11250125 DOI: 10.1016/S0531-5565(00)00220-5]
28 **Lotz M**, Guerne PA. Interleukin-6 induces the synthesis of tissue inhibitor of metalloproteinases-1/erythroid potentiating activity (TIMP-1/EPA). *J Biol Chem* 1991; **266**: 2017-2020 [PMID: 1846608]
29 **Svensson CI**. Interleukin-6: a local pain trigger? *Arthritis Res Ther* 2010; **12**: 145 [PMID: 21067533 DOI: 10.1186/ar3138]
30 **Wojdasiewicz P**, Poniatowski LA, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis: review article. Hindawi Publishing Corporation. Mediators of Inflammation, 2014: 1-20 [DOI: 10.1155/2014/561459]
31 **John T**, Müller RD, Oberholzer A, Zreiqat H, Kohl B, Ertel W, Hostmann A, Tschoeke SK, Schulze-Tanzil G. Interleukin-10 modulates pro-apoptotic effects of TNF-alpha in human articular chondrocytes in vitro. *Cytokine* 2007; **40**: 226-234 [PMID: 18023359 DOI: 10.1016/j.cyto.2007.10.002]
32 **Wang Y**, Lou S. Direct protective effect of interleukin-10 on articular chondrocytes in vitro. *Chin Med J* (Engl) 2001; **114**: 723-725 [PMID: 11780336]
33 **Kaneda H**, Waddell TK, de Perrot M, Bai XH, Gutierrez C, Arenovich T, Chaparro C, Liu M, Keshavjee S. Pre-implantation multiple cytokine mRNA expression analysis of donor lung grafts predicts survival after lung transplantation in humans. *Am J Transplant* 2006; **6**: 544-551 [PMID: 16468964 DOI: 10.1111/j.1600-6143.2005.01204.x]

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ORIGINAL ARTICLE

Retrospective Study

Titanium elastic nailing in diaphyseal femoral fractures of children below six years of age

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Author contributions: All the authors contributed equally to this work; Donati F, Mazzitelli G, Marzetti E and Maccauro G designed the research; Donati F, Lillo M, Menghi A, Conti C and Valassina A performed the research; Donati F, Conti C, Marzetti E and Maccauro G analyzed the data; Donati F, Mazzitelli G, Lillo M and Marzetti E wrote the paper.

Institutional review board statement: The study was reviewed and approved by the Internal ethics committee of orthopedics and traumatology department of Policlinico Gemelli Hospital.

Informed consent statement: All involved persons (subjects or legally authorized representative) gave their informed consent (written or verbal) prior to study inclusion.

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Abstract

AIM

To report the clinical and radiographic results of titanium elastic nail (TEN) in diaphyseal femoral fractures of children below age of six years.

METHODS

A retrospective analysis of 27 diaphyseal femoral fractures in children younger than six years treated with TEN between 2005 and 2015 was conducted. Patients were immobilized in a cast for 5 wk and the nails were removed from 6 to 12 wk after surgery. Twenty-four cases were clinically and radiographically re-evaluated using the Flynn's scoring criteria, focusing on: Limb length discrepancy, rotational deformity, angulation, hip and knee range of motion (ROM), functional status, complications, and parent's satisfaction.

RESULTS

Sixteen males and eight females with a mean age of 3.2 years at the time of treatment were re-evaluated at an average follow-up of 58.9 mo. No cases of delayed union were observed. The mean limb lengthening was 0.3 cm. Four cases experienced limb lengthening greater than 1 cm and always minor than 2 cm. Twelve point five percent of the cases showed an angulation < 10°. Complete functional recovery (hip and knee ROM, ability to run and

jump on the operated limb) occurred in 95.7% of cases. Complications included two cases of superficial infection of the TEN entry point, one case of refracture following a new trauma, and one TEN mobilization. According to the Flynn's scoring criteria, excellent results were obtained in 79.2% of patients and satisfactory results in the remaining 20.8%, with an average parent's satisfaction level of 9.1/10.

CONCLUSION

TEN is as a safe, mini-invasive and surgeon-friendly technique and, considering specific inclusion criteria, it represents a useful and efficacy option for the treatment of diaphyseal femoral fractures even in patients younger than six years of age.

Key words: Titanium elastic nailing; Pediatric femoral fractures; Elastic stable intramedullary nailing; Surgical treatment; Femural shaft

Core tip: A retrospective analysis of 27 diaphyseal femoral fractures in children younger than six years treated with titanium elastic nailing (TEN) was conducted. Clinical and radiographic evaluations performed using Flynn's scoring criteria at an average follow-up of 58.9 mo showed 79.2% of excellent results and 20.8% satisfactory results, without delayed union or major complications. Considering the good clinical and radiographic results at mid-term follow-up, TEN showed to be a safe, mini-invasive and surgeon-friendly technique even in patients younger than six years of age.

Donati F, Mazzitelli G, Lillo M, Menghi A, Conti C, Valassina A, Marzetti E, Maccauro G. Titanium elastic nailing in diaphyseal femoral fractures of children below six years of age. *World J Orthop* 2017; 8(2): 156-162 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i2/156.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i2.156

INTRODUCTION

The treatment of diaphyseal femoral fractures in pediatric age has traditionally been a matter of debate. Several conservative and surgical treatments have been proposed[1]. The treatment choice is typically based on patient's age, fracture type[2], associated injuries, and the physical characteristics of the child. Diaphyseal femoral fractures in children less than six years of age are usually treated with nonsurgical methods, such as casting, tractions or Pavlik harness[3]. These methods show good clinical and radiological results at mid- and long-term follow-up and represent the gold standard treatment[4]. However conservative treatments are not suitable in specific cases such as polytraumatized patients, unstable fracture with risk of redisplacement and difficulty to obtain an acceptable reduction.

Other concerns have been moved to conservative treatments like the long hospitalization, the necessity of general anesthesia and treatment in the operating theatre, prolonged weight-bearing restrictions and the high cost associated, sparking a renewed interest in surgical approaches[5].

Intramedullary nailing with titanium elastic nails (TENs) offers several advantages, including early union, lower rate of malunion, spare of the physis, early mobilization and weight-bearing, mini-invasive approach with easy implant removal, and high patients' and parents' satisfaction rates. Good results at mid-term follow-up have been reported in children older than six years of age[6]. Little is known on the effectiveness of TEN for the treatment of diaphyseal femoral fractures in pre-school children. The present study was therefore undertaken to verify the clinical and surgical outcomes of intramedullary nailing with TEN in a sample of children younger than six years presenting with diaphyseal femoral fractures.

MATERIALS AND METHODS

Study design and participants

The study was reviewed and approved by the Internal ethics committee of Orthopedics and Traumatology Department of Teaching Hospital "Agostino Gemelli" (Rome, Italy). We conducted a retrospective analysis in 27 patients younger than six years of age, surgically treated for diaphyseal femoral fractures in our center between 2005 and 2015. The sample comprised eighteen males and eight females with a mean age of 3.2 years (range: 1-6 years). The right femur was involved in 15 cases. One patient presented with bilateral femoral fracture, and one with an open fracture. The inclusion criteria for operative treatment should be reserved for certain cases such as polytraumatized patients, unstable fracture with risk of redisplacement and difficulty to obtain an acceptable reduction.

Twenty-four patients were treated for undisplaced fracture classified as 32-D/4.1 or 32-D/5.1 according to the AO pediatrics classification, while 3 cases showed slightly comminuted fractures classified as 32-D/4.2 or 32-D/5.2 (Figure 1).

Eight cases presented with associated lesions, involving the head, the abdom, or the thorax, or other fractures (one patellar fracture, three humeral fractures). Patients with associated neurological damage or pathological fracture were excluded. The more frequent cause of trauma was car accident (14 cases). The patients did not receive any other surgical treatment before orthopedic surgery. They were immobilized in a cast or with a skin traction and they were surgically treated as soon as their general conditions allowed surgery to be performed (on average, 36 h from their admission to the Emergency Department). The criteria of treatment were determined by a single operator and surgery performed by four different surgeons.

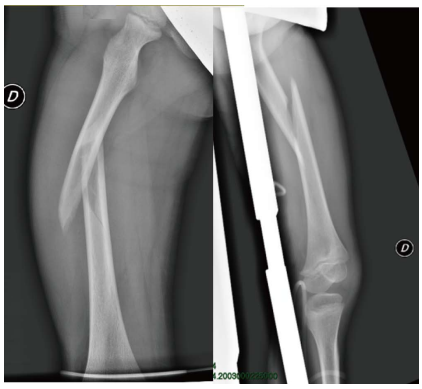

Figure 1 Undisplaced diaphyseal femoral fracture classified as 32-D/5.1 according to AO pediatrics classification. Associated injuries, such as thoracic or abdominal traumata, often require surgical management of this kind of fracture.

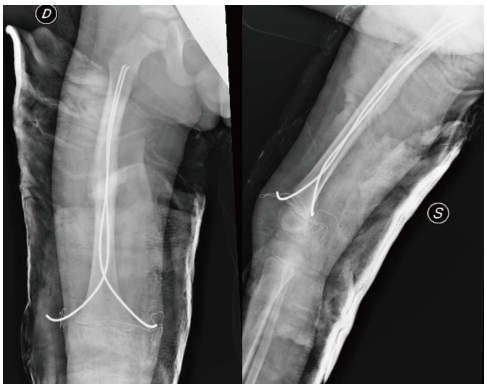

Figure 3 X-ray control at 5 wk of follow-up: Weight-bearing was allowed when advanced consolidation of the fracture with an evident bone callus formation was evident. Titanium elastic nail was then planned to be removed.

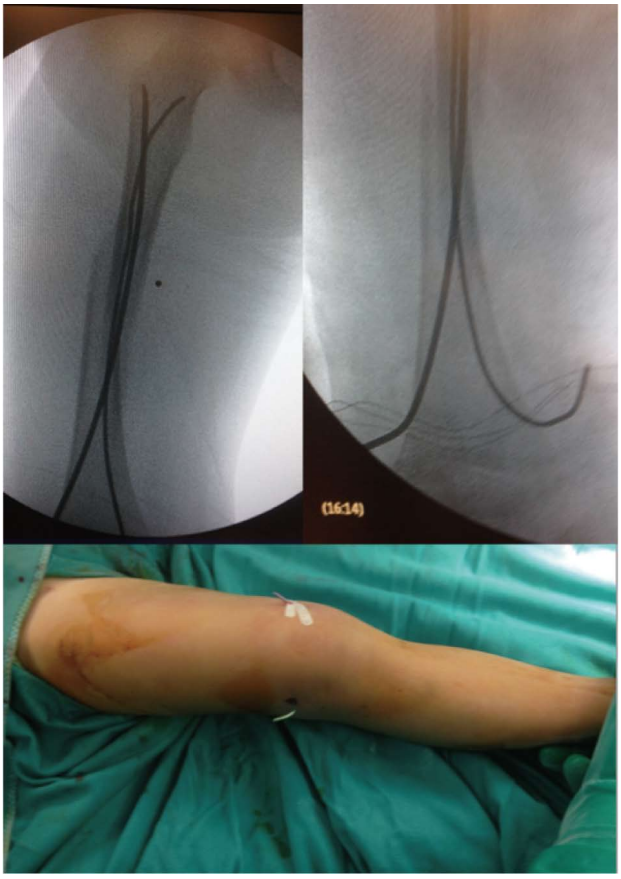

Figure 2 Intraoperative X-rays showing the correct positioning of titanium elastic nail. Entry points were performed, almost 2.5 cm proximal to the distal physis, one medial and one lateral. To facilitate the removal of the titanium elastic nail, its tail could be left over the skin surface as evident from the clinical intraoperative picture.

Surgical procedure and postoperative management

Surgery was performed under general anesthesia, and reduction under fluoroscopic guide with the patient in supine position without the necessity of traction operating table. Only in 1 case was necessary to perform open reduction for soft tissue interposition. Two TENs of identical diameter (Synthes Italy, Milan®) were used calculating the diameter as the 40% of the medullary canal[7]. In two cases it was not possible to drive the second nail in the proximal fragment, and a nail with smaller diameter was used. The entry points in the bone were performed using a drill bit with a diameter of 3.5 mm, almost 2.5 cm proximal to the distal physis, one medial and one lateral. The nail was inserted retrogradely after adequate pre-bending to improve stability[8]. Long-knee brace was used in the postoperative period for an average of five weeks. Patients were discharged from hospital after an average of 5.7 d, and were followed up in our outpatients clinic after one week, at the fifth postoperative week, and at the end of treatment (8-14 wk from surgery). Patients were mobilized without weight-bearing during the fifth to seventh postoperative week, while full weight-bearing was allowed from six to eight weeks after surgery, depending on the fracture type, radiographic results and associated injuries. TENs were removed under general anesthesia when the fracture was considered healed, at an average of 7.8 wk (range: 6-12 wk) postoperatively, without encountering any intraoperative problems (Figures 2 and 3).

Patient follow-up

The clinical evaluation was always performed in the presence of at least one of the patient's parents and after signing a detailed consensus about the study. The patients were evaluated in supine and standing positions focusing on limb length discrepancy, pelvic asymmetries, rotational deformity, axial angulation, and hip and knee range of motion (ROM). The occurrence of complications was explored by reviewing medical records whenever available or through the use of an ad hoc questionnaire.

A self-evaluation test was administered to the patient's parents to explore the functional level obtained by the patients about running, jumping on the injured limb, and participating in common sports or physical activity at the same level of other children. The parent's satisfaction about the treatment management was expressed on a scale ranging from 0 to 10.

The results were classified as excellent, satisfactory

Table 1 Flynn scoring criteria for titanium elastic nail

	Excellent result	Satisfactory result	Poor result
Leg length discrepancy	< 1 cm	< 2 cm	> 2 cm
Malalignment	< 5 degrees	< 10 degrees	> 10 degrees
Pain	None	None	Present
Complication	None	Minor and resolved complication	Major complication or lasting morbidity

According to Flynn scoring criteria for titanium elastic nail, a malalignment over 5°, internal or external rotation over 5° and shortening over 1 cm were considered pathological, in addition to the presence of pain or complications.

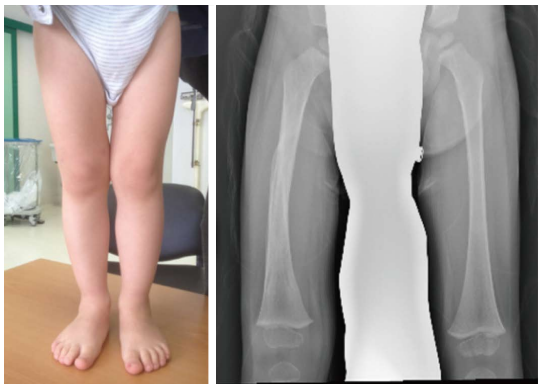

Figure 4 Clinical and radiographic examination 12 mo after fracture with residual varus deformity (< 10°) of the fractured femur. At longer follow-up, no axial deformities were observed in any patient, while the lengthening of the fractured femur was a common finding, but always < 2 cm.

or poor according to the Flynn scoring criteria for TEN[9] (Table 1).

Radiographic evaluations were performed on the last full weight-bearing limb radiographs, in available antero-posterior and lateral views. Only in case of clinically evident limb length differences or malalignment, new X-rays were obtained. Limb lengthening and axial and rotational deformity were always considered in comparison to the contralateral limb.

RESULTS

The average clinical follow-up was 58.9 mo (12-113 mo). Of the 27 cases, 24 were available for a new clinical and radiographic evaluation. Three cases were lost at follow-up because they lived in a different region. No functional limitations or complications were reported by those three cases according to phone interview and to available information.

No cases of delayed union were recorded. The mean limb lengthening was 0.3 cm (-0.5 cm/+1.6 cm), with three cases of shortening and seven of lengthening. In four cases, the limb length discrepancy was > 1 cm, but never > 2 cm.

Twelve point five percent of the cases showed a femoral angulation > 5°, but always < 10° (two varus and one valgus). No cases of significant rotational deformity were observed (Figure 4).

Complete hip ROM was recovered by 100% of patients. One patient showed a knee flection < 120° after an associated patellar fracture treated for hardware removal three weeks before our evaluation (Figure 5).

Complete functional recovery was reported by 95.7% of cases. All patients were able to run and to jump on the fractured femur. The most practiced sports were swimming and soccer. The average parent's satisfaction rate was 9.1/10. Lower results were observed in the cases who needed longer hospitalization or cast immobilization. No significant aesthetic concerning was reported by any of the patients.

The reported complications included two cases of superficial infection/cutaneous irritation of the TEN entry point resolved after TEN removal or with short-term oral antibiotic treatment, one refracture of the same femur occurred three months after TEN removal following a new trauma, one TEN mobilization managed with prolonged casting and healed 10 wk from the trauma without surgery.

According to the Flynn's scoring criteria, excellent results were registered in 79.2% of the cases, and satisfactory results in the remaining 20.8%.

DISCUSSION

The treatment of diaphyseal femoral fractures in preschool age is still debated. Conservative treatments remain the primary approach in most children of six years of age and younger considering the high healing power, the high remodeling power and the wide range of acceptance in this group of patients[1,10]. All conservative treatments have shown to be safe and to offer good clinical results. However, none of them has shown a clear superiority over the other methods[5,11]. Pavlik harness application *vs* spica casting were compared without showing any differences in clinical or radiographic outcomes[3]. Conservative treatments have many advantages being less invasive and practically without risk of soft tissues or growth plate injuries that are described in surgical procedures. On the other hand, conservative treatments present some important limitations: Prolonged skin traction with long hospitalization, significant patient discomfort, difficulties with hygienic care, and long weight-bearing restrictions[12]. Moreover, casting needs to be done in the operation theatre under general anaesthesia with similar time of surgical procedures, and similar radiation exposure for closed reductions in which sometimes it is necessary to use a specific invasive device[4].

Considering such limitations, surgical treatments have

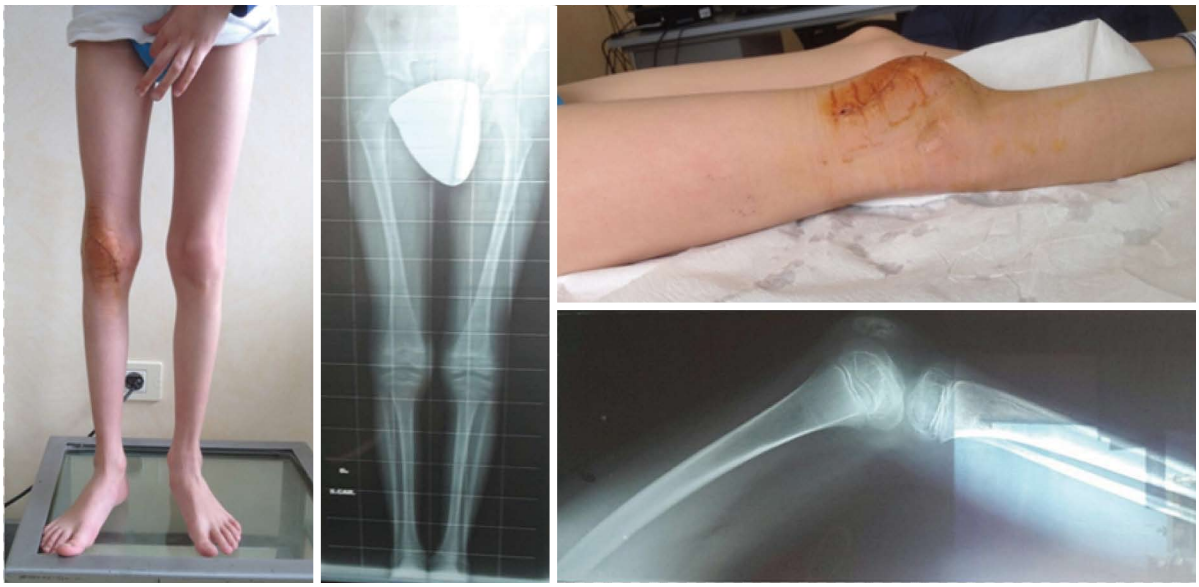

Figure 5 One patient had a limitation in knee flexion due to associated patellar fracture that was treated for hardware removal three weeks before our evaluation.

been increasingly used, particularly in patients with multiple traumata. Associated injuries involving the abdomen, the thorax, the spine or the head could represent a contraindication to conservative treatment[13,14].

Different studies compared clinical and radiographic results obtained with conservative and surgical treatment after femoral fracture in adolescence. A recent systematic literature review of 531 femoral fractures confirmed comparable clinical results, with a slightly higher risk of malunion between conservative and surgical treatment (11.5% *vs* 8.1%), but a lower risk of complications (1% *vs* 4%)[5]. The authors concluded that there was insufficient evidence to determine if long-term function differed between surgical and conservative treatment.

Some authors recommend considering the characteristics of the fracture (*e.g.*, degree of displacement and possible comminution) and the child's weight (higher or lower than 80 pounds/35 kg) when deciding on the type of fracture treatment[1,3,7].

TEN showed to be a safe and useful treatment in the management of such condition allowing for easier nursing and avoiding pressure ulcer[11]. Analyzing the good results obtained, TEN has become the first choice treatment even in isolated femoral fractures in children older than six years of age and under 45 kg of weight[6]. Most children and adolescents with femoral fractures can be treated successfully with a brief hospital course without compromising care or outcomes[15].

Surgical management is being increasingly used to assure optimal alignment, allow early motion, or facilitate early weight bearing[16]. Intramedullary nailing with TEN offers a stable fixation controlling also the rotational deformity if applied according to the known basic surgical rule[17]. Moreover, TEN is mininvasive, surgeon-friendly with a mean surgical time (after an appropriate learning curve) comparable with conservative treatment, and with a low complication rate[13,18].

Nevertheless, it is still unclear what the first-option treatment should be in pre-school children with diaphyseal femural fracture. Indeed, these patients have a great potential of growth and bone remodeling after fracture. For many types of fractures, both nonsurgical and surgical methods have yielded good results, but conservative treatment has traditionally been the first choice[1,4].

Considering the experience reported in older children undergone intramedullary nailing with TEN, it is evident that, besides clinical and radiographic outcomes, other parameters need to be taken into account for treatment choice[18].

Long hospitalization with long time in traction or uncomfortable immobilization is no longer acceptable in many situations. A faster recovery with early motion and weight-bearing should therefore be prioritized also in very young patients. In addition, surgical treatment allows for reducing the care costs relative to conservative options[15].

In our experience, treatment with TEN showed good mid-term clinical and radiographic results in patients younger than six years, in the absence of severe complications and with a high level of parents satisfaction rate even though a second operation to remove the pins was performed in each case treated.

Our results support the analysis of Rapp *et al*[19] who extended the indication to TEN as the standard treatment to patients at least 3-year-old. External fixation is another option that could be considered in patients younger than six years, but it is less comfortable for the patients and less accepted by their parents, besides requiring longer time of treatment to achieve optimal healing[20,21].

It should be considered that good results with TEN are only obtained when surgeons have a good

knowledge of the technique[22,23]. Complications are indeed mainly caused by technical errors including insertion of too thin nails, frame asymmetry, and implant malorientation[24]. This implies that the surgeon's experience remains one of the most important factors in the choice of treatment[25].

Finally, radiation exposure could be a critical point of TEN treatment. However, even if intraoperative fluoroscopic exposure is higher than with conservative treatment, the higher stability obtained and the lower rate of malunion, allow reducing the number of postoperative X-ray control radiographs[5].

Considering the good clinical and radiographic results at mid-term follow-up, TEN showed to be a safe, mini-invasive and surgeon-friendly technique even in patients younger than six years of age. Titanium elastic nailing, with specific indications, represents a useful and efficacy option for the treatment of diaphyseal femoral fractures even in patients younger than six years of age especially when the surgeon possesses good experience with this surgical technique. Further studies are necessary to evaluate if this method has any significant advantages in comparison to conservative treatments.

COMMENTS

Background

The treatment of diaphyseal femoral fractures in pediatric age is typically selected on the base of patient's age, fracture type, associated injuries, and the physical characteristics of the child. Diaphyseal femoral fracture in children less than six years of age is usually treated conservatively with several limitations. Intramedullary nailing with titanium elastic nails (TENs) shows good results at mid-term follow-up in children older than six years of age. The present study was therefore undertaken to verify the clinical and surgical outcomes of intramedullary nailing with TEN in a sample of children younger than six years presenting with diaphyseal femoral fractures.

Research frontiers

Different studies compared clinical and radiographic results obtained with conservative and surgical treatment after femoral fracture in adolescence: both nonsurgical and surgical methods have yielded good results. A recent systematic review confirmed comparable clinical results, but conservative treatment was demonstrated more expensive, and was associated with longer hospitalization and longer weight bearing restriction. External fixation is another option that could be considered in patients younger than six years, but it is less comfortable for the patients and less accepted by their parents, besides requiring longer time of treatment to achieve optimal healing. On this basis, Rapp *et al* proposed to extended the indication to TEN as the standard treatment to patients at least 3-year-old.

Innovations and breakthroughs

This retrospective study confirmed that TEN leads to good clinical and radiological results allowing optimal alignment, early motion and early weight bearing. TEN demonstrated to be effective for the treatment of diaphyseal femoral fractures even in patients younger than six years of age: It is a safe and surgeon-friendly technique and it is indicated particularly in patients with multiple traumata, and it guarantees a low rate of complications.

Applications

TEN represents a useful and efficacy option for the treatment of diaphyseal femoral fractures even in patients younger than six years of age especially when the surgeon possesses a good experience with this surgical technique.

Terminology

TEN: Titanium elastic nail.

Peer-review

The authors demonstrated an excellent result for treatment of diaphyseal femoral fractures in children with TEN. The paper is well written.

REFERENCES

1 **Buckley SL**. Current trends in the treatment of femoral shaft fractures in children and adolescents. *Clin Orthop Relat Res* 1997; **338**: 60-73 [PMID: 9170363 DOI: 10.1097/00003086-199705000-00009]

2 **Slongo TF**, Audigé L. Fracture and dislocation classification compendium for children: the AO pediatric comprehensive classification of long bone fractures (PCCF). *J Orthop Trauma* 2007; **21**: S135-S160 [PMID: 18277238]

3 **Podeszwa DA**, Mooney JF, Cramer KE, Mendelow MJ. Comparison of Pavlik harness application and immediate spica casting for femur fractures in infants. *J Pediatr Orthop* 2004; **24**: 460-462 [PMID: 15308892 DOI: 10.1097/00004694-200409000-00002]

4 **Catena N**, Sénès FM, Riganti S, Boero S. Diaphyseal femoral fractures below the age of six years: Results of plaster application and long term followup. *Indian J Orthop* 2014; **48**: 30-34 [PMID: 24600060 DOI: 10.4103/0019-5413.125487]

5 **Madhuri V**, Dutt V, Gahukamble AD, Tharyan P. Interventions for treating femoral shaft fractures in children and adolescents. *Cochrane Database Syst Rev* 2014; **(7)**: CD009076 [PMID: 25072888 DOI: 10.1002/14651858.CD009076.pub2]

6 **Saikia K**, Bhuyan S, Bhattacharya T, Saikia S. Titanium elastic nailing in femoral diaphyseal fractures of children in 6-16 years of age. *Indian J Orthop* 2007; **41**: 381-385 [PMID: 21139795 DOI: 10.4103/0019-5413.33876]

7 **Flynn JM**, Skaggs DL, Sponseller PD, Ganley TJ, Kay RM, Leitch KK. The surgical management of pediatric fractures of the lower extremity. *Instr Course Lect* 2003; **52**: 647-659 [PMID: 12690889]

8 **Ligier JN**, Metaizeau JP, Prévot J, Lascombes P. Elastic stable intramedullary nailing of femoral shaft fractures in children. *J Bone Joint Surg Br* 1988; **70**: 74-77 [PMID: 3339064]

9 **Flynn JM**, Hresko T, Reynolds RA, Blasier RD, Davidson R, Kasser J. Titanium elastic nails for pediatric femur fractures: a multicenter study of early results with analysis of complications. *J Pediatr Orthop* 2001; **21**: 4-8 [PMID: 11176345]

10 **Bowyer GW**, Clarke NM. Fractures of the femur in children. *J Bone Joint Surg Am* 1995; **77**: 1784-1785 [PMID: 7593090]

11 **Sanders JO**, Browne RH, Mooney JF, Raney EM, Horn BD, Anderson DJ, Hennrikus WL, Robertson WW. Treatment of femoral fractures in children by pediatric orthopedists: results of a 1998 survey. *J Pediatr Orthop* 2001; **21**: 436-441 [PMID: 11433152 DOI: 10.1097/00004694-200111000-00028]

12 **Khoriati AA**, Jones C, Gelfer Y, Trompeter A. The management of paediatric diaphyseal femoral fractures: a modern approach. *Strategies Trauma Limb Reconstr* 2016; **11**: 87-97 [PMID: 27401456 DOI: 10.1007/s11751-016-0258-2]

13 **Bhaskar A**. Treatment of long bone fractures in children by flexible titanium nails. *Indian J Orthop* 2005; **39**: 166-168 [DOI: 10.4103/0019-5413.36715]

14 **Metaizeau JP**. Stable elastic intramedullary nailing for fractures of the femur in children. *J Bone Joint Surg Br* 2004; **86**: 954-957 [PMID: 15446516 DOI: 10.1302/0301-620X.86B7.15620]

15 **Buechsenschuetz KE**, Mehlman CT, Shaw KJ, Crawford AH, Immerman EB. Femoral shaft fractures in children: traction and casting versus elastic stable intramedullary nailing. *J Trauma* 2002; **53**: 914-921 [PMID: 12435943 DOI: 10.1097/00005373-200211000-00017]

16 **Flynn JM**, Luedtke LM, Ganley TJ, Dawson J, Davidson RS, Dormans JP, Ecker ML, Gregg JR, Horn BD, Drummond DS. Comparison of titanium elastic nails with traction and a spica cast to treat femoral fractures in children. *J Bone Joint Surg Am* 2004; **86-A**:

770-777 [PMID: 15069142]
17 **Gwyn DT**, Olney BW, Dart BR, Czuwala PJ. Rotational control of various pediatric femur fractures stabilized with titanium elastic intramedullary nails. *J Pediatr Orthop* 2004; **24**: 172-177 [PMID: 15076602 DOI: 10.1097/01241398-200403000-00007]
18 **Narayanan UG**, Hyman JE, Wainwright AM, Rang M, Alman BA. Complications of elastic stable intramedullary nail fixation of pediatric femoral fractures, and how to avoid them. *J Pediatr Orthop* 2004; **24**: 363-369 [PMID: 15205616 DOI: 10.1097/01241398-200407000-00004]
19 **Rapp M**, Kaiser MM, Grauel F, Gielok C, Illing P. Femoral shaft fractures in young children (& lt; 5 years of age): operative and non-operative treatments in clinical practice. *Eur J Trauma Emerg Surg* 2015; Epub ahead of print [PMID: 26335539]
20 **Aronson J**, Tursky EA. External fixation of femur fractures in children. *J Pediatr Orthop* 1992; **12**: 157-163 [PMID: 1552016 DOI: 10.1097/01241398-199203000-00003]
21 **Bar-On E**, Sagiv S, Porat S. External fixation or flexible intramedullary nailing for femoral shaft fractures in children. A prospective, randomised study. *J Bone Joint Surg Br* 1997; **79**: 975-978 [PMID: 9393916 DOI: 10.1302/0301-620X.79B6.7740]
22 **Letts M**, Jarvis J, Lawton L, Davidson D. Complications of rigid intramedullary rodding of femoral shaft fractures in children. *J Trauma* 2002; **52**: 504-516 [PMID: 11901327 DOI: 10.1097/00005373-200203000-00015]
23 **Ward WT**, Levy J, Kaye A. Compression plating for child and adolescent femur fractures. *J Pediatr Orthop* 1992; **12**: 626-632 [PMID: 1517424 DOI: 10.1097/01241398-199209000-00012]
24 **Lascombes P**, Haumont T, Journeau P. Use and abuse of flexible intramedullary nailing in children and adolescents. *J Pediatr Orthop* 2004; **26**: 827-834 [PMID: 17065959 DOI: 10.1097/01.bpo.0000235397.64783.d6]
25 **Andreacchio A**, Marengo L, Canavese F, Pedretti L, Memeo A. Comparison between external fixation and elastic stable intramedullary nailing for the treatment of femoral shaft fractures in children younger than 8 years of age. *J Pediatr Orthop B* 2016; **25**: 471-477 [PMID: 27261769 DOI: 10.1097/BPB.0000000000000342]

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ORIGINAL ARTICLE

Clinical Trials Study

Comparative clinical study of ultrasound-guided A1 pulley release *vs* open surgical intervention in the treatment of trigger finger

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Author contributions: Nikolaou VS analyzed data and edited the manuscript; Malahias MA conducted ultrasound exams and wrote the manuscript; Nikolaou VS and Malahias MA have contributed equally to this work; Kaseta MK and Sourlas I assisted during the operations; Babis GC had the final checking and proof editing of the manuscript.

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Abstract

AIM

To investigate the effectiveness of ultrasound-guided release of the first annular pulley and compare results with the conventional open operative technique.

METHODS

In this prospective randomized, single-center, clinical study, 32 patients with trigger finger or trigger thumb, grade Ⅱ-Ⅳ according to Green classification system, were recruited. Two groups were formed; Group A (16 patients) was treated with an ultrasound-guided percutaneous release of the affected A1 pulley under local anesthesia. Group B (16 patients) underwent an open surgical release of the A1 pulley, through a 10-15 mm incision. Patients were assessed pre- and postoperatively (follow-up: 2, 4 and 12 wk) by physicians blinded to the procedures. Treatment of triggering (primary variable of interest) was expressed as the "success rate" per digit. The time for taking postoperative pain killers, range of motion recovery, QuickDASH test scores (Greek version), return to normal activities (including work), complications and cosmetic results were assessed.

RESULTS

The success rate in group A was 93.75% (15/16) and in group B 100% (16/16). Mean times in group A patients were 3.5 d for taking pain killers, 4.1 d for returning to normal activities, and 7.2 and 3.9 d for complete extension and flexion recovery, respectively. Mean QuickDASH scores in group A were 45.5 preoperatively and, 7.5, 0.5 and 0 after 2, 4, and 12 wk postoperatively. Mean times in group B patients were 2.9 d for taking pain killers, 17.8 d for returning to normal activities, and 5.6 and 3 d for complete extension and flexion recovery. Mean QuickDASH scores in group B were 43.2 preoperatively and, 8.2, 1.3 and 0 after 2, 4, and 12 wk postoperatively. The cosmetic results found excellent or good in 87.5% (14/16) of group A patients, while in 56.25% (9/16) of group B patients were evaluated as fair or poor.

CONCLUSION

Treatment of the trigger finger using ultrasonography resulted in fewer absence of work days, and better cosmetic results, in comparison with the open surgery technique. It is a promising method that represents excellent results without major complications, so that it could be possibly be established as a first-line treatment in the trigger finger's disease.

Key words: Ultrasound-guided; Trigger finger; A1 release; Comparative; V-lance knife; Percutaneous; Minimally-invasive

Core tip: In this randomized, prospective clinical trial, of 32 patients with trigger finger or trigger thumb, ultrasound assisted treatment of the A1 pulley, revealed better outcome in comparison with the open technique. Patients had fewer work absence days and improved surgical scar. To the best of our knowledge this is the first randomized trial in this field. These promising results have to be further confirmed with larger trials in the future.

Nikolaou VS, Malahias MA, Kaseta MK, Sourlas I, Babis GC. Comparative clinical study of ultrasound-guided A1 pulley release *vs* open surgical intervention in the treatment of trigger finger. *World J Orthop* 2017; 8(2): 163-169 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i2/163.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i2.163

INTRODUCTION

Stenosing tenosynovitis with mechanical impingement of the flexor tendons at the A1 pulley is a common condition affecting the digits in the following order of decreasing prevalence: Thumb, ring, middle, small and index. A nodule or thickening in the flexor tendon becomes trapped proximal to the pulley, making finger extension difficult.

There have been described several management approaches in the treatment of trigger finger disease. Nonsurgical management includes corticosteroid injection and splinting. However, according to a a level I systematic review[1] corticosteroid injections are effective in just 57% of patients. Additionally, that technique can result in up to 29% recurrence[2]. Furthermore, many patients treated by conservative means, like immobilization or injections, may additionally require surgery[3]. In a recent clinical trial, designed to compare the effectiveness of 2 splint designs in treating trigger finger[4], the results showed positive outcomes in 50%-77% of the patients, depending on the type of splinting.

On the other hand, many authors support the superiority of surgical procedures for the definite treatment of the disease[5]. Indeed, the percutaneous and open surgery methods have been proved more efficient than simple corticosteroid injection, regarding the cure and relapse of the disease[5,6]. Conventional open surgical technique remains the gold standard of treatment options[7]. However, surgical treatment also has complications, including scarring, surgical site infections and nerve injuries, in addition to possible disease relapse[8].

Percutaneous surgical release of trigger finger is a preferable alternative to open surgery[9], although a potential disadvantage can be the injury to either nerve or tendon due to the limited visibility[7]. Many hand surgeons avoid this treatment option due to the close proximity to the digital nerve[10]. According to a meta-analysis of current literature[11], blind percutaneous release has become more and more popular lately, with overall increased success rates.

Ultrasound can be a helpful tool for better success by means of assisting the placement of the the needle during percutaneous procedure[12]. There is a controversy regarding the safety and usefulness of this technique. Paulius *et al*[13] showed that ultrasound-guided treatment has disadvantages like tendon injuries, neural or vascular lacerations and no complete release of the first annular pulleys. As an answer to them, Wu *et al*[14] support the usage of ultrasound assistence to avoid iatrogenic damage.

In a recent systematic review of current evidence, it is revealed that percutaneous release with ultrasonography, resulted in higher success rate than non-sonography release[11]. Despite that, till now, no randomized controlled trials could be found at the Medline and Cochrane Database, comparing open surgery to ultasound-guided percutaneous release.

This lack of reliable trials comparing open surgery to ultrasound-guided A1 pulley release is pronounced. In the present randomized controlled trial, we tried to compare the efficacy of a single ultrasound-guided percutaneous A1 pulley release with conventional open surgery in terms of ability to correct the trigger finger.

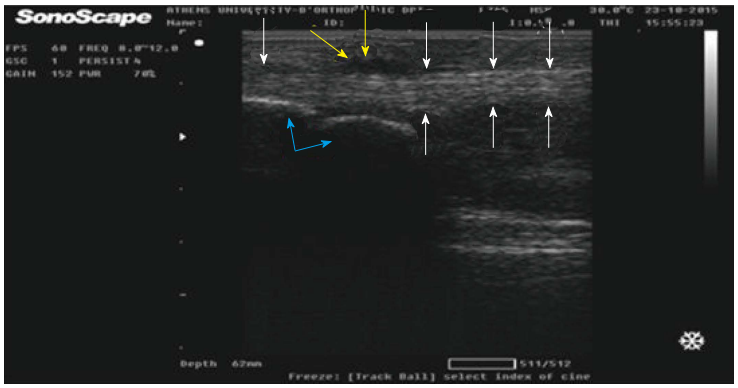

Figure 1 Longitudinal view of the middle finger's flexor tendons (white arrows) volarly to the metacarpal-phalangeal joint (blue double arrow). The A1 pulley appears swollen and anechoic (yellow arrows), establishing the trigger finger disease.

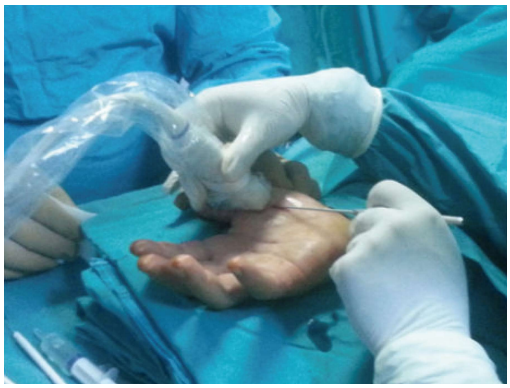

Figure 2 Positioning of the V-Lance Knife almost parallel to the probe.

MATERIALS AND METHODS

We conducted a randomized, prospective, controlled, single-center, clinical trial of 32 patients with resistant - after conservative treatment - trigger finger or trigger thumb, suffering at least for 3 mo. The majority of the patients were middle-aged women (62.5% females, mean age: 45.5 years old), evaluated as grade Ⅱ to Ⅳ according to Green classification system of the trigger finger disease.

We excluded patients under 18 years old, these who were treated with a previous operation or a corticosteroid injection for their disease and those who were suffering by inflammatory arthritis, tumor or autoimmune disease. Moreover, we did not include patients with multiple trigger fingers trying to evaluate our study groups strictly using the model one patient-one trigger finger. We did not exclude patients with insulin-dependent diabetes mellitus and a history of other tendon related pathology of the upper extremity, although it is known that they might be linked with a higher rate of treatment failure[15].

The patients were clinically and ultrasonographically examined and then they were randomly divided into two groups using a closed envelope. The ultrasonography was performed with a portable grey scale ultrasound (frequency of 10-12 MHz, 5-12 MHz, Linear Array, A6 Portable Ultrasonic Diagnostic System, Sonoscape Company Limited, Shenzhen, China) by a doctor of our department. The patients were informed with an oral and written manner for their options of treatment and they received clear explanations about their suggested treatment. For confirmation, they signed full written consent.

Group A (16 patients) was treated with an ultrasound-guided percutaneous release of the affected first annular pulley under local anesthesia and without any corticosteroid injection.

In addition, group B (16 patients) underwent a conventional open surgical release of the A1 pulley, through a 10-15 mm incision. The technique in group A included initially a sonographically guided local anesthetic injection, proximally to the metacarpal-phalangeal joint (Figure 1). The infiltration was done under sterile conditions (sterilization of the skin, coverage of the ultrasound probe with sterile pad, use of appropriate gel) by a physician that simultaneously managed the ultrasound device (one man's technique). Under continuous sonographic imaging of the digital neurovascular structures, the physician inserted percutaneously - through a negligible section < 1 mm - an ophthalmic corneal/scleral V-Lance knife (Alcon, Novartis company), over flexor tendons (Verdan's zone 3, proximally to the A1 pulley) and towards their longitudinal axis (Figure 2). Then, the knife was advanced distally, just below A1 pulley (Figure 3) and pressed palmary so as to loosen the thicken pulley (the intersecting part).

Thus, after having withdrawn the V-Lance knife (which had created the necessary space intrasheath), a thin hook with a long neck was introduced under the - now extended - A1 pulley (Figure 4). The hook penetrated the annular ligamentous structure facing palmary in order to protect the flexor tendons and subsequently removed proximally (in a steady quick move) carrying along and dissecting the A1 pulley. Intraoperatively and right after the performed dissection, each patient was clinically and sonographically evaluated for the achieved resolution of the triggering.

All patients were estimated with the completion of Q-DASH score before and after the operation (1, 4, 12 wk). Resolution of triggering (primary variable of interest) was expressed as the "success rate" per digit. The time for taking postoperative pain killers, range of motion recovery, return to normal activities (including work), complications and cosmetic results were assessed. Differences among groups were analysed using Students *t* test. Statistical significant difference was considered if *P*

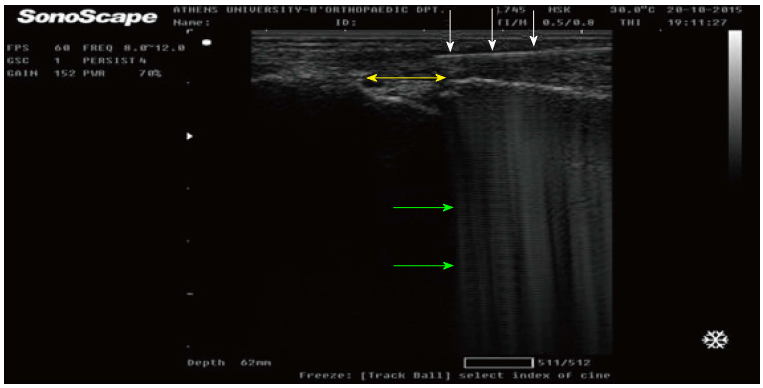

Figure 3 Longitudinal ultrasound-guided release of the A1 pulley. The knife -with its acoustic shadowing (green arrows) - is clearly visible (white arrows). Its tip is advanced over the metacarpal-phalangeal joint (yellow arrow), parallel to the superficial flexor tendon.

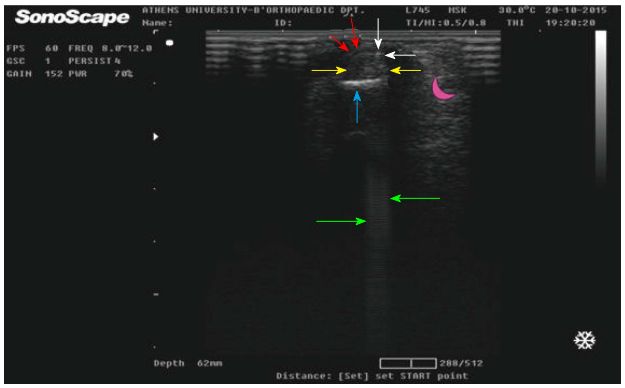

Figure 4 In order to be assured for the right position of the knife, we are transferred in transverse view of the tendons (flexor's transverse cut: Yellow arrows, lying on the bone: Light blue arrow). Here, we certify that the tip of the knife (tip as a white dot: white arrows, sending its characteristic acoustic shadow: Green arrows) is attaching the volar end of the tendons (without penetrating them), under the A1 pulley (the sheath is appeared as a thin line under the red arrows). Moreover, it is vital to avoid the neurovascular digital structures (digital artery in the curved side of the purple moon).

< 0.05.

The same doctor did the procedure in all patients (Group A and Group B) and evaluated them prior to the injection through Q-DASH questionnaire, clinical and ultrasound examination. Another doctor evaluated the patients in the follow-up period. This physician was blinded to the procedure (ultrasound-guided or open) and to the pre-injection scores of these patients as far as Q-DASH, resolution of triggering, painkillers and return to normal activities, but he was non blinded as far cosmetic results, range of motion and complications. Instructions for return to work (or usual activities in elderly people) were different in group A patients than in group B. We were able to be more aggressive with group A patients which we advised to start their work from the first postoperative day. On the contrary, group B patients could not be managed to start working before removing their sutures (12-14 d).

Our study protocol (plus our written consent form) was approved by our Health's Institution Scientific Committee and the Athens University, School of Medicine.

RESULTS

We were able to visualize the flexor tendons under the A1 pulley and recognise the digital neurovascular bundles in all group A patients. The whole percutaneous procedure was real-time documented and there was no mentioned intraoperative complication in anyone of our patients.

We managed to obtain follow-up in 100% (32 out of 32) of our patients. The success rate in group A was 93.75% (15/16) and in group B 100% (16/16) (P > 0.05). There was just one patient (female, 53 years old, white collar worker, with uncontrolled hypothyroeidism, index finger) who appeared to have no improvement in her triggering after the percutaneous ultrasound-guided procedure. Apart from this exception, both techniques proved to be well tolerated, with no side effects, infections or complaints for persistent pain.

Mean times in group A patients were 3.5 d for taking pain killers, and 7.2 and 3.9 d for complete extension and flexion recovery, respectively (Table 1). Mean Quick DASH scores in group A were 45.5 preoperatively and, 7.5, 0.5 and 0 after 2, 4, and 12 wk postoperatively (Figure 5A).

Mean times in group B patients were 2.9 d for taking pain killers, and 5.6 and 3 d for complete extension and flexion recovery (Table 2). Mean QuickDASH scores in group B were 43.2 preoperatively and, 8.2, 1.3 and 0 after 2, 4, and 12 wk postoperatively (Figure 5B). These differences were not statistically significant (P > 0.05) among the two groups.

However, mean time for returning to normal activities in group A patients was 4.1 d as opposite to 17.8 d for Group B patients (P < 0.05).

Additionally, the cosmetic results found excellent or good in 87.5% (14/16) of group A patients, while in 56.25% (9/16) of group B patients were evaluated as fair or poor (P < 0.05) (Figure 6).

DISCUSSION

According to the literature, there is an emerging number of cadaveric and clinical studies investigating the use of ultrasound in hand and wrist tendinopathies[15-17]. Especially in the trigger finger disease we were able to find a wide variety of anatomic or therapeutic trials[18-20].

Ultrasound examination can diagnose secondary causes of trigger fingering[21], while it could be a valuable

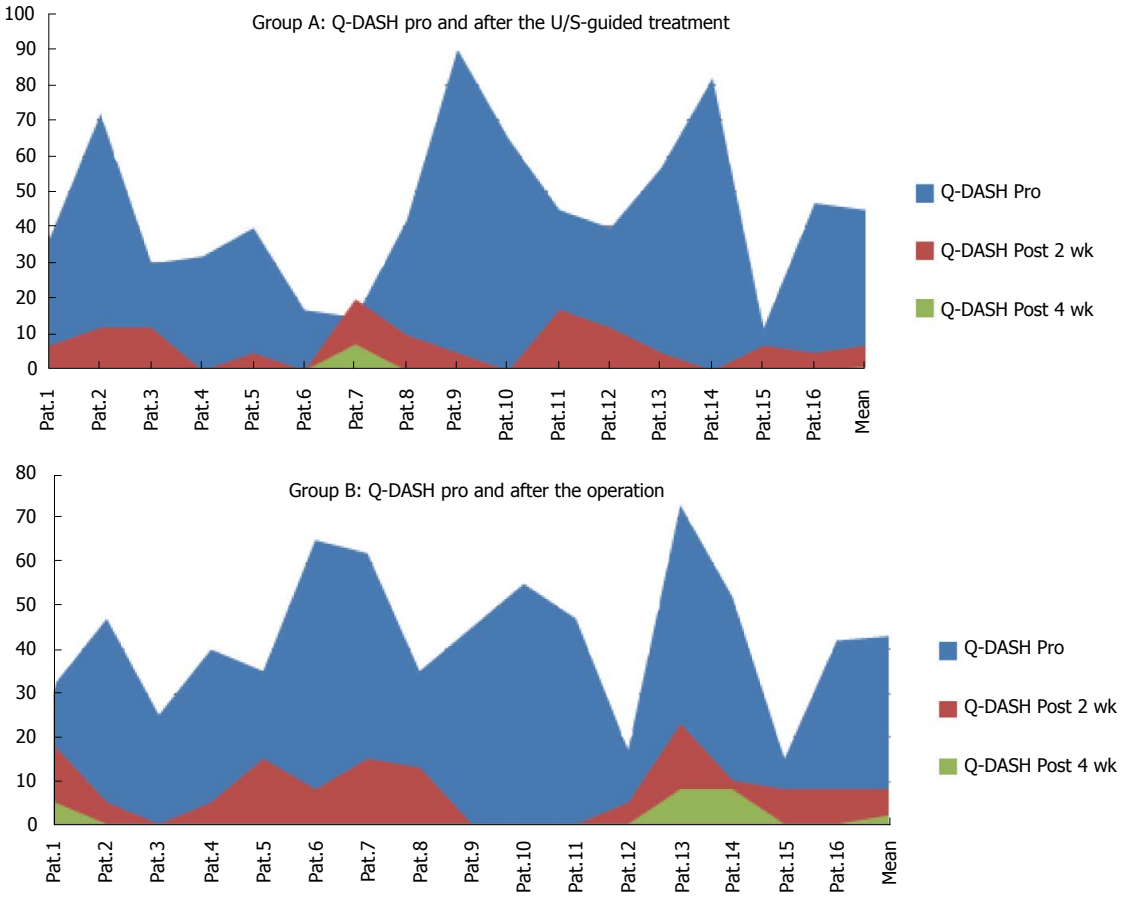

Figure 5 The Q-DASH fluctuation per patient in (A) and (B) respectively.

Table 1 Group A, data per patient: Days for: (1) taking pain killers; (2) returning to normal activities; (3) complete extension; and (4) flexion recovery

Group A	Post painkillers (d)	Return to normal (d)	Full extension (d)	Full flexion (d)
Patient 1	4	3	8	4
Patient 2	7	8	9	5
Patient 3	1	2	3	1
Patient 4	5	6	5	3
Patient 5	1	3	6	2
Patient 6	2	2	5	0
Patient 7	3	2	7	6
Patient 8	5	4	10	7
Patient 9	0	2	4	1
Patient 10	1	2	8	4
Patient 11	6	10	12	7
Patient 12	1	0	5	2
Patient 13	3	3	6	5
Patient 14	4	4	11	5
Patient 15	10	8	7	5
Patient 16	3	6	9	6
Total	56	65	115	63
Mean	3.5	4.1	7.2	3.9

Table 2 Group B, data per patient: days for: (1) taking pain killers; (2) returning to normal activities; (3) complete extension; and (4) flexion recovery

Group B	Post painkillers (d)	Return to normal (d)	Full extension (d)	Full flexion (d)
Patients 1	5	23	7	3
Patients 2	0	15	5	4
Patients 3	2	14	1	1
Patients 4	1	15	3	1
Patients 5	3	17	11	4
Patients 6	3	15	4	3
Patients 7	4	21	8	4
Patients 8	6	22	9	5
Patients 9	0	14	1	1
Patients 10	2	18	6	3
Patients 11	5	18	6	5
Patients 12	1	16	2	2
Patients 13	6	23	16	3
Patients 14	4	22	4	3
Patients 15	3	17	2	4
Patients 16	1	15	5	2
Total	46	285	90	48
Mean	2.9	17.8	5.6	3

tool in guiding therapeutic procedures. However, it can demand extra time and effort and the potential clinical benefits compared to the blind technique can be questionable[22].

According to Rojo-Manaute *et al*[23], good knowledge of the anatomy, and excellent handling of the ultrasound machine, can result to safe and successfull treatment of the trigger finger. Thus, offering an alternative to

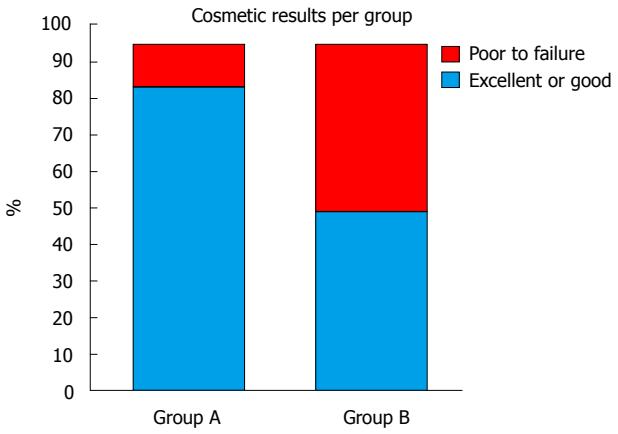

Figure 6 Regarding the cosmetic results, there is a clear difference between the two groups, in favor of the ultrasound-treated patients.

traditional open surgery. This specific procedure can be performed in the medical office with the use of a portable ultrasound device for the purpose of improving the cost-effectiveness of the treatment and reducing the surgery-related anxiety of patients. Furthermore, this technique promises to minimize postoperative short-term morbidity[24].

Rajeswaran *et al*[25] described an ultrasound-guided procedure using a modified hypodermic needle to resolve trigger finger. He documented no complications and a complete resolution of triggering in 91% of his patients[25]. Besides, using a knife result in a complete pulley release significantly better compared to the needle technique[26]. On the other hand, in an experimental cadaveric study, ultrasound-guided percutaneous A1 pulley release resulted in repeated injuries of the tendon sheath and of the proximal neural or vascular structures[13].

Finally, in the most recent study, Lapègue *et al*[27] conclude that US-guided treatment of the trigger finger is feasible in current practice, with minimal complications, even if their trial showed a 17% postoperative persistance of triggering.

In our study we aimed to prove that an ultrasound assisted release of the A1 pulley is - at least - not inferior than the open technique in a matched controlled population, regarding the clinical outcome scores. Strong points of our trial are that as far as we know, this is the first prospective randomized trial publishedin the English speaking literature. We have used different qualitative and quantitative scales to document our results. Apropos of indexes like Q-DASH, resolution of triggering, painkillers and return to normal activities, the follow-up of our patients was blinded.

Limitations of this study also merrit to be mentioned. Statistical power is reduced due to the small sample size in the present study (n = 32). This could have played a role in reducing the significance of some of the statistical tests. A post hoc power analysis, using the GPower software (Faul and Erdfelder, 1992) showed that on the basis of the means, among groups, an n of approximately 60 (30 in each group) would be needed to give better statistical power at the recommended 0.80 level. Additionally, We had only short- to mid-term results in the follow-up of our patients but at the other end of the spectrum this seems to be the usual postoperative protocol according to the literature[28]. Another weakness of our study is that it was not as cost-effective as it could be. That was because we avoided treating our ultrasound-guided patients at the medical office but exclusively in the operative theater in order to eradicate extrinsic factors between the two groups.

Our study revealed that ultrasound assisted release of the A1 pulley resulted in less days of work absence and better cosmetic results, in comparison with the traditional open technique. Notwithstanding, it is necessary more clinical trials to be followed through on this area of interest in order to obtain more secure conclusions.

ACKNOWLEDGMENTS

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COMMENTS

Background

Stenosing tenosynovitis with mechanical impingement of the flexor tendons at the A1 pulley is a common condition affecting the digits in the following order of decreasing prevalence: Thumb, ring, middle, small and index. A nodule or thickening in the flexor tendon becomes trapped proximal to the pulley, making finger extension difficult. There have been described several management approaches in the treatment of trigger finger disease. Surgery is recommended in those cases that conservative treatment has failed. Conventional open surgical technique remains the gold standard of treatment. However, complications do exist, such as painful scarring, infections and nerve damage, in addition to recurrence of the disease.

Research frontiers

In a recent systematic review of current evidence, it is revealed that percutaneous release with sonography guidance had a significantly higher success rate than non-sonography guidance. Despite that, no randomized controlled trials exists comparing open surgery to ultrasound-guided percutaneous release. In the present randomized controlled trial, they compared the efficacy of a single ultrasound-guided percutaneous A1 pulley release with conventional open surgery in terms of ability to correct the trigger finger. To the best of our knowledge this is the first randomized trial in this field.

Applications

Ultrasound-guided release of the A1 pulley yielded better results compared to the traditional open technique, in respect to fewer working days lost and improved cosmetic results. It is a promising method that produces excellent results without major complications, so that it could be possibly be established as a first-line treatment in the trigger finger's disease. However, in order to be established as a first-line treatment in the trigger finger's disease, it is necessary more clinical trials to be followed through on this area of interest.

Terminology

Trigger finger: Stenosing tenosynovitis with mechanical impingement of the flexor tendons at the A1 pulley. Condition affects the digits in the following order

of decreasing prevalence: Thumb, ring, middle, small and index. A nodule or thickening in the flexor tendon becomes trapped proximal to the pulley, making finger extension difficult.

Peer-review

This manuscript investigated the usefulness of ultrasonography for the surgical treatment of finger.

REFERENCES

1 **Fleisch SB**, Spindler KP, Lee DH. Corticosteroid injections in the treatment of trigger finger: a level I and II systematic review. *J Am Acad Orthop Surg* 2007; **15**: 166-171 [PMID: 17341673]
2 **Rhoades CE**, Gelberman RH, Manjarris JF. Stenosing tenosynovitis of the fingers and thumb. Results of a prospective trial of steroid injection and splinting. *Clin Orthop Relat Res* 1984: 236-238 [PMID: 6488636]
3 **Benson LS**, Ptaszek AJ. Injection versus surgery in the treatment of trigger finger. *J Hand Surg Am* 1997; **22**: 138-144 [PMID: 9018627 DOI: 10.1016/S0363-5023(05)80194-7]
4 **Tarbhai K**, Hannah S, von Schroeder HP. Trigger finger treatment: a comparison of 2 splint designs. *J Hand Surg Am* 2012; **37**: 243-249, 249.e1 [PMID: 22189188 DOI: 10.1016/j.jhsa.2011.10.038]
5 **Wang J**, Zhao JG, Liang CC. Percutaneous release, open surgery, or corticosteroid injection, which is the best treatment method for trigger digits? *Clin Orthop Relat Res* 2013; **471**: 1879-1886 [PMID: 23208122 DOI: 10.1007/s11999-012-2716-6]
6 **Sato ES**, Gomes Dos Santos JB, Belloti JC, Albertoni WM, Faloppa F. Treatment of trigger finger: randomized clinical trial comparing the methods of corticosteroid injection, percutaneous release and open surgery. *Rheumatology* (Oxford) 2012; **51**: 93-99 [PMID: 22039269 DOI: 10.1093/rheumatology/ker315]
7 **Guler F**, Kose O, Ercan EC, Turan A, Canbora K. Open versus percutaneous release for the treatment of trigger thumb. *Orthopedics* 2013; **36**: e1290-e1294 [PMID: 24093706 DOI: 10.3928/01477447-20130920-22]
8 **Turowski GA**, Zdankiewicz PD, Thomson JG. The results of surgical treatment of trigger finger. *J Hand Surg Am* 1997; **22**: 145-149 [PMID: 9018628 DOI: 10.1016/S0363-5023(05)80195-9]
9 **Uçar BY**. Percutaneous surgery: a safe procedure for trigger finger? *N Am J Med Sci* 2012; **4**: 401-403 [PMID: 23050250 DOI: 10.4103/1947-2714.100988]
10 **Uras I**, Yavuz O. Percutaneous release of trigger thumb: do we really need steroid? *Int Orthop* 2007; **31**: 577 [PMID: 17404732 DOI: 10.1007/s00264-006-0288-3]
11 **Zhao JG**, Kan SL, Zhao L, Wang ZL, Long L, Wang J, Liang CC. Percutaneous first annular pulley release for trigger digits: a systematic review and meta-analysis of current evidence. *J Hand Surg Am* 2014; **39**: 2192-2202 [PMID: 25227600 DOI: 10.1016/j.jhsa.2014.07.044]
12 **Jou IM**, Chern TC. Sonographically assisted percutaneous release of the a1 pulley: a new surgical technique for treating trigger digit. *J Hand Surg Br* 2006; **31**: 191-199 [PMID: 16376004 DOI: 10.1016/j.jhsb.2005.11.003]
13 **Paulius KL**, Maguina P. Ultrasound-assisted percutaneous trigger finger release: is it safe? *Hand* (N Y) 2009; **4**: 35-37 [PMID: 18830758 DOI: 10.1007/s11552-008-9137-8]
14 **Wu KC**, Chern TC, Jou IM. Ultrasound-assisted percutaneous trigger finger release: it is safe. *Hand* (N Y) 2009; **4**: 339 [PMID: 19291330 DOI: 10.1007/s11552-009-9179-6]
15 **Chan JK**, Choa RM, Chung D, Sleat G, Warwick R, Smith GD. High resolution ultrasonography of the hand and wrist: three-year experience at a District General Hospital Trust. *Hand Surg* 2010; **15**: 177-183 [PMID: 21089192 DOI: 10.1142/S0218810410004813]
16 **Draghi F**, Bortolotto C. Intersection syndrome: ultrasound imaging. *Skeletal Radiol* 2014; **43**: 283-287 [PMID: 24337446 DOI: 10.1007/s00256-013-1786-1]
17 **Sato J**, Ishii Y, Noguchi H, Takeda M. Sonographic analyses of pulley and flexor tendon in idiopathic trigger finger with interphalangeal joint contracture. *Ultrasound Med Biol* 2014; **40**: 1146-1153 [PMID: 24613641 DOI: 10.1016/j.ultrasmedbio.2014.01.009]
18 **Yang TH**, Lin YH, Chuang BI, Chen HC, Lin WJ, Yang DS, Wang SH, Sun YN, Jou IM, Kuo LC, Su FC. Identification of the Position and Thickness of the First Annular Pulley in Sonographic Images. *Ultrasound Med Biol* 2016; **42**: 1075-1083 [PMID: 26831343 DOI: 10.1016/j.ultrasmedbio.2015.12.007]
19 **Kim SJ**, Lee CH, Choi WS, Lee BG, Kim JH, Lee KH. The thickness of the A2 pulley and the flexor tendon are related to the severity of trigger finger: results of a prospective study using high-resolution ultrasonography. *J Hand Surg Eur Vol* 2016; **41**: 204-211 [PMID: 26568540 DOI: 10.1177/1753193415615076]
20 **Sato J**, Ishii Y, Noguchi H, Takeda M. Sonographic appearance of the flexor tendon, volar plate, and A1 pulley with respect to the severity of trigger finger. *J Hand Surg Am* 2012; **37**: 2012-2020 [PMID: 22939830]
21 **Kara M**, Ekiz T, Sumer HG. Hand pain and trigger finger due to ganglion cyst: an ultrasound-guided diagnosis and injection. *Pain Physician* 2014; **17**: E786 [PMID: 25415796]
22 **Cecen GS**, Gulabi D, Saglam F, Tanju NU, Bekler HI. Corticosteroid injection for trigger finger: blinded or ultrasound-guided injection? *Arch Orthop Trauma Surg* 2015; **135**: 125-131 [PMID: 25381472 DOI: 10.1007/s00402-014-2110-9]
23 **Rojo-Manaute JM**, Rodríguez-Maruri G, Capa-Grasa A, Chana-Rodríguez F, Soto Mdel V, Martín JV. Sonographically guided intrasheath percutaneous release of the first annular pulley for trigger digits, part 1: clinical efficacy and safety. *J Ultrasound Med* 2012; **31**: 417-424 [PMID: 22368132]
24 **Hopkins J**, Sampson M. Percutaneous tenotomy: Development of a novel, percutaneous, ultrasound-guided needle-cutting technique for division of tendons and other connective tissue structures. *J Med Imaging Radiat Oncol* 2014; **58**: 327-330 [PMID: 25088140 DOI: 10.1111/1754-9485.12113]
25 **Rajeswaran G**, Lee JC, Eckersley R, Katsarma E, Healy JC. Ultrasound-guided percutaneous release of the annular pulley in trigger digit. *Eur Radiol* 2009; **19**: 2232-2237 [PMID: 19399506 DOI: 10.1007/s00330-009-1397-3]
26 **Smith J**, Rizzo M, Lai JK. Sonographically guided percutaneous first annular pulley release: cadaveric safety study of needle and knife techniques. *J Ultrasound Med* 2010; **29**: 1531-1542 [PMID: 20966464]
27 **Lapègue F**, André A, Meyrignac O, Pasquier-Bernachot E, Dupré P, Brun C, Bakouche S, Chiavassa-Gandois H, Sans N, Faruch M. US-guided Percutaneous Release of the Trigger Finger by Using a 21-gauge Needle: A Prospective Study of 60 Cases. *Radiology* 2016; **280**: 493-499 [PMID: 26919442 DOI: 10.1148/radiol.2016151886]
28 **Jongjirasiri Y**. The results of percutaneous release of trigger digits by using full handle knife 15 degrees: an anatomical hand surface landmark and clinical study. *J Med Assoc Thai* 2007; **90**: 1348-1355 [PMID: 17710976]

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ORIGINAL ARTICLE

Observational Study

Lower limb intracast pressures generated by different types of immobilisation casts

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Abstract

AIM

To determine if complete, split casts and backslabs [plaster of Paris (POP) and fiberglass] generate different intracast pressures and pain.

METHODS

Increased swelling within casts was modeled by a closed water system attached to an expandable bag placed directly under different types of casts applied to a healthy lower limb. Complete fiberglass and POP casts, split casts and backslabs were applied. Twenty-five milliliter aliquots of saline were injected into the system and the generated intracast pressures were measured using a sphygmomanometer. The subject was blinded to the pressure scores to avoid bias. All casts were applied to the same right limb on the same subject to avoid the effects of variations in anatomy or physiology on intracast pressures. Pain levels were evaluated using the Visual Analogue Score after each sequential saline injection. Each type of cast was reapplied four times and the measurements were repeated on four separate occasions. Sample sizes were determined by a pre-study 90% power calculation to detect a 20% difference in intracast pressures between cast groups.

RESULTS

A significant difference between the various types of

casts was noted when the saline volume was greater than 100 mL (P = 0.009). The greatest intracast pressure was generated by complete fiberglass casts, which were significantly higher than complete POP casts or backslabs (P = 0.018 and P = 0.008 respectively) at intracast saline volumes of 100 mL and higher. Backslabs produced a significantly lower intracast pressure compared to complete POP only once the saline volume within casts exceeded 225 mL (P = 0.009). Intracast pressures were significantly lower in split casts (P = 0.003). Split POP and fiberglass casts produced the lowest intracast pressures, even compared to backslabs (P = 0.009). Complete fiberglass casts generated the highest pain levels at manometer pressures of 75 mmHg and greater (P = 0.001). Split fiberglass casts had significantly reduced pain levels (P = 0.001). In contrast, a split complete POP cast did not produce significantly reduced pain levels at pressures between 25-150 mmHg. There was no difference in pain generated by complete POP and backslabs at manometer pressures of 200 mmHg and lower.

CONCLUSION

Fibreglass casts generate significantly higher intracast pressures and pain than POP casts. Split casts cause lower intracast pressures regardless of material, than complete casts and backslabs.

Key words: Fracture; Pressure; Lower limb; Plaster of Paris; Cast; Fiberglass; Backslab; Compartment syndrome

Core tip: Little information is available regarding whether different lower limb casts generate different intracast pressures and pain during swelling, increasing the risk of compartment syndrome. Increased swelling within casts was modeled by a closed water system attached to an expandable bag placed directly under different types of casts. Our study suggests that split casts generate lower intracast pressures than backslabs, which are traditionally thought to accommodate swelling better. Fibreglass casts generate significantly higher intracast pressures and pain levels than plaster of Paris casts. Judicious use of complete casts, particularly fiberglass, and backslabs may be advisable for lower limb immobilisation.

Chaudhury S, Hazlerigg A, Vusirikala A, Nguyen J, Matthews S. Lower limb intracast pressures generated by different types of immobilisation casts. *World J Orthop* 2017; 8(2): 170-177 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i2/170.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i2.170

INTRODUCTION

It is common practice to apply lower limb casts to manage non-displaced fractures, following lower limb surgery or the temporary stabilisation of ankle fractures awaiting surgery so as to maintain a plantar grade position and to prevent contracture. Charnley originally described the principle of three-point loading of casts in the management of fractures[1]. Fractures and subsequent immobilization with a constraining cast are associated with a potentially devastating risk of compartment syndrome, which results from elevated pressures within a confined space that results in occlusion of the arterial blood supply to muscles. Consequently it has become usual practice to apply backslabs instead of complete casts to obviate this risk. Casts can be applied either as backslabs, or as complete casts that may or may not be split. Splitting of casts is thought to allow for swelling, although they are no longer able to provide three point fixation. Clinical experience from the senior author has suggested that backslabs can also be associated with pain and compartment syndrome.

Previous studies have demonstrated that skin surface pressure under a cast correlates to intracompartmental pressure[2]. There has been no detailed analysis to date of the effect of swelling on intracast pressures generated by backslabs or different commonly utilized casts materials applied as complete casts, and whether splitting the cast alleviates these pressures. In view of the increased risk of pain and compartment syndrome following fractures and subsequent immobilization with a cast, it is important to address whether different casting materials and types vary in their ability to accommodate swelling.

Backslabs are commonly applied to the acutely fractured limb as a temporizing measure to provide splintage and prevent displacement. This modality is employed on the assumption that the backslab will accommodate swelling, whereas application of a complete cast is thought to constrain any ensuing swelling. The effects of complete casts on generating intracast pressures within the upper limb have been investigated in a small number of studies, but have not been investigated in such detail in the lower limb. Younger *et al*[3] compared the cast pressures associated with forearm plaster of Paris (POP) backslabs and complete POP casts that were split with different methods. The authors concluded that a split and spread cast was better able to accommodate intracompartmental swelling compared to backslabs. A study by Moir *et al*[4] investigating intracast pressures in distal radius fractures showed that intracast pressures fall over the first week as swelling subsides. Interestingly, they demonstrated that a small immediate pressure rise is recorded as soon as the backslab is completed, even if completion occurs as late as 14 d. Another study using encircling distal radius plasters that were applied post manipulation of Colles fractures, failed to show any sustained increase in pressure. Despite this, the authors advocate that this technique is to be avoided and proposed a U-slab as a more favourable option in order to avoid the risk of Volkmann's ischaemic contracture[5].

Split casts have been advocated by many as an alternative to backslabs, allowing sufficient compliance for swelling whilst retaining enough rigidity to support

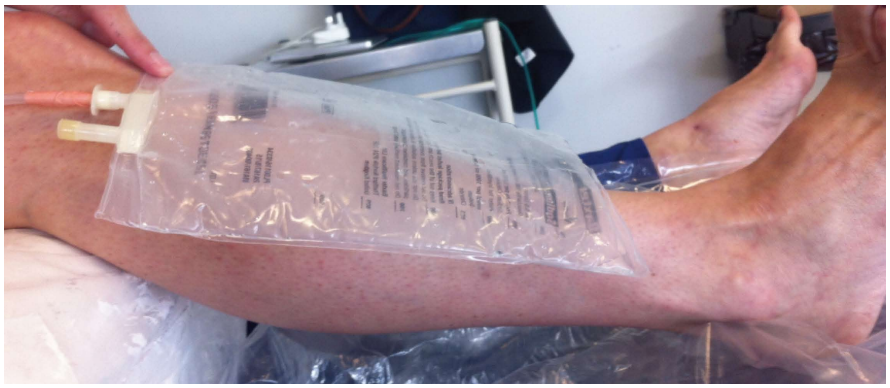

Figure 1 Photo demonstrating the application of a 1-L emptied expandable bag onto a healthy right lower leg.

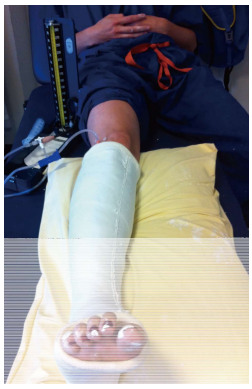

Figure 2 Photo demonstrating the placement of a closed water system circuit attached to a 1-L expandable bag under different types of casts, which had been applied to a healthy right lower limb. An intravenous giving set was connected the emptied bag with a three-way tap.

the fracture. A single split in cast in animal study was shown to reduce cast pressure by 65%[6]. Weiner *et al*[7] investigated the effect of bivalving casts and spreading each side by approximately half a centimeter, and subsequently measured the effects on intramuscular pressures in lower leg anterior and posterior compartments in healthy volunteers. It was reported that bivalving casts significantly reduced the pressures by 47% and 33% in the anterior and posterior compartment respectively ($P < 0.05$).

Two of the most commonly used materials for casts are POP and fiberglass; differences in their mechanical properties are well documented. Fibreglass is more expensive and less easy to mould, however it is lighter and less permeable to water than POP. This study addressed whether different types of commonly utilized plaster materials for forming lower limb casts generate different surface pressures. As backslabs concentrate any pressures over a smaller surface area, we hypothesized that backslabs may generate higher intracast pressures than complete casts.

The primary aim of this study was to evaluate the intracast pressures generated by different types of commonly used casts used to immobilize lower limb fractures, such as a complete POP or fiberglass casts, and how they compared to POP backslabs. This study also assessed whether splitting the casts significantly reduced the intracast pressures. A secondary aim was to ascertain whether there were differences in subjective pain levels associated with intracast pressure changes generated by different cast materials based on the senior author's experience of compressive pain in postoperative patients being immediately relieved by removal of the back slab. Our working null hypothesis was that there is no difference in the intracast pressures or pain generated by different complete casts or backslabs. Our second null hypothesis was that split complete casts would not have reduced intracast pressures or associated pain levels compared to complete casts.

MATERIALS AND METHODS

Measurements of intracast pressures

This study modeled increased swelling within casts that may occur after lower limb injuries or surgery. A closed water system circuit attached to a 1-L expandable bag (Figure 1) was placed directly under different types of casts that had been applied to a healthy right lower limb (Figure 2). Intracast pressures were measured from the right leg for all of the readings, with the ankle in a neutral position with the knee extended while the subject rested on an examination bed. An intravenous giving set was connected to the emptied bag with a three-way tap. The three-way tap was connected to a sphygmomanometer through one portal and a 50 mL syringe through another portal, with a Luer lock used to secure all lines. Twenty-five milliliter aliquots of saline were injected into the system and the intracast pressures were directly measured using a sphygmomanometer (Figure 3). Measurements were started after an initial injection of 25 mL of saline, which were increased in increments of 25 mL until a total of 300 mL of saline had been injected. Two commonly utilized cast materials, fibreglass and POP were applied to the healthy lower limb before measurements were taken in a random order. The subject was blinded to the pressure scores in order to avoid bias.

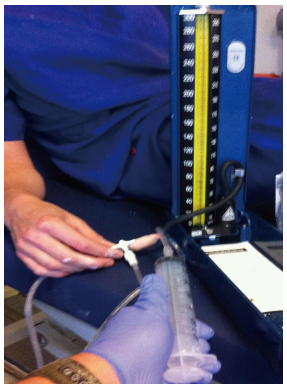

Figure 3 Photo demonstrating how 25 mL aliquots of saline were injected into the system and the surface cast pressures were directly measured using a sphygmomanometer.

During each pressure reading, a subjective assessment of any pain was also made using the Visual Analogue Score (VAS). The VAS score ranges from 1 to 10, with 10 indicating the most severe pain. Between each recording, the system was fully drained of all liquid before recommencing the next casting. The sphygmomanometer was returned to zero in between castings. The measurements were terminated early before 300 mL had been injected if the subject reported a VAS score of 10 or when three identical consecutive pressure readings were measured after injection of sequential 25 mL aliquots. Each type of cast was reapplied four times and the entire measurement process was repeated on four separate occasions. A pre-study power calculation based upon pilot data determined that $n = 4$ was sufficient to achieve 90% power to detect a 20% difference in intracast pressures between different cast groups, with alpha = 0.05. In order to reduce the effects of bias or multiple castings on VAS pain scores, a random order was selected for application of the different cast materials to try to reduce variability.

Plastering technique

A single healthy subject with no history of lower limb trauma was fitted with sequential casts. All casts were applied to the same right limb on the same subject to avoid the effects of any variations in anatomy or physiology on intracast pressures that may arise from using different subjects. The subject had no previous experience of any casts.

In order to reduce variability in application techniques, the plastering for the different cast groups was carried out in exactly the same manner by a single orthopaedic plaster technician with over 15 years of experience. The expandable bag was placed on the anterolateral aspect of the right calf. Marks on the calf delineated exactly where the bag should be placed for all castings and the saline bag was taped in place to assist reproducible placement. A 4-inch stockinette was used, followed by 2 layers of Velband® (Velband®, Smith and Nephew, Hull, United Kingdom) before the top layers of the casts were applied using a standard technique. For the POP casts, 3 rolls (Gypsona®, BSN Medical, France) were used per cast and for the fibreglass casts (BSN Medical) 4 rolls were utilized. When splitting of the cast was required, a single medial split was made along the medial edge of the tibia and the cast was cut to skin. Backslabs were applied with a single slab of POP posteriorly, consisting of 4 layers of POP. The backslabs were further reinforced on the medial and lateral sides, as per standard local protocol. The casts were allowed to harden fully before the data was collected from the lower leg.

Statistical analysis

Any differences between the 5 cast groups were assessed using a repeated measures ANOVA with a Bonferroni multiple comparison test to compare individual cast types and account for potential type-I errors associated with multiple statistical tests. All tests were two tailed and a significance level of $P < 0.05$ was set. GraphPad Prism 5 (Graph Pad Software, LaJolla, California) software was used for statistical analysis.

RESULTS

The results indicated that the introduction of fluid into the different casts generated different intracast pressures (Table 1). A significant difference between the various types of casts was noted when the saline volume was greater than 100 mL ($P = 0.009$, Figure 4). The greatest intracast pressure was measured from complete fiberglass casts and this was significantly greater than complete POP casts ($P = 0.018$) and backslabs ($P = 0.008$) at intracast saline volumes of 100 mL and higher. Backslabs produced a significantly lower intracast pressure compared to complete POP only once the saline volume within casts exceeded 225 mL ($P = 0.009$).

Split POP casts generated the lowest intracast pressure of all the different casts. Split POP casts produced significantly less intracast pressure compared to backslabs when saline volumes were greater than 100 mL. At this volume of 100 mL, a significant reduction in intracast pressures were noted after splitting of both the complete POP and complete fiberglass casts ($P = 0.003$). Once both types of complete casts had been split, there was no significant difference between the two different groups of split casts.

The effects of different types of casts on pain levels were also investigated. Fiberglass casts generated significantly greater pain levels when saline volumes were as low as 75 mL ($P = 0.001$) and continued to produce the highest pain levels at all measured volumes between 75-200 mL ($P < 0.05$, Figure 5). Splitting the complete fiberglass cast at 75 mL of saline significantly reduced pain levels ($P = 0.001$) and this trend was also seen between 100-200 mL of saline ($P < 0.001$). In contrast, splitting a complete POP cast did not significantly reduce the pain levels at saline volumes between 25-150 mL. When the intracast volumes were set at 175 mL, splitting the complete POP cast does result in a significant reduction in pain ($P = 0.013$). This trend towards no reduction in pain is also seen at saline volumes between 200-250 mL ($P <$

Table 1 Summary of intracast pressures and pain scores recorded after application of the different cast types

		Mean	Std. deviation	Std. error	95%CI for mean		Minimum	Maximum	*P*-value
					Lower bound	Upper bound			
Intracast pressure (mmHg)	Backslab	47.05	31.8	4.79	37.38	56.71	2	120	< 0.001
	Full POP	72.28	60.3	9.66	52.73	91.83	2	230	
	Split POP	17.15	7.53	1.29	14.52	19.77	1	28	
	Fibreglass	82.73	67.01	12.23	57.71	107.76	2	240	
	Split Fibreglass	26.58	21.33	3.25	20.02	33.15	0	70	
	Total	47.88	48.48	3.52	40.94	54.82	0	240	
Pain (VAS score)	Backslab	3.99	2.9	0.44	3.11	4.87	0	10	< 0.001
	Full POP	4.77	3.73	0.6	3.56	5.98	0	10	
	Split POP	1.04	1.06	0.18	0.67	1.41	0	3	
	Fibreglass	5.8	3.37	0.62	4.54	7.06	0	10	
	Split Fibreglass	1.9	2.09	0.32	1.25	2.54	0	7	
	Total	3.43	3.24	0.24	2.97	3.9	0	10	

POP: Plaster of Paris; VAS: Visual Analog Scores.

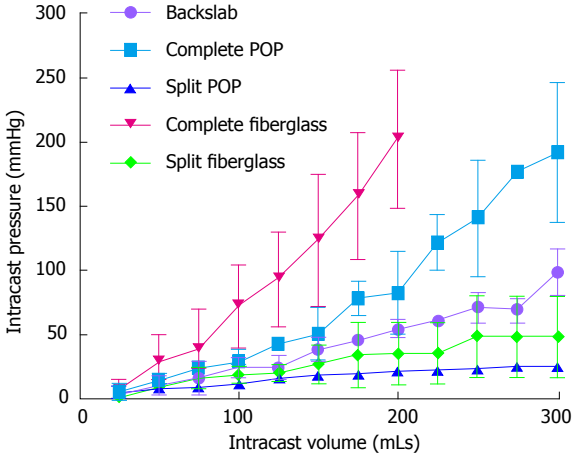

Figure 4 Graph indicating intracast pressures (mmHg) generated by different types of lower limb casts (mean + standard error bars). Both complete fiberglass and complete plaster of Paris casts (POP) generated the greatest casts pressures. The surface pressures were significantly reduced when these casts were split. Split POP and fiberglass casts generated significantly less pressure than backslabs.

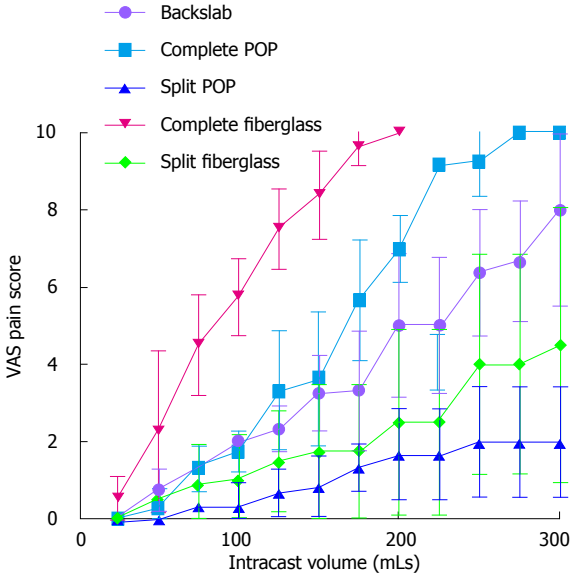

Figure 5 Graph indicating pain levels generated by different types of lower limb casts, as measured by Visual Analog Scores (mean + standard error bars). Complete fiberglass casts generated the highest pain levels. Split fiberglass casts produced significantly less pain at intracast volumes of 75 mL and greater. There was no significant difference in pain generated by complete plaster of Paris casts (POP) and backslabs when the intracast volume was 200 mL or lower. VAS: Visual Analog Scores.

0.003).

DISCUSSION

Closed splinting techniques with casts are commonly used in orthopaedics as a temporizing management technique for both conservatively and operatively treated lower limb injuries to prevent secondary equinus deformities. POP casts are frequently applied in the immediate acute setting, and these are often later changed to synthetic casts. Controversies exist between the ideal cast material and application mode. Important material properties that need to be considered for orthopaedic splints include strength, stiffness, compliance and weight. If constrictive casts increase the extra or intracast pressure in swollen lower limbs carries, they can potentially contribute to compartment syndrome, as well as other complications such as increasing pain, skin necrosis, circulatory compromise and fracture displacement. Thus, minimizing pressures associated with casts is imperative.

This study found that different casts produce different intracast pressures and fiberglass casts generate significantly higher intracast pressures than POP casts, rejecting our null hypothesis. These findings are consistent with results from published studies[8]. Fiberglass casts are frequently utilized to form casts due to a number of advantageous material properties, including its lighter weight compared to POP. The time taken to reach maximum strength is much shorter in fiberglass compared to POP[9] and the strength and stiffness achieved with fiberglass has been shown to be greater than POP[10,11]. The polyurethane in standard fiberglass undergoes a chemical change during hardening[12]. We hypothesize that fiberglass casts generated higher intracast pressures

due to their higher recoil element, which is not applicable to POP, and their lower compliance[8]. Compliance between fiberglass and POP has been compared in previous studies. Fiberglass was shown to require a greater volume change to generate the same pressure rise during the initial stages of swelling[13]. However, once a certain pressure threshold had been exceeded, fiberglass pressures were found to rise steeply with less volume change. Our study found that once the intracast volume of saline exceeded 75 mL, fiberglass casts produced a rapid rise in intracast pressures. Stress relaxation has been demonstrated in both POP and fiberglass and attributed to the composite nature of fiberglass and POP, as well as the mesh design. These properties are presumed to allow relaxation within the materials over a constant volume distention, ultimately allowing pressures to reduce. Clinically this is advantageous as otherwise peak pressures generated by both materials would be much higher and sustained for longer periods[13]. In view of the persistently higher pressures demonstrated by fiberglass casts in this study, the authors advocate POP casts over fiberglass for injured lower limbs in the acute phase, particularly for the first 24 h.

Backslabs were associated with significantly higher intracast pressures than split POP casts at saline volumes of greater than 125 mL, suggesting that split POP generate less intracast pressure when the swelling and volume rises within a cast. Interestingly, these results suggest that split POP are more effective than backslabs at avoiding the generation of high intracast pressures when the swelling and volume of saline within the cast increases. Ultimately, split POP casts may be a safer choice for casting technique in situations when swelling is expected, such as immediately following fractures or post-operatively. According to our results, backslabs were associated with lower intracast pressures in comparison to complete fiberglass or POP casts. Despite the fact that backslabs only cover a smaller surface area compared to complete casts, backslabs do not concentrate the intracast pressures and thus our null hypothesis was rejected. This study supports the widely assumed theory that backslabs are better able to facilitate acute swelling and supports the use of backslabs immediately after injury or after surgery when further swelling is anticipated. While backslabs may accommodate further swelling, this must be balanced against the risk that once the swelling reduces, backslab provide less resistance to deforming forces compared to complete casts which ultimately increases the potential for fracture displacement. While Charnley's three-point loading of casts for the management of fractures is a commonly accepted and applied principle[1], this appears to be more difficult to achieve with backslabs. Wytch *et al*[14] used intracast pressure measuring techniques to demonstrate that loading in backslabs is low and although this is improved with moulding, they did not find evidence of Charnley's three-point loading principle.

Issues of generating high intracast pressures are applicable to both upper and lower limb fractures, as the former are also often managed with an initial backslab that may later be converted into a complete cast. As an example, a common preliminary method of managing Colles fracture includes application of an initial dorsoradial plaster that is later completed to a complete below elbow cast once a sufficient time period has elapsed and the risk of significant swelling is assumed to have diminished.

Splitting the casts resulted in a universal decrease in intracast pressures, regardless of cast material. However the reduction in cast pressures following splitting was more marked in fiberglass than in POP casts. This study suggests that splitting complete casts, particularly fiberglass casts, may be advisable in clinical scenarios associated with acute limb swelling. This difference may be attributable to the greater ability of fiberglass to recoil at the site of splitting the cast.

Measuring compliance of material and pressures generated from encasement with a cast has been investigated with a variety of different methodologies. This study utilized a saline bladder system rather than an air-filled system as it is easier to detect any leaks. Sensors can directly be applied to the skin to measure surface cast pressures, however they do not allow a spectrum of recordings to be carried out in a dynamic volumetric distension system, as was permitted by our study design. A study used a modified Sengstaken tube to investigate intracast pressures generated within backslabs that had been applied following surgical fixation of ankle fractures in 15 patients[15]. The mean pressure rise reported was 3.4 mmHg and the maximum measured pressure was 20.2 mmHg. The study also showed that maximum pressure peaked within 2 h of surgical fixation. This study measured a much wider range of manometer and surface pressures.

A number of limitations are associated with this study. A healthy subject was used and a saline system was used to emulate soft tissue swelling that may occur in an acutely fractured lower limb and the authors appreciate that this is not a direct measurement of compartment pressure. Previous studies investigating intracast pressures have found lower readings in healthy subjects compared to injured patients[5]. However, the aim of this study was to investigate the effects of soft tissue swelling on intracast pressures and this could be achieved using a healthy subject. This study cannot extrapolate how intracast pressures are related to intracompartmental pressures or compartment syndrome, even though a strong correlation between extra and intracompartmental pressures has been previously demonstrated[16]. The direct effect of different casts on intracompartmental pressures was beyond the scope of this study and ideally should be addressed by future studies. All measurements in this study were performed on a single subject to avoid inter-subject variations in pain threshold, thus avoiding potential bias. However, there was potential for the subject to become sensitized to pain, following repeated measurements after multiple cast applications. To avoid this, different casts were applied in a random order. Although the subject was blinded to pressure readings, the subject would have been aware of the increase in pressure as the study progressed with each individual

cast and may have anticipated increasing pain.

This study only investigated the pressures generated immediately after cast application and did not model any delayed increases that may occur following swelling of fractured limbs as a healthy limb was utilized. Patrick *et al*[5] measured intracast pressures in healthy subjects and patients with Colles fractures. In the Colles fracture group they observed a first and second peak phenomenon, whereby pressures rose immediately after application of the plaster and then rose again after an average of 13 h before gradually declining to reach a resting value after 72 h. The first peak was observed in healthy subjects however the second peak was not and the authors concluded that the second peak was due to delayed swelling associated with the fracture. Attempts were made to keep the infusion rate constant, but this was not verified by any measurements. A previous study showed using pressure volume dynamics that fluid infused at a faster rate led to a quicker pressure rise and decreased accommodation in POP and fibreglass. Interestingly, the decreased stiffness observed in the two materials at slower infusion rates was more apparent at lower pressures in the POP group than the fibreglass[13].

External splinting is widely utilized in orthopaedics and trauma to stabilize fractures or support surgical constructs. Casts are associated with rare but potentially devastating complications of compartment syndrome and skin necrosis. This study demonstrated that as the volume within a cast rose, complete fibreglass casts generated significantly higher intracast pressures than complete POP casts. Complete fiberglass and POP casts were associated with significantly greater pressures than backslabs. Splitting casts confirmed a universal decrease in intracast pressures regardless of the material utilized. Backslabs are traditionally thought to allow greater swelling and produce lower pressures within the cast, yet our findings suggest that split POP produces the lowest intracast pressures and may be the most appropriate casting technique in situations where swelling is anticipated. Thus judicious use of complete casts, particularly fiberglass casts may be advisable in cases where significant swelling is anticipated in fractured limbs. The application of split POP casts in the immediate acute setting may be more beneficial in high-risk patients such as neuropathic, diabetic and unconscious patients. Further research is required to determine the pressure rises associated with a broader range of casts such as soft casts and hybrid fiberglass reinforced POPs as well as whether the stockinette or Velband® generate higher constraint and pressures than other materials.

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COMMENTS

Background

Lower limb fractures with subsequent immobilisation with a cast are associated with a potential risk of developing compartment syndrome.

Research frontiers

Different types of casts could potentially produce different intracast pressures which could ultimately increase intracompartmental pressures. There has been no detailed analysis to date of the effect of swelling on intracast pressures generated by backslabs or different commonly utilized cast materials applied as complete casts, and whether splitting the cast alleviates the pressures.

Innovations and breakthroughs

Introduction of fluid into different casts was used as a surrogate for volume expansion. This generated different intracast pressures. When increase in saline volume was greater than 100 mL, a significant difference in intracast pressures was observed between various types of casts. Intracast pressures were significantly greater in complete fibreglass casts in comparison to complete plaster of Paris (POP) casts and backslabs. Backslabs produced a significantly lower intracast pressure compared to complete POP casts only once the saline volume within casts exceeded 225 mL. Split POP casts generated the lowest intracast pressures of all casts and less than backslabs when saline volume exceeded 100 mL. Splitting casts reduced intracast pressures of both POP casts and fibreglass casts. When split, no significant difference was observed in intracast pressures between the two types of split casts. Fibreglass casts produced greater pain levels when saline volume was as low as 75 mL and it continued to produce the highest pain levels. The data indicates that split fiberglass casts were associated with significantly less pain than complete fiberglass casts. Splitting the complete POP cast did not significantly reduce the pain levels until saline volume was 175 mL.

Applications

Judicious use of complete casts, particularly fibreglass casts and backslabs may be advisable for lower limb immobilisation. The use of a split cast for lower limb immobilisation in the immediate acute setting may be more beneficial for high risk patients such as neuropathic, diabetic and unconscious patients.

Terminology

POP cast: Plaster of Paris is a hemihydrated calcium sulfate material which solidifies when mixed with water. It is used as a cast for immbolisation of a fractured limb. Fibreglass is a synthetic alternative to the traditional POP. The fibreglass bandages are impregnated with a quick setting water-soluble resin. It is a lighter, water proof cast used for immobilisation of fractured limbs. Backslabs are partial casts applied to the posterior aspect of the limb. They are held onto the limb with a bandage.

Peer-review

This is a good manuscript on a clinical relevant issue. Style and study design are fine.

REFERENCES

1 **Charnley J**. The closed treatment of common fractures. *Br J Surg* 1957; **191**: 299 [DOI: 10.1002/bjs.18004519119]
2 **Uslu MM**, Apan A. Can skin surface pressure under a cast reveal intracompartmental pressure? *Arch Orthop Trauma Surg* 2000; **120**: 319-322 [PMID: 10853903 DOI: 10.1007/s004020050472]
3 **Younger AS**, Curran P, McQueen MM. Backslabs and plaster casts: which will best accommodate increasing intracompartmental pressures? *Injury* 1990; **21**: 179-181 [PMID: 2401552 DOI: 10.1016/0020-1383(90)90091-8]
4 **Moir JS**, Wytch R, Ashcroft GP, Neil G, Ross N, Wardlaw D. Intracast pressure measurements in Colles' fractures. *Injury* 1991; **22**: 446-450 [PMID: 1757134 DOI: 10.1016/0020-1383(91)90126-

Y]
5 **Patrick JH**, Levack B. A study of pressures beneath forearm plasters. *Injury* 1981; **13**: 37-41 [PMID: 7319627 DOI: 10.1016/0020-1383(81)90088-7]
6 **Garfin SR**, Mubarak SJ, Evans KL, Hargens AR, Akeson WH. Quantification of intracompartmental pressure and volume under plaster casts. *J Bone Joint Surg Am* 1981; **63**: 449-453 [PMID: 7204445]
7 **Weiner G**, Styf J, Nakhostine M, Gershuni DH. Effect of ankle position and a plaster cast on intramuscular pressure in the human leg. *J Bone Joint Surg Am* 1994; **76**: 1476-1481 [PMID: 7929495]
8 **Marson BM**, Keenan MA. Skin surface pressures under short leg casts. *J Orthop Trauma* 1993; **7**: 275-278 [PMID: 8326434 DOI: 10.1097/00005131-199306000-00013]
9 **Berman AT**, Parks BG. A comparison of the mechanical properties of fiberglass cast materials and their clinical relevance. *J Orthop Trauma* 1990; **4**: 85-92 [PMID: 2313436 DOI: 10.1097/00005131-199003000-00015]
10 **Mihalko WM**, Beaudoin AJ, Krause WR. Mechanical properties and material characteristics of orthopaedic casting material. *J Orthop Trauma* 1989; **3**: 57-63 [PMID: 2709205 DOI: 10.1097/00005131-198903010-00011]
11 **Charles MN**, Yen D. Properties of a hybrid plaster-fibreglass cast. *Can J Surg* 2000; **43**: 365-367 [PMID: 11045095]
12 **Mohler LR**, Pedowitz RA, Byrne TP, Gershuni DH. Pressure generation beneath a new thermoplastic cast. *Clin Orthop Relat Res* 1996; **(322)**: 262-267 [PMID: 8542703]
13 **Deshpande SV**. An experimental study of pressure-volume dynamics of casting materials. *Injury* 2005; **36**: 1067-1074 [PMID: 16098335]
14 **Wytch R**, Ashcroft P, Kalisse CG, Neil G, Ross N, Ward D. Interface pressures in below elbow casts. *Clin Biomech* (Bristol, Avon) 1991; **6**: 25-30 [PMID: 23916341 DOI: 10.1016/0268-0033(91)90038-R]
15 **Bowyer GW**, Iu M, Reynard JM. Pressure in plaster backslabs after surgery for ankle fractures. *Injury* 1993; **24**: 121-122 [PMID: 8505118 DOI: 10.1016/0020-1383(93)90203-I]
16 **Davids JR**, Frick SL, Skewes E, Blackhurst DW. Skin surface pressure beneath an above-the-knee cast: plaster casts compared with fiberglass casts. *J Bone Joint Surg Am* 1997; **79**: 565-569 [PMID: 9111402]

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EVIDENCE-BASED MEDICINE

Internet and social media usage of orthopaedic patients: A questionnaire-based survey

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Abstract

AIM

To evaluate social media usage of orthopaedic patients to search for solutions to their health problems.

METHODS

The study data were collected using face-to-face questionnaire with randomly selected 1890 patients aged over 18 years who had been admitted to the orthopaedic clinics in different cities and provinces across Turkey. The questionnaire consists of a total of 16 questions pertaining to internet and social media usage and demographics of patients, patients' choice of institution for treatment, patient complaints on admission, online hospital and physician ratings, communication between the patient and the physician and its effects.

RESULTS

It was found that 34.2% (n = 647) of the participants consulted with an orthopaedist using the internet and 48.7% (n = 315) of them preferred websites that allow users to ask questions to a physician. Of all question-askers, 48.5% (n = 314) reported having found the answers helpful. Based on the educational level of the participants, there was a highly significant difference between the rates of asking questions to an orthopaedist

using the internet (P = 0.001). The rate of question-asking was significantly lower in patients with an elementary education than that in those with secondary, high school and undergraduate education (P = 0.001) The rate of reporting that the answers given was helpful was significantly higher in participants with an undergraduate degree compared to those who were illiterate, those with primary, elementary or high school education (P = 0.001). It was also found that the usage of the internet for health problems was higher among managers-qualified participants than unemployed-housewives, officers, workers-intermediate staff (P < 0.05).

CONCLUSION

We concluded that patients have been increasingly using the internet and social media to select a specific physician or to seek solution to their health problems in an effective way. Even though the internet and social media offer beneficial effects for physicians or patients, there is still much obscurity regarding their harms and further studies are warranted for necessary arrangements to be made.

Key words: Patient; Internet; Orthopedist; Social media; Communication

Core tip: There is an ongoing increase in the use of social media and internet for health information. Patients can share their health-related experiences or issues online *via* social media and discussion forums or can consult with experienced physicians. Despite benefits and advantages of social media for patient-physician relationship, legal liability and possible harms and risks of the shared information and communication should be born in mind.

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INTRODUCTION

The effects of patient-physician communication through social media or internet have long been of interest[1,2]. Facebook, Twitter, My Space and Linked In have been reported to be the most commonly used social networking sites around the world, being Facebook the most popular, whose use has increased rapidly in recent years[3]. Social media tools enable patients to communicate with their physicians faster online and help them clarify their understanding of their illness, express themselves better and share their problems visually or in writing[4,5]. Social media tools have been increasingly used as a means to share their health issues and seek solutions and have changed the nature of traditional patient-physician relationship[6-8]. On the other hand, problems arising from the interpretation and implementation of the information shared online have recently gained attention. In addition, there are possible risks associated with the spread of unnecessary and inaccurate information easily and the legal gaps in this area[9,10]. Therefore, further research and specific arrangements should be made on how, to what extent and when social media and internet to be used. As far as we are aware, there are few studies dedicated to address how orthopaedic patients use social media for their health issues, choice of hospital and physician and patient-physician relationships. The identification of how orthopaedic patients view and use social media can shed light on studies and arrangements of physicians, health bureaucracy and health legislation committees in our country.

The objective of this study was to identify the prevalence of orthopaedic patients' usage of internet and social media and the effects of internet and social media on hospital and physician selection, patient-physician communication and choice of treatment.

MATERIALS AND METHODS

A face-to-face questionnaire with a total of randomly selected 1890 patients aged over 18 years who were admitted to the orthopaedic clinics of private and public hospitals in different regions of Turkey between January 2016 and March 2016 was conducted. The participants were informed about the content and purpose of the questionnaire and were asked to fill in the questionnaire. Patients' identity information was not included in the questionnaire and each questionnaire was numbered. All data were collected and analyzed. Participants received no financial or educational incentive. The questionnaire consisted of a total of 16 questions pertaining to patients' personal information (age, sex, educational level, occupation), the healthcare institution the questionnaire was conducted, patients' complaints on admission, duration of complaints, the effects of social media and internet on patients' choice of hospital and physician and patient-physician communication and patients' usage of internet and social media (Table 1).

Statistical analysis

Statistical analysis was performed using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, United States). Data were analyzed using descriptive statistics (mean, standard deviation, median, frequency, rate, minimum, maximum) whereas qualitative data were compared using the Pearson χ^2 test, Fisher Freeman Halton test and Yates' continuity correction test (Yates corrected χ^2). P values of < 0.01 and 0.05 were considered statistically significant.

RESULTS

Of all participants, 52% (n = 982) were females and 48% (n = 908) were males. The mean age of the

Table 1 Questions designed to identify patients' usage of internet and social media

Age
Sex
Occupation
Educational level
Place of residence
Hospital where the questionnaire was administered
Question 1: What's your complaint?
Question 2: How long have you had this complaint?
Question 3: Have you ever been examined in an orthopaedic clinic?
Question 4: Have you ever had an orthopaedic surgery?
Question 5: Did the internet have an impact on your choice of this hospital?
Question 6: Which one(s) of the following had an impact on your choice of hospital? (you can select more than one option)
Question 7: Which one(s) of the following had an impact on your choice of physician? (you can select more than one option)
Question 8: Have you ever asked an orthopaedist his/her opinion about your disease using the internet?
Question 9: Which options do you prefer to ask an orthopaedist his/her opinion? (you can select more than one option)
Question 10: With which of the following you can describe the answers you were given? (you can select more than one option)
Question 11: Have you ever sent a friend request to an orthopaedist on Facebook?
Question 12: Do you have orthopaedist friends on Facebook?
Question 13: Do you think that orthopaedists should keep in contact with you through the internet?
Question 14: Which one(s) of the following do you use to ask your physician a question? (you can select more than one option)
Question 15: Have you ever attempted to treat your disease/orthopaedic problem based on the information you obtained from the internet?
Question 16: What do you think about having X-rays performed in the nearest hospital and sending them to your physician over the internet for your post-operative follow ups?

Table 2 Participants' demographics

		n	%
Educational level	Illiterate	119	6.6
	Primary school	598	33.2
	Secondary school	214	11.9
	High school	500	27.7
	Undergraduate	330	18.3
	Master's degree	42	2.3
Occupation	layperson (unemployed or retired)	546	28.9
	Officer	80	4.2
	Housewife	587	31.1
	Worker - Intermediate staff	342	18.1
	High-status position in the public sector	139	7.4
	Manager in the private sector - Qualified	116	6.1
	Other	80	4.2
Hospital where the study was conducted	Training and Research Hospital Public	400	21.2
	University Hospital	694	36.7
	City Public Hospital	546	28.9
	Province Public Hospital	135	7.1
	Private Hospital	115	6.1
Complaint(s)	Knee pain	469	24.8
	Low-back pain	329	17.4
	Shoulder pain	217	11.5
	Foot pain	346	18.3
	Fracture treatment	217	11.5
	Hip pain	147	7.8
	Prosthesis surgery	38	2.0
	Arthroscopy	32	1.7
	Fracture surgery	98	5.2

participants was 40.64 ± 15.35 years (18-88 years) (Table 2).

The rate of the effect of internet on participants' choice of hospital was 50.9% (*n* = 962) and on participants' choice of physician was 39.4%. It was found that 14.4% (*n* = 273) of the participants preferred the Ministry of Health's (MH) Centralized Hospital Appointment System whereas 2.9% (*n* = 54) used Facebook to select a physician online. Of all participants, 34.2% (*n* = 647) reported having asked an orthopaedist his/her opinion about their diseases using the internet and the question-askers most often preferred the web-sites allowing question-asking. In addition, 48.5% (*n* = 314) of the question-askers reported that the answers given were helpful (Table 3).

Of the participants, 46.7% (*n* = 883) thought that orthopaedists should keep in contact with patients over

Table 3 The distribution of participants' choice of hospital or physician and the distribution of data about asking an orthopaedist his/her opinion about a disease (*n* = 1890)

	n	%
The effect of the internet on hospital choice	962	50.9
[1]Which one(s) of the following had an impact on your hospital choice		
Centralized Hospital Appointment system	212	22.0
Website of the hospital	100	10.4
Hospital rating websites	100	10.4
Peer advice on the internet	66	6.9
Facebook	57	5.9
Other (182MHRS call center)	487	50.6
[1]Which one(s) of the following had an impact on your physician choice		
Random choice from the MHRS system	723	14.4
Other patients' advices on the internet	169	8.9
Physician rating websites	101	5.3
Website of the hospital	123	6.5
Physician personal website	110	5.8
Facebook	54	2.9
Other(MHRS 182 call center)	1146	60.6
Asking an orthopaedist his/her opinion about a disease using the internet	647 (n)	34.2 (%)
[1]Which option(s) do you prefer to ask an orthopaedist his/her opinion?		
Websites allowing asking physicians questions	315	48.7
Physician's personal website	149	23.0
Facebook	103	15.9
E-mail	72	11.1
With which of the following can you describe the answers you were given?		
Helpful	314	48.5
Effective in my choice of hospital/physician	137	21.2
I became more confused	102	15.8

[1]More than one option was selected.

the internet. The rate of asking an orthopaedist his/her opinion about their diseases in participants aged between 18-30 years was statistically significantly higher than that in patients aged between 31-45 years, 46-60 years, 61-75 years and older than 75 years (P = 0.001; P = 0.001; P = 0.001; P < 0.01, respectively). It was noted that males used internet more often for asking questions compared to females (P < 0.01). Of all participants, 19.5% (n: 368) attempted to treat their orthopaedic problems/diseases using the information they obtained online. There was a strong statistically significant relationship in the rate of participants' using online information to treat their orthopedic problems/diseases according to the age groups (P = 0.001; P < 0.01). The rate of attempting to treat their orthopedic diseases/problems using online information was statistically significantly higher in the participants aged between 18-30 years than that in those aged between 61-75 years and older than 75 years (P = 0.030; P = 0.003; P = 0.049; P < 0.05) (Table 4). Thirty-four percent of the patients wanted to get postoperative X-ray controls performed using the internet whereas 66% of the participants stated that postoperative follow-ups should be face-to-face.

There was a strong statistically significant difference in the rates of answering "yes" to the question of "Have you ever asked an orthopedist his/her opinion about your disease" according to the educational level of the participants (P = 0.001; P < 0.01). The rate of answering "yes" to the question of "Have you ever asked an orthopedist his/her opinion about your disease using the internet" was statistically significantly lower in participants who were illiterate compared to that in those with secondary, high school and undergraduate education (P = 0.004; P = 0.003; P = 0.001; P < 0.01). Similarly, the rate answering "yes" to the question of "Have you ever asked an orthopedist his/her opinion about your disease using the internet" was statistically significantly lower among participants with elementary level of education compared to that in those with secondary, high school and undergraduate education" (P = 0.022; P = 0.010; P = 0.001; P < 0.05) (Table 5). The rate of reporting that the answers given was helpful was significantly higher in participants with an undergraduate degree compared to those who were illiterate, those with primary, elementary or high school education (P = 0.014; P = 0.001; P = 0.004; P = 0.001, respectively). The rate of stating "I became more confused" was significantly lower in patients with an undergraduate degree compared to those with elementary and secondary education (P = 0.006; P = 0.001) (Table 5).

According to the occupational status, the rate of internet use for asking an orthopaedist a question was higher in managers-qualified employees compared to unemployed-housewives, officers, workers-intermediate staff (P = 0.001; P = 0.013; P = 0.001). The rate of reporting that the answers given by the orthopaedist were useful was significantly higher in managers-qualified employees compared to unemployed participants-

Table 4 The distribution of data about befriending with an orthopaedist, utilizing the information obtained and postoperative follow-ups (*n* = 1890)

	n	(%)
Sending friend request to an orthopaedist on Facebook	162	(8.6)
Befriending with an orthopaedist on Facebook	142	(7.5)
Do you think that orthopaedists should keep in contact with you over the internet?		
Not necessary	1007	(53.3)
Necessary	883	(46.7)
[1]Which one(s) of the following do you prefer to ask your physician a question?		
LinkedIn	17	(0.9)
Twitter	54	(2.9)
Facebook	144	(7.6)
Text-message to cell-phone	150	(7.9)
E-Mail	176	(9.3)
What's App	204	(10.8)
Call his/her cell-phone	814	(43.1)
Other	301	(15.9)

[1]More than one option was selected.

Table 5 Asking an orthopaedist his/her opinion over the internet and interpreting the information obtained according to educational level *n* (%)

	Educational Level						*P*
	Illiterate	Primary	Secondary	High-school	Under graduate	Post graduate	
Participants who asked an orthopaedist his/her opinion about a disease?							
Yes	26 (21.8)	173 (28.9)	80 (37.4)	181 (36.2)	147 (44.5)	14 (33.3)	[1]0.001[b]
No	93 (78.2)	425 (71.1)	134 (62.6)	319 (63.8)	183 (55.5)	28 (66.7)	
With which one(s) of the following can you describe the answers you were given?							
Helpfull							
Yes	5 (19.2)	34 (19.7)	12 (15)	29 (16)	10 (6.8)	1 (7.1)	[2]0.021[a]
No	21 (80.8)	139 (80.3)	68 (85)	152 (84)	137 (93.2)	13 (92.9)	
I became more confused							
Yes	11 (42.3)	71 (41)	24 (30)	89 (49.2)	102 (69.4)	7 (50)	[1]0.001[b]
No	15 (57.7)	102 (59)	56 (70)	92 (50.8)	45 (30.6)	7 (50)	
Participants who attempted to treat their orthopaedic diseases based on the information they obtained from the internet							
Yes	17 (14.3)	92 (15.4)	32 (15)	112 (22.4)	78 (23.6)	8 (19)	[1]0.004[b]
No	102 (85.7)	506 (84.6)	182 (85)	388 (77.6)	252 (76.4)	34 (81)	

[a]$P < 0.05$, [b]$P < 0.01$. [1]Pearson χ^2 test; [2]Fisher Freeman Halton test.

housewives and workers-intermediate staff ($P = 0.001$, $P = 0.002$). The rate of stating "I became more confused" about the answers they were given was significantly lower in unemployed participants-housewives than managers-qualified employees ($P = 0.003$) (Table 6).

DISCUSSION

In recent years, social media or internet have evolved as a new communication tool between patients and physicians that is becoming increasingly popular and developed[11]. About 4% of daily searches on the internet daily are health-related globally[12]. The prevalence of the social media usage in patient-physician communication and the effects of the social media and internet on patients' choice of physician and hospital and their search for treatment options have been increasingly addressed in recent studies[11,13].

In the United States, 41% of the adults use forums, blogs and websites allowing patients to ask physicians questions whereas 35% make online research for the physician who will treat them, and 28% for the hospital they will be treated at[14]. The internet or social media and Facebook were reported to be the most commonly used social media tools in England[10]. A similar study of orthopedic patients by Curry *et al*[15] reported that over 50% of patients had used social media for their orthopedic issues and 26% had seen a physician review site before their initial visit. Similar to these findings, 34.2% of all orthopaedic patients used internet to ask a physician questions about their diseases and 46.7% reported that orthopaedists should keep in contact with their patients over the internet. It was found that patients prefer websites allowing asking questions to orthopaedists (48.7%). On the other hand, social networking sites of a private type such as Facebook was less commonly used in patient-physician communication and only 7.5% of the patients friended

Table 6 The comparison of the participants' asking an orthopaedist his/her opinion and applying the information they obtained according to their occupations

	Occupations										*P*
	Unemployed - Housewife		Officer		Worker		Manager-Qualified		Other		
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	
Participants who asked an orthopaedist his/her opinion about a disease											
Yes	349	30.8	26	32.5	97	28.4	123	48.2	52	65	[1]0.001[b]
No	784	69.2	54	67.5	245	71.6	132	51.8	28	35	
Which one(s) of the following do you prefer to ask an orthopaedist his/her opinion?											
Facebook											
Yes	59	16.9	3	11.5	24	24.7	14	11.4	3	5.8	[2]0.018[a]
No	290	83.1	23	88.5	73	75.3	109	88.6	49	94.2	
Twitter											
Yes	12	3.4	1	3.8	4	4.1	8	6.5	2	3.8	[2]0.645
No	337	96.6	25	96.2	93	95.9	115	93.5	50	96.2	
Physician's personal website											
Yes	76	21.8	9	34.6	17	17.5	32	26	15	28.8	[1]0.236
No	273	78.2	17	65.4	80	82.5	91	74	37	71.2	
Websites allowing asking physicians questions											
Yes	177	50.7	13	50	35	36.1	62	50.4	28	53.8	[1]0.113
No	172	49.3	13	50	62	63.9	61	49.6	24	46.2	
With which one(s) of the following can you describe the answers you were given?											
I became more confused											
Yes	67	19.2	5	19.2	11	11.3	9	7.3	10	19.2	[2]0.012[a]
No	282	80.8	21	80.8	86	88.7	114	92.7	42	80.8	
Helpful											
Yes	150	43	12	46.2	42	43.3	79	64.2	31	59.6	[1]0.001[b]
No	199	57	14	53.8	55	56.7	44	35.8	21	40.4	
Participants who attempted to treat their orthopaedic diseases based on the information they obtained from the internet											
Yes	193	17	19	23.8	86	25.1	58	22.7	12	15	[1]0.005[b]
No	940	83	61	76.3	256	74.9	197	77.3	68	85	

[a]$P < 0.05$, [b]$P < 0.01$. [1]Pearson χ^2 test; [2]Fisher Freeman Halton test.

an orthopaedist on Facebook. Since websites such as Facebook are social networking tools based on close-friendship, a friend request from a patient is accepted only by few physicians[16], the reason of which may be physicians' concerns about patient privacy and ethical considerations. A review by Moorhead *et al*[1] reported that effective mechanisms should be developed for the maintenance of privacy and confidentiality of the information exchanged online between patients and physicians and there are several gaps in the use of social media for health communication. Bacigalupe suggested that physicians should limit social media contact with their patients *via* social networking tools such as Facebook[17]. It should be born in mind that smartphones, particularly, enable rapid access to social networking sites, thus creating legal risks resulting from rapid spread of an inaccurate content online without verifying it before. Accordingly, Terry reported that a content shared online could be found and exploited, no matter what your privacy setting was, and be used against you in a suit filed in a possible violation of privacy[18]. We believe that physicians should be careful about the accuracy and transparency of the content shared online and respect for patients with regard to personal liability and the protection of patient privacy, should avoid appearing to provide medical advice and should routinely monitor their social media accounts backward.

The WhatsApp messenger available for smartphones enables an effective and rapid communication between patients and physicians. Jagannathan *et al*[19] reported that the WhatsApp application of smartphones enables sending patient X-rays and clinical photographs or sharing problems effectively and emphasized patient privacy as a disadvantage of the application. A study on how doctors view and use social media in Australia showed that 67% of physicians preferred e-mail to communicate with their patients[20]. In our study, a majority of the patients preferred to communicate with their physicians using mobile phones (43.1%), which were followed by the WhatsApp (10.9%). Contact *via* e-mail was less common (9.3%), the reason why can be the common use of mobile phones for communication in our country, physician's or patients' finding it more difficult to communicate *via* e-mail or patients' desire to reach their physicians easily and rapidly. Similarly, physicians have to give out their personal cell-phone numbers to patients to communicate *via* WhatsApp, which can bring patient-physician relationship to an informal level. Therefore, we believe that communication *via* e-mail is more formal.

With the advancements of the internet and the creation of various social networks, patients today

have the opportunity to do their routine follow ups online with the physician. Curry *et al*[15] concluded that orthopaedic patients who travelled between 120-180 miles from the hospital were more likely to use social media for health communication. In this study, 34% of the patients reported that it would be better to send X-rays performed in a hospital to the physician *via* social media tools, which can be attributed to transportation difficulties or easy communication through social media. On the other hand, a majority of patients in our country reported (66%) that follow-ups should be face-to-face with the physician. In light of these data, even though the internet and social media are predicted to be increasingly used in patient follow-ups in our country, in consistent with advances around the world, we believe that the traditional physician-patient relationship is still important for patients.

In this study, the use of the internet and social media was highest in patients aged between 18-30 years and those with an undergraduate level of education. Consistent with our findings, the literature documents that the prevalence of internet and social media usage was higher among young adults and those with high educational level[15,21,22]. Of the participants who asked physicians questions using social media tools, 45.5% stated that the answers given were helpful. In addition, patients with an undergraduate degree were less confused with the answers they were given whereas illiterate participants or those with primary or secondary education became more confused with the answers they received. We believe that as the educational level increases, so does the capacity to understand and interpret the information in communication between individuals. Younger patients with high educational level particularly showed higher tendency to treat themselves based on the responses they were given by physicians. Accordingly, we believe that physicians should be aware of the patient's age, educational level and expectations before giving patients treatment-related information using social media tools in order to avoid being placed in legal or ethical jeopardy.

There is an ongoing increase in the use of social media and internet for health information. About 61% of United States adults looked online for health information in 2008, which reached 72% in 2013[23]. Patients can share their health-related experiences or issues online *via* social media and discussion forums or can consult with experienced physicians. In addition, physicians have the opportunity to have more information about their patients[24-26]. Motivation, encouragement and shared experiences are important features of social network services, particularly for patients[27]. It has been reported that patients who had access to accurate information about their diseases over the internet displayed higher motivation and treatment compliance[28]. On the other hand, it appears to be difficult to reach high-quality and reliable information due to the probability of the collection or spread of unnecessary and inaccurate information through social media, resulting in confusion in patient-physician relationship[24,29]. Therefore, even though automated scanner tools and alerting systems have been developed by social network servers to prevent harms of the internet and social media, users should compare and verify the accuracy of the information shared[30]. Moen *et al*[31] reported that communication over the internet may cause asymmetric results in the patient-physician relationship. Kietzmann *et al*[32] suggested that long-term results of social media are yet to be fully explored, therefore, how social media activities vary in terms of function and impact should be monitored and understood and a congruent social media strategy should be developed and the social media setting and the frequency of conversations as well as being aware of what other users do in that platform and acting accordingly are of importance for a reliable health communication[32].

There is a distinct difference between the culture of traditional medicine (which values privacy, confidentiality, one-on-one interactions and professional conduct) and that of social media (which values openness, informality and transparency, connection)[33]. Accordingly, several professional associations published guidelines to discourage physicians from interacting with their patients on social networking sites, such as Facebook[34,35]. It is beyond doubt that patients' desire to contact with their physicians about their diseases and maintain the communication over the internet and social media will continue increasing. Therefore, possible advantages and disadvantages should be highlighted to enable physicians to use social media effectively and safely. Further comprehensive studies are warranted to fully elucidate physicians' usage of the internet and social media and to identify current problems and to propose options and solutions. In addition, we believe that professional associations should play an active role regarding studies and necessary arrangements for identifying how patient-physician communication should be on the internet and social media.

In conclusion, even though internet and social media usage among orthopaedic patients for health communication or seeking solutions to health issues varied according to age, educational level and occupational status, its prevalence was found to be high in this study. Despite benefits and advantages of social media for patient-physician relationship, legal liability and possible harms and risks of the shared information and communication should be born in mind. Therefore, future comprehensive studies are warranted for establishing a healthy and effective communication between patient and health-care provider over the internet and social media and for the execution of necessary arrangements.

COMMENTS

Background

Social media tools enable patients to communicate with their physicians faster online and help them clarify their understanding of their illness, express

themselves better and share their problems visually.

Research frontiers

Of all participants, 34.2% (n = 647) reported having asked an orthopedist his/her opinion about their diseases using the internet and the question-askers most often preferred the web-sites allowing question-asking. The rate of asking an orthopedist his/her opinion about their diseases in participants aged between 18-30 years was statistically significantly higher than that in patients aged between 31-45 years, 46-60 years, 61-75 years and older than 75 years. According to the occupational status, the rate of internet use for asking an orthopedist a question was higher in managers-qualified employees compared to unemployed-housewives, officers, workers-intermediate staff.

Innovations and breakthroughs

The use of the internet and social media was highest in patients aged between 18-30 years and those with an undergraduate level of education. Younger patients with high educational level particularly showed higher tendency to treat themselves based on the responses they were given by physicians.

Applications

There is an ongoing increase in the use of social media and internet for health information. Physicians should be careful about the accuracy and transparency of the content shared online and respect for patients with regard to personal liability and the protection of patient privacy, should avoid appearing to provide medical advice and should routinely monitor their social media accounts backward.

Terminology

Facebook, Twitter, My Space and LinkedIn have been reported to be the most commonly used social networking sites around the world, being Facebook the most popular. Social media tools are commonly used by orthopedists to communicate with their patients.

Peer-review

This is a very interesting manuscript.

REFERENCES

1 **Moorhead SA**, Hazlett DE, Harrison L, Carroll JK, Irwin A, Hoving C. A new dimension of health care: systematic review of the uses, benefits, and limitations of social media for health communication. *J Med Internet Res* 2013; **15**: e85 [PMID: 23615206 DOI: 10.2196/jmir.1933]

2 **Azu MC**, Lilley EJ, Kolli AH. Social media, surgeons, and the Internet: an era or an error? *Am Surg* 2012; **78**: 555-558 [PMID: 22546128]

3 **Hitwise**. Top 20 sites and engines. [accessed 2011 May 3]. Available from: URL: http://www.hitwise.com/us/datacenter/main/dashboard-10133.html

4 **Goffman E**. The presentation of self in everyday life. New York: Doubleday Anchor Books, 1959

5 **Kamel Boulos MN**, Wheeler S. The emerging Web 2.0 social software: an enabling suite of sociable technologies in health and health care education. *Health Info Libr J* 2007; **24**: 2-23 [PMID: 17331140 DOI: 10.1111/j.1471-1842.2007.00701.x]

6 **Dawson J**. Doctors join patients in going online for health information. *New Media Age* 2010: 7

7 **St-Laurent-Gagnon T**, Coughlin KW. Paediatricians, social media and blogs: Ethical considerations. *Paediatr Child Health* 2012; **17**: 267-272 [PMID: 23633902]

8 **Payette MJ**, Albreski D, Grant-Kels JM. „You'd know if you , friended' me on Facebook": legal, moral, and ethical considerations of online social media. *J Am Acad Dermatol* 2013; **69**: 305-307 [PMID: 23866862 DOI: 10.1016/j.jaad.2013.02.024]

9 **Jennings A**, Powell J, Armstrong N, Sturt J, Dale J. A virtual clinic for diabetes self-management: pilot study. *J Med Internet Res* 2009; **11**: e10 [PMID: 21821504 DOI: 10.2196/jmir.1111]

10 **Nordqvist C**, Hanberger L, Timpka T, Nordfeldt S. Health professionals' attitudes towards using a Web 2.0 portal for child and adolescent diabetes care: qualitative study. *J Med Internet Res* 2009; **11**: e12 [PMID: 19403464]

11 **Grover M**. Defining the patient-physician relationship in the era of facebook. *Acad Med* 2010; **85**: 1262 [PMID: 20671446 DOI: 10.1097/ACM.0b013e3181e5c0d2]

12 **Bass SB**, Ruzek SB, Gordon TF, Fleisher L, McKeown-Conn N, Moore D. Relationship of Internet health information use with patient behavior and self-efficacy: experiences of newly diagnosed cancer patients who contact the National Cancer Institute's Cancer Information Service. *J Health Commun* 2006; **11**: 219-236 [PMID: 16537289 DOI: 10.1080/10810730500526794]

13 **Saleh J**, Robinson BS, Kugler NW, Illingworth KD, Patel P, Saleh KJ. Effect of social media in health care and orthopedic surgery. *Orthopedics* 2012; **35**: 294-297 [PMID: 22495836 DOI: 10.3928/01477447-20120327-05]

14 **Fox S**, Jones S. The Social Life of Health Information. 2009. [accessed 2013 Apr 04]. Available from: URL: http://www.pewinternet.org.Reports/2007/Information-Searches

15 **Curry E**, Li X, Nguyen J, Matzkin E. Prevalence of internet and social media usage in orthopedic surgery. *Orthop Rev* (Pavia) 2014; **6**: 5483 [PMID: 25317312 DOI: 10.4081/or.2014.5483]

16 **Moubarak G**, Guiot A, Benhamou Y, Benhamou A, Hariri S. Facebook activity of residents and fellows and its impact on the doctor-patient relationship. *J Med Ethics* 2011; **37**: 101-104 [PMID: 21160080 DOI: 10.1136/jme.2010.036293]

17 **Bacigalupe G**. Is there a role for social technologies in collaborative healthcare? *Fam Syst Health* 2011; **29**: 1-14 [PMID: 21417520 DOI: 10.1037/a0022093]

18 **Terry NP**. Physicians and patients who friend or tweet: Constructing a legal framework for social networking in a highly regulated domain. *Indiana Law Review* 2010; **43**: 285-295 [DOI: 10.18060/4040]

19 **Jagannathan M**. Efficacy of communication amongst staff members at plastic and reconstructive surgery section using smartphone and mobile Whats App. *Indian J Plast Surg* 2013; **46**: 506-507 [PMID: 24459339]

20 **Brown J**, Ryan C, Harris A. How doctors view and use social media: a national survey. *J Med Internet Res* 2014; **16**: e267 [PMID: 25470407 DOI: 10.2196/jmir.3589]

21 **Rozental TD**, George TM, Chacko AT. Social networking among upper extremity patients. *J Hand Surg Am* 2010; **35**: 819-823.e1 [PMID: 20227837 DOI: 10.1016/j.jhsa.2009.12.043]

22 **Pazarcı O**, Golge UH, Camurcu Y, Saygılı H, Kılınc S, Keskinbicki MV, Korkmaz M. Internet use by orthopedic and traumatology patients in Turkey. *Cumhuriyet Medical Journal* 2015; **37**: 269-275 [DOI: 10.7197/cmj.v37i4.5000124235]

23 **Internet World Stats (IWS)**. Internet Usage & Population Statistics, 2012. Available from: URL: http://www.internetworldstats.com/stats.html

24 **Adams SA**. Blog-based applications and health information: two case studies that illustrate important questions for Consumer Health Informatics (CHI) research. *Int J Med Inform* 2010; **79**: e89-e96 [PMID: 18701344 DOI: 10.1016/j.ijmedinf.2008.06.009]

25 **Hwang KO**, Ottenbacher AJ, Green AP, Cannon-Diehl MR, Richardson O, Bernstam EV, Thomas EJ. Social support in an Internet weight loss community. *Int J Med Inform* 2010; **79**: 5-13 [PMID: 19945338 DOI: 10.1016/j.ijmedinf.2009.10.003]

26 **Gajaria A**, Yeung E, Goodale T, Charach A. Beliefs about attention-deficit/hyperactivity disorder and response to stereotypes: youth postings in Facebook groups. *J Adolesc Health* 2011; **49**: 15-20 [PMID: 21700151 DOI: 10.1016/j.jadohealth.2010.09.004]

27 **Takahashi Y**, Uchida C, Miyaki K, Sakai M, Shimbo T, Nakayama T. Potential benefits and harms of a peer support social network service on the internet for people with depressive tendencies: qualitative content analysis and social network analysis. *J Med Internet Res* 2009; **11**: e29 [PMID: 19632979 DOI: 10.2196/jmir.1142]

28 **Barlow JH**, Stapley J, Ellard DR, Gilchrist M. Information and self-management needs of people living with bleeding disorders: a survey.

Haemophilia 2007; **13**: 264-270 [PMID: 17498075 DOI: 10.1111/j.1365-2516.2007.01444.x]
29 **Hughes B**, Joshi I, Lemonde H, Wareham J. Junior physician's use of Web 2.0 for information seeking and medical education: a qualitative study. *Int J Med Inform* 2009; **78**: 645-655 [PMID: 19501017 DOI: 10.1016/j.ijmedinf.2009.04.008]
30 **Adams SA**. Revisiting the online health information reliability debate in the wake of "web 2.0": an inter-disciplinary literature and website review. *Int J Med Inform* 2010; **79**: 391-400 [PMID: 20188623 DOI: 10.1016/j.ijmedinf.2010.01.006]
31 **Moen A**, Smørdal O, Sem I. Web-based resources for peer support - opportunities and challenges. *Stud Health Technol Inform* 2009; **150**: 302-306 [PMID: 19745318 DOI: 10.3233/978-1-60750-044-5-302]
32 **Kietzmann JH**, Hermkens K, McCarthy IP, Silvestre BS. Social media? Get serious! Understanding the functional building blocks of social media. *Business Horizons* 2011; **54**: 241-251 [DOI: 10.1016/j.bushor.2011.01.005]
33 **George DR**. "Friending Facebook?" A minicourse on the use of social media by health professionals. *J Contin Educ Health Prof* 2011; **31**: 215-219 [PMID: 21953663 DOI: 10.1002/chp.20129]
34 **Dolan P**. Rebuff patient Facebook friend overtures, British Medical Assn. advises. AMA MedNews. [updated 2011 Aug 1]. Available from: URL: http://www.ama-assn.org/ama
35 **Federation of State Medical Boards**. Model Policy Guidelines for the Appropriate Use of Social Media and Social Networking in Medical Practice. Euless, TX: Federation of State Medical Boards. [updated 2012 Apr]. Available from: URL: http://www.fsmb.org/pdf/pub-social-media-guidelines.pdf

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EVIDENCE-BASED MEDICINE

Knee osteoarthritis: Therapeutic alternatives in primary care

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Abstract

AIM

To discusses pharmacological and non-pharmacological therapeutic alternatives for managing knee osteoarthritis in primary care by primary health care nurse practitioners.

METHODS

A case example is presented, the evidence-based guideline recommendations of the Osteoarthritis Research Society International and the American Academy of Orthopaedic Surgeons are reviewed, and a plan of care is developed.

RESULTS

Osteoarthritis is the most common form of arthritis seen in primary care, and it is a major public health issue because the aging population and widespread obesity have drastically increased incidence. Osteoarthritis is clinically associated with escalating chronic pain, physical disability, and decreased quality of life. Early diagnosis of mild osteoarthritis in relatively young patients presents an opportunity for primary health care providers to manage pain, increase quality of life, and decrease risk of disability.

CONCLUSION

Primary health care providers can implement these recommendations in their own practices to provide care to patients with knee osteoarthritis based on current best evidence.

Key words: Osteoarthritis; Knee; Primary care; Nurse practitioner; Guidelines

Core tip: Osteoarthritis is the most common form of arthritis seen in primary care, and it is a major public health issue because the aging population and widespread obesity have drastically increased incidence. Osteoarthritis is clinically associated with escalating chronic pain, physical disability, and decreased quality of life. Early diagnosis of mild osteoarthritis in relatively young patients presents an opportunity for primary health care providers to manage pain, increase quality of life, and decrease risk of disability. This manuscript presents and discusses pharmacological and non-pharmacological therapeutic alternatives for managing knee osteoarthritis in primary care by primary health care nurse practitioners. A case

example is presented, the evidence-based guideline recommendations of the Osteoarthritis Research Society International and the American Academy of Orthopaedic Surgeons are reviewed, and a plan of care is developed. Primary health care providers can implement these recommendations in their own practices to provide care to patients with knee osteoarthritis based on current best evidence.

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INTRODUCTION

An active 56-year-old man presented to his primary health care nurse practitioners (PHCNP) and reported increasing left knee pain. He described the pain as a constant ache that increased with prolonged periods of sitting and after playing sports, and noted that it seemed to have started gradually over the preceding six months. On physical exam, he was noted to be 5'10" and weigh 190 lbs, with a body mass index (BMI) of 27. His vital signs were within normal range. He had a mild amount of swelling to the anterior medial aspect of his left knee; no redness, heat or gross deformities; full extension but limited flexion to 95 degrees; no instability; and a negative McMurray's circumduction test. His strength was grossly normal and equal in both legs and his gait was unremarkable.

This patient's past medical history included gastro-esophageal reflux (GERD), irritable bowel syndrome, and previous right hamstring strain. He is an avid recreational athlete player, non-smoker, social drinker, and he denies any drug use. Current medication includes, pantoprazole 40 mg by mouth once daily for GERD, and over the counter ibuprofen and acetaminophen for intermittent knee pain. His has an anaphylactic medication allergy to penicillin, and is also allergic cats and dogs. He attends his family physician's office for an annual physical once per year, and his prostate, colon cancer screening, and immunizations are up to date.

This patient's PHCNP ordered a left knee ultrasound and left knee X-ray, and instructed him to try over the counter acetaminophen and/or ibuprofen for pain relief. This patient returned to clinic two weeks later to review the results. His X-rays revealed early osteoarthritic changes in his medial compartment and his ultrasound showed a small joint effusion with no abnormalities in the surrounding structures. The patient described that he experienced only limited pain relief with ibuprofen and acetaminophen, and his physical examination was unchanged.

MATERIALS AND METHODS

Osteoarthritis is the most common form of arthritis seen in primary care[1]. Risk factors for osteoarthritis include obesity, family history, female sex, trauma, and older age[2], and approximately 25% of patients over 40 years of age and 85% of patients over 65 have radiographic evidence of osteoarthritis[3]. According to Uphold and Graham, osteoarthritis is the "progressive structural breakdown of articular cartilage that lines the joint surfaces"[3]. Osteoarthritis is a major public health issue because the aging population and widespread obesity have drastically increased incidence[4]. Osteoarthritis is clinically associated with escalating chronic pain, physical disability, and decreased quality of life.

Early diagnosis of mild osteoarthritis in relatively young patients presents an opportunity for PHCNPs to manage pain, increase quality of life, and decrease risk of disability[5]. Some patients and health care providers may accept chronic pain as a symptom of osteoarthritis without extensive trialing of non-pharmacological or pharmacological treatments, but inadequate pain management may lead to disability and sedentary activity, subsequently increasing risks for obesity, hypertension, dyslipidemia, coronary artery disease, and diabetes[5].

Therapeutic goals

The therapeutic goals for patients such as the one in this case example are to alleviate or eliminate knee pain, restore joint mobility, decrease inflammation, improve surrounding muscle strength to protect structures of the knee, minimalize complications, and maintain independence and quality of life. This patient expressed the importance of playing sports, as it is his primary form of exercise and an important social activity. He also expressed apprehension about taking oral medications long-term and a preference for non-pharmacological treatment.

Therapeutic alternatives: Pharmacological

According to several clinical practice guidelines, the use of pharmacological therapy to treat pain associated with osteoarthritis should be initiated in a step-wise approach in combination with non-pharmacological therapy[2,3,6-8]. The Osteoarthritis Research Society International (OARSI) recommends beginning with acetaminophen in patients who report mild to moderate pain from osteoarthritis, but health care providers may consider alternative therapy in the presence of severe pain or inflammation[8]. The American Academy of Orthopaedic Surgeons (AAOS) reported inconclusive evidence to support the use of acetaminophen, with one cited study concluding no clinical or significant difference in comparison to a placebo[7]. Others recommend beginning with acetaminophen because it has a relatively low risk profile, in comparison to other analgesic medications[2].

Nutritional supplements such as glucosamine and chondroitin are available over the counter and are proposed to maintain joint cartilage[6]. According the AAOS "at this time, both glucosamine and chondroitin sulphate have been extensively studied. Despite the availability of the literature, there is essentially no evidence

that minimum clinically important outcomes have been achieved compared to placebo, whether evaluated alone or in combination"[7]. The OARSI stated that glucosamine and/or chondroitin may provide symptomatic relief in patients with osteoarthritis, but should be discontinued if no apparent benefit within 6 mo of treatment, although continuation is not likely harmful[8].

Topical analgesics and capsaicin have also been used in the initial treatment of mild osteoarthritis[6]. Topical analgesics, such as topical diclofenac, are recommended by the AAOS and OARSI as a potential treatment for patients who have contraindications to oral analgesics[8,9]. According to the OARSI, efficient pain relief from topical analgesics can take up to two weeks and the patient may experience local irritation. There is no high quality to support routine treatment of osteoarthritis with topical capsaicin, and the burning sensation of the cream is often tolerated poorly by patients[6].

Non-steroidal anti-inflammatory drugs (NSAIDs) are highly effective in the treatment of osteoarthritis pain and inflammation[6,8,9], but their use in many patients with osteoarthritis requires caution due to increased risk of gastrointestinal bleeding, renal dysfunction, blood pressure elevation, and adverse cardiac events[2,3]. The OARSI recommends starting NSAIDs at the lowest dose possible and avoiding long-term use. Patients at risk of gastrointestinal bleeding may be prescribed a proton pump inhibitor for gastroprotection. Cyclooxygenase-2 inhibitors are a form of NSAIDs that have decreased gastrointestinal complications, but are more expensive and carry a higher risk of cardiovascular events[2,6].

Opioids have the potential to manage pain in advanced osteoarthritis that has not responded to other pharmacological therapies[2], but their use requires close monitoring for signs of abuse or adverse effects such as drowsiness, constipation, and dizziness[6,8]. Stronger opioids should only be prescribed in exceptional circumstances or in patients for whom surgical intervention is planned. According to the College of Nurses of Ontario[10-15], nurse practitioners are not authorized to prescribe opioids; therefore, patients requiring opioids for osteoarthritis pain management should be referred to a physician.

Intra-articular injections with either corticosteroids or hyaluronic acid may be considered in patients who fail to experience pain relief with pharmacological and non-pharmacological therapies[6]. Intra-articular corticosteroid injections may provide the patient short-term relief for 4-8 wk and one joint should only be injected 3-5 times per year[3]. The AAOS reported inconclusive evidence supporting intra-articular corticosteroid injections.

Intra-articular hyaluronic acid is controversial in the literature, with significant variation in recommendations. The AAOS does not recommend the use of hyaluronic acid for patients with osteoarthritis due to conflicting evidence and high variability[7]. A recent systematic review and network meta-analysis suggested that intra-articular treatments were superior to NSAIDS in the treatment of osteoarthritis, but these effects may be primarily as a result of large intra-articular placebo effects[16].

Therapeutic alternatives: Non-pharmacological

PHCNPs should begin the treatment of osteoarthritis with a patient education session about the condition and expand on plans of care incorporating best available evidence[6]. Non-pharmacological treatment frequently involves life-style modification and should be tailored to fit with patient preferences. For example, strong guideline recommendations highlight the importance of weight-loss in patients with BMIs greater than 25[3,6,8,9]. Murphy and Helmick described that "strong epidemiological evidence links obesity to an increased risk of symptomatic knee osteoarthritis and knee replacement"[10]. Sinusas[2] reported that a 5%-10% weight loss from baseline was sufficient for reducing disability in patients with osteoarthritis, and pain significantly decreased if patients lost more than 6 kg. For optimal care, weight management may involve encouraging patients to participate in exercise programs and referring patients to dieticians for counselling.

The AAOS strongly recommends that patients participate in exercise programs that encourage physical activity according to national guidelines and involve components of strengthening and low-impact aerobic exercise[7]. Strengthening exercises should be individualized to improve muscular support of the affected joint and aerobic exercises should be encouraged for long-term functional outcomes[11]. It is important for patients to minimize movements that aggravate their osteoarthritis and balance physical activity with periods of rest to minimize pain[3]. A recently published Cochrane review reported high-quality evidence demonstrating that individuals with osteoarthritis who engaged in exercise experienced reduced pain and improved quality of life[4]. The OARSI recommends aquatic exercise for patients with symptomatic osteoarthritis, but another Cochrane review reported further research is required on the long-term benefit of aquatic exercise in patients with osteoarthritis[12].

Acupuncture and physiotherapy modalities are also cited as possible non-pharmacological interventions for patients with symptomatic osteoarthritis[6,8,9]. The AAOS does not support the use of acupuncture for the relief of pain secondary to osteoarthritis due to inconclusive evidence[7], but the OARSI reported that acupuncture might provide some symptomatic relief according to a single randomized control trial[8,13]. The AAOS cited inconclusive evidence to support the use of physiotherapy modalities such as transcutaneous electrical nerve conduction for pain relief[7], but the OARSI indicated that heat or cryotherapy might be effective for relieving symptoms in hip or knee osteoarthritis[8].

External supports such as knee braces and footwear insoles are also discussed in the literature as possible non-pharmacological therapy for patients with knee osteoarthritis. Knee braces are recommended for patients who have associated mild to moderate valgus or varus instability and want to maintain active lifestyles,

but they are often costly and cumbersome for patients to wear[6,8,11]. Lateral wedged insoles for patients with medial tibio-femoral compartment osteoarthritis may mildly decrease pain and improve instability[3,8]. The AAOS does not support the use of lateral wedge insoles based on four studies that found no significant benefit for pain and physical function[7].

RESULTS

In this case example, the PHCNP should arrange another clinic appointment with this patient to discuss his treatment options regarding pharmacological and non-pharmacological care. Reaching therapeutic goals through a plan of care should involve equal input from both the PHCNP and the patient, also known as shared decision-making[14]. Although PHCNPs provide medical evidence and clinical experience, patients provide important information about their values, beliefs, and lifestyle. When developing plans of care with patients, it is important for PHCNPs to recognize when clinical presentations or treatments are outside their scope of practice or beyond their expertise, in order to provide appropriate referrals according to nurse practitioner practice guidelines[15]. For example, patients with severe osteoarthritis should be referred if they require opioid prescriptions, intra-articular injections outside of the training or scope of the nurse practitioner, or surgical intervention.

Treatment for this patient's left knee osteoarthritis will focus on managing his pain and inflammation, improving mobility and function, and maintaining his independence. This patient has expressed the importance of continuing to play sports and personal preference for minimal duration of oral medications. Over the counter acetaminophen and/or ibuprofen for approximately three weeks has provided minimal pain relief. According to the step-wise approach outlined in the evidence, the next step is to prescribe an oral NSAID in combination with non-pharmacological therapy[3,6]. Due to his preference to not take oral medications, the PHCNP should first recommend a topical analgesic prior to moving up to oral NSAIDs as indicated by the treatment guidelines[6].

Therefore, the first step in this patient's pharmacological plan of care is to try topical analgesics as directed for one week to the left knee. A topical analgesic was selected based on his personal preferences, risk of adverse gastrointestinal effects from oral NSAIDS, high safety rating, low cost, and simplicity of use. The PHCNP should discuss the potential of low adherence due to ongoing application, possibility of adverse topical irritation, and the duration of treatment required.

The second step in this patient's pharmacological plan of care would be to start a low dose of oral NSAIDs, if topical analgesics did not meet therapeutic goals or patient preferences. The PHCNP should ensure that he continues pantoprazole while taking oral NSAIDS and is aware of the risk of gastrointestinal bleeding[6]. Combination pills that consist of NSAIDs and proton pump inhibitors are available for patients at increased risk of adverse gastrointestinal effects, but are much more costly than taking the medications separately and no more effective[6]. The PHCNP should present the options of paying more or taking an extra medication.

Non-pharmacological treatment of this patient's left knee osteoarthritis will focus on improving surrounding muscle strength to protect structures of the knee, reducing complications, and restoring mobility and function. The PHCNP may begin by suggesting six to eight weeks off from sports. Health education should include explaining the importance of maintaining a healthy body weight and recommending at least thirty minutes of moderate low-impact physical activity on most days of the week[3]. If significant dietary changes are required to achieve weight loss, the PHCNP may refer this patient to a dietician for guidance.

Referral to a physiotherapist could assist this patient in developing a structured low-impact aerobic exercise routine and strengthening program. If this patient does not have coverage or cannot afford physiotherapy, the PHCNP may want to recommend local community programs and resources through the arthritis society[17]. This patient may also want to try treating his knee with ice for fifteen to twenty minutes three times per day for treatment of acute inflammation[8,17].

DISCUSSION

The PHCNP should follow up with this patient in one week to assess the effectiveness of the topical analgesic and non-pharmacological treatment. At this time, his pain, mobility, independence, level of activity, and adherence to therapy will be assessed. The PHCNP should also continue to provide health education as required to address health care needs and therapeutic goals. If therapeutic goals were not met by the topical analgesic, the PHCNP and this patient could consider the second step of the pharmacological care plan; which is to discuss trialing a low dose oral NSAID for a short period of time. The PHCNP and this patient should continue regular follow up appointments until therapeutic goals are reached, at which point this patient could consider slowly returning to athletic and recreational activities.

COMMENTS

Background

Osteoarthritis is the most common form of arthritis seen in primary care, and it is a major public health issue because the aging population and widespread obesity have drastically increased incidence. Osteoarthritis is clinically associated with escalating chronic pain, physical disability, and decreased quality of life. Early diagnosis of mild osteoarthritis in relatively young patients presents an opportunity for primary health care providers to manage pain, increase quality of life, and decrease risk of disability.

Research frontiers

This manuscript presents and discusses pharmacological and non-pharmacological therapeutic alternatives for managing knee osteoarthritis in primary care by primary health care nurse practitioners. A case example is presented, the evidence-based guideline recommendations of the Osteoarthritis Research

Society International and the American Academy of Orthopaedic Surgeons are reviewed, and a plan of care is developed.

Innovations and breakthroughs

According to several clinical practice guidelines, the use of pharmacological therapy to treat pain associated with osteoarthritis should be initiated in a step-wise approach in combination with non-pharmacological therapy. Nutritional supplements such as glucosamine and chondroitin are available over the counter and are proposed to maintain joint cartilage. Topical analgesics and capsaicin have also been used in the initial treatment of mild osteoarthritis. Non-steroidal anti-inflammatory drugs are highly effective, but their use in many patients requires caution due to increased risk of gastrointestinal bleeding, renal dysfunction, blood pressure elevation, and adverse cardiac events. Intra-articular hyaluronic acid is controversial in the literature, with significant variation in recommendations. Non-pharmacological treatment frequently involves life-style modification and should be tailored to fit with patient preferences.

Applications

The therapeutic goals for patients with osteoarthritis are to alleviate or eliminate knee pain, restore joint mobility, decrease inflammation, improve surrounding muscle strength to protect structures of the knee, minimalize complications, and maintain independence and quality of life. Reaching therapeutic goals through a plan of care should involve equal input from both the primary health care providers and the patient, also known as shared decision-making.

Terminology

According to Uphold and Graham, osteoarthritis is the "progressive structural breakdown of articular cartilage that lines the joint surfaces". Osteoarthritis is a major public health issue because the aging population and widespread obesity have drastically increased incidence. Osteoarthritis is clinically associated with escalating chronic pain, physical disability, and decreased quality of life.

Peer-review

In this Evidence-Based Medicine article, the authors present and discuss pharmacological and non-pharmacological therapeutic alternatives for managing knee osteoarthritis in primary care by primary health care nurse practitioners. Primary health care providers can implement these recommendations in their own practices to provide care to patients with knee osteoarthritis based on current best evidence.

REFERENCES

1 **Hall J**, Premji A. Toronto Notes 2015. 31st edition. Toronto, ON: Toronto Notes for Medical Students, 2015
2 **Sinusas K**. Osteoarthritis: diagnosis and treatment. *Am Fam Physician* 2012; **85**: 49-56 [PMID: 22230308]
3 **Uphold CR**, Graham MV. Clinical Guidelines in Family Practice. 5th ed. Gainesville, Florida: Barmarrae Books, 2013
4 **Fransen M**, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. *Br J Sports Med* 2015; **49**: 1554-1557 [PMID: 26405113 DOI: 10.1136/bjsports-2015-095424]
5 **Roos EM**, Arden NK. Strategies for the prevention of knee osteoarthritis. *Nat Rev Rheumatol* 2016; **12**: 92-101 [PMID: 26439406 DOI: 10.1038/nrrheum.2015.135]
6 RxTx, 2015. Available from: URL: http//www.e-therapeutics.ca/search
7 **American Academy of Orthopaedic Surgeons**. Treatment of Osteoarthritis of the knee: Evidence-based guideline. 2nd edition. 2013. Available from: URL: http//www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf
8 **Rhon D**. Re: Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008; 16: 137-62. *Osteoarthritis Cartilage* 2008; **16**: 1585; author reply 1589 [PMID: 18515155 DOI: 10.1016/j.joca.2008.04.019]
9 **Yates AJ**, McGrory BJ, Starz TW, Vincent KR, McCardel B, Golightly YM. AAOS appropriate use criteria: optimizing the non-arthroplasty management of osteoarthritis of the knee. *J Am Acad Orthop Surg* 2014; **22**: 261-267 [PMID: 24668356 DOI: 10.5435/JAAOS-22-04-261]
10 **Murphy L**, Helmick CG. The impact of osteoarthritis in the United States: a population-health perspective: A population-based review of the fourth most common cause of hospitalization in U.S. adults. *Orthop Nurs* 2012; **31**: 85-91 [PMID: 22446800 DOI: 10.1097/NOR.0b013e31824fcd42]
11 **Feeley BT**, Gallo RA, Sherman S, Williams RJ. Management of osteoarthritis of the knee in the active patient. *J Am Acad Orthop Surg* 2010; **18**: 406-416 [PMID: 20595133]
12 **Bartels EM**, Lund H, Hagen KB, Dagfinrud H, Christensen R, Danneskiold-Samsøe B. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Syst Rev* 2007; **(4)**: CD005523 [PMID: 17943863 DOI: 10.1002/14651858.CD005523.pub2]
13 **Foster NE**, Thomas E, Barlas P, Hill JC, Young J, Mason E, Hay EM. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. *BMJ* 2007; **335**: 436 [PMID: 17699546 DOI: 10.1136/bmj.39280.509803.BE]
14 **Washington K**, Shacklady C. Patients' Experience of Shared Decision Making Using an Online Patient Decision Aid for Osteoarthritis of the Knee--A Service Evaluation. *Musculoskeletal Care* 2015; **13**: 116-126 [PMID: 25345930 DOI: 10.1002/msc.1086]
15 **College of Nurses of Ontario**. Practice Standard: Nurse Practitioner, 2016. Available from: URL: http//www.cno.org/globalassets/docs/prac/41038_strdrnec.pdf
16 **Bannuru RR**, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med* 2015; **162**: 46-54 [PMID: 25560713 DOI: 10.7326/M14-1231]
17 **The Arthritis Society**. Physical Activity and Exercise, 2015. Available from: URL: http//arthritis.ca/manage-arthritis/living-well-with-arthritis/physical-activity-and-exercise

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META-ANALYSIS

Total hip replacement: A meta-analysis to evaluate survival of cemented, cementless and hybrid implants

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Abstract

AIM

To determine whether cemented, cementless, or hybrid implant was superior to the other in terms of survival rate.

METHODS

Systematic searches across MEDLINE, CINAHL, and Cochrane that compared cemented, cementless and hybrid total hip replacement (THR) were performed. Two independent reviewers evaluated the risk ratios of revision due to any cause, aseptic loosening, infection, and dislocation rate of each implants with a pre-determined form. The risk ratios were pooled separately for clinical trials, cohorts and registers before pooled altogether using fixed-effect model. Meta-regressions were performed to identify the source of heterogeneity. Funnel plots were analyzed.

RESULTS

Twenty-seven studies comprising 5 clinical trials, 9 cohorts, and 13 registers fulfilled the research criteria and analyzed. Compared to cementless THR, cemented THR have pooled RR of 0.47 (95%CI: 0.45-0.48), 0.9 (0.84-0.95), 1.29 (1.06-1.57) and 0.69 (0.6-0.79) for revision due to any reason, revision due to aseptic loosening, revision due to infection, and dislocation respectively. Compared to hybrid THR, the pooled RRs of cemented THR were 0.82 (0.76-0.89), 2.65 (1.14-6.17), 0.98 (0.7-1.38), and 0.67 (0.57-0.79) respectively. Compared to hybrid THR, cementless THR had RRs of 0.7 (0.65-0.75), 0.85 (0.49-1.5), 1.47 (0.93-2.34) and 1.13 (0.98-1.3).

CONCLUSION

Despite the limitations in this study, there was some tendency that cemented fixation was still superior than other types of fixation in terms of implant survival.

Key words: Total hip replacement; Implant survival;

Cemented; Cementless; Hybrid; Meta-analysis

Core tip: To determine whether cemented, cementless, or hybrid implant was superior to the other in terms of survival rate, a meta-analysis of 27 studies, comprising 5 clinical trials, 9 cohorts, and 13 registers, were performed to evaluate the risk ratios of revision due to any cause, aseptic loosening, infection, and dislocation rate. The risk ratios were pooled separately for clinical trials, cohorts and registers before pooled altogether using fixed-effect model. Meta-regressions were performed to identify the source of heterogeneity. Despite the limitations in this study, there was some tendency that cemented fixation was still superior than other types of fixation in terms of implant survival.

Phedy P, Ismail HD, Hoo C, Djaja YP. Total hip replacement: A meta-analysis to evaluate survival of cemented, cementless and hybrid implants. *World J Orthop* 2017; 8(2): 192-207 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i2/192.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i2.192

INTRODUCTION

Rationale

Currently, total hip replacement is one of the most performed orthopaedic surgeries. In Sweden, the number of THR performed increased by 20% from 1986-1997 and up to 68% in Netherland during the same period of observation[1]. In Organisation for Economic Cooperation and Development countries, the rate of THR increase from 50-130/100000 inhabitants to 60-200/100000 inhabitants in the late 1990s[2]. In United States, more than 200000 THR are conducted annually[3].

Superiority of either cemented or cementless implants has been a longstanding debate. Wroblewski *et al*[4] in 1993 reported the superiority of either implants could not be determined on a scientific basis. Rorabeck *et al*[5,6] reported similar clinical outcome by any of those implants. Zimmerman *et al*[7] agreed that no significant differences in clinical and functional outcome between the implants and reported non-cemented prosthesis to be more costly. Emerson *et al*[8] found cementless titanium stems offered better resistance to osteolysis and mechanical failure.

Morshed *et al*[9] conducted a meta-analysis in 2007 and found no difference in survival between those two groups. Since then, many larger studies with longer duration of follow-up had been conducted and resulted in different results thus resuming the controversy.

Objective

We conducted a meta-analysis of articles published after January 2000 comparing the cemented, cementless and hybrid THR implants to evaluate the superiority of each in terms of risk of revision due to any reason, revision due to infection, revision due to aseptic loosening, and dislocation.

MATERIALS AND METHODS

The structure of this study was written in accordance with the PRISMA checklist for systematic review and meta-analysis[10].

Selection criteria

All studies including randomized clinical trials and cohorts reporting direct comparison between cementless, hybrid and cemented implant in primary THR were included. Recent reports from national registry were also included in this study. The inclusion criteria was pre-determined: (1) all patients over 18 years of age; (2) primary total hip replacement; and (3) revision due to any reason as the primary endpoint. Studies about inverse hybrid arthroplasty were excluded from the analysis. These studies were restricted according to these characteristics: (1) published after January 2000; (2) English language; (3) available abstract; and (4) original research.

Information source and search strategy

In June 2012, literature search was conducted across MEDLINE, CINAHL, and The Cochrane Library using strategies listed in appendices 1. Manual search was also conducted to identify studies that were not included by the initial MeSH keyword search. All identified articles were retrieved from previously mentioned databases.

Study selection

Two reviewers independently performed the study selection in accordance with the aforementioned selection criteria by screening the titles and abstracts. Studies were excluded if they don't meet the selection criteria. If the information required determining eligibility was not found in the abstract, a full-text search was run after data extraction. The studies included were determined from the discussion of two reviewers in accordance with the selection criteria. Reviewers were not blinded to any study characteristic such as journal, author or institution. Algorithm in selecting studies included in this meta-analysis is shown in Figure 1.

Data collection process and data items

All results were checked for consistency between the two reviewers independently. Any discrepancies were be judged by a third independent reviewer. Data extraction was performed using a predetermined standardized form as shown in Tables 1 and 2. Study quality was first assessed using sample size, study design, duration of follow up and variability of result. Overall level of evidence was also assessed.

Synthesis of results

Risk ratios were calculated to determine risk of revision due to any cause, revision due to aseptic loosening,

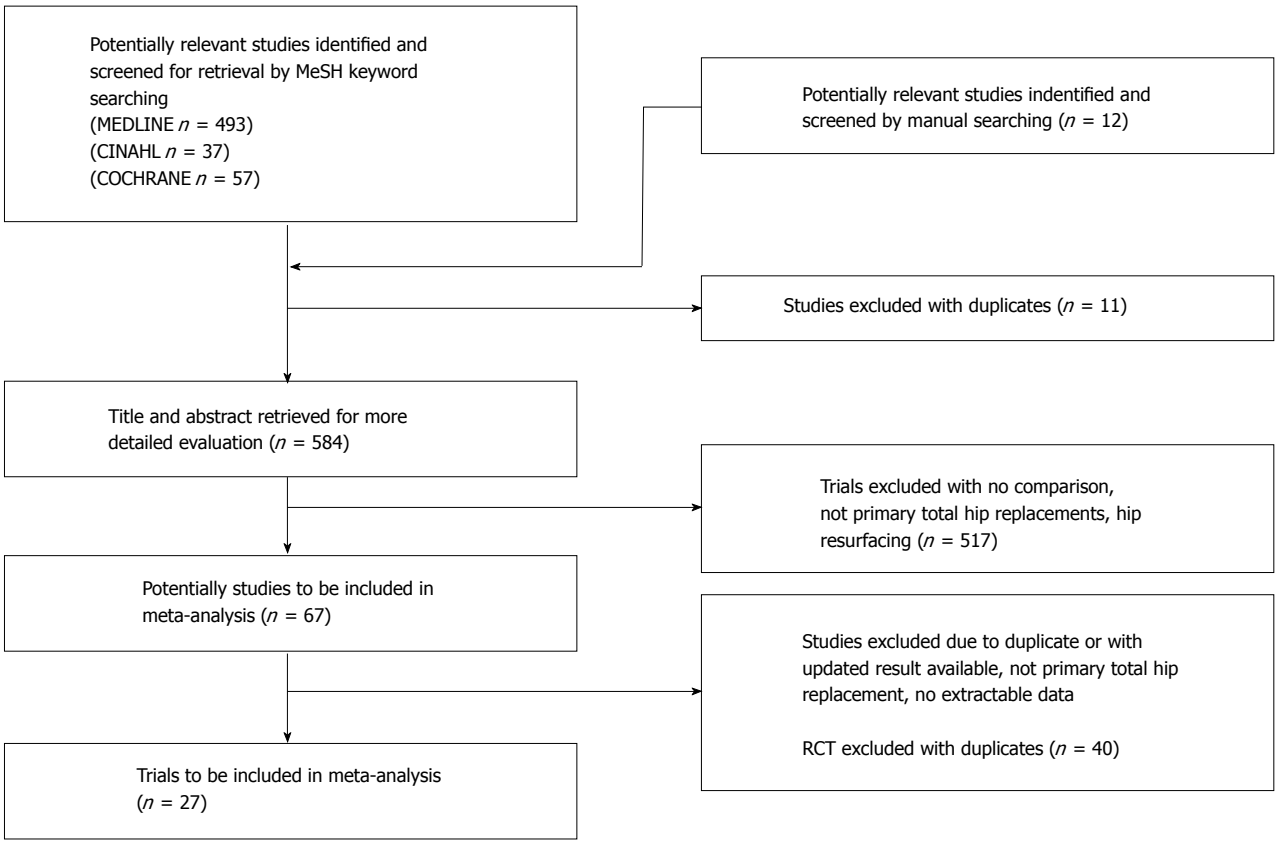

Figure 1 Study selection algorithm.

revision due to infection, and dislocation between each implants. Data were analysed separately for clinical trials, cohorts and registers before pooled altogether. Fixed-effect model was used in the determination of the risk ratio. In comparison with high heterogeneity, we preformed meta-regression to evaluate to identify the source of heterogeneity. Funnel plots for all included trials was constructed to assess the degree of publication bias. The results of the study were graded according to grading system advocated by Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Statistical test was performed using the meta-analysis software of Review Manager 5, Meta-regression was conducted using STATA 10, and grading of the results was performed using GRADEprofiler 3.6.

RESULTS

Following algorithm for study selection, 27 studies were left for final analysis[8,11-36]. Characteristics of the included studies were outlined in Table 1.

Cemented vs cementless THR

Revision of any component due to any reason: Two RCTs, one cohort, and ten registers addressed revision of any component due to any reason. The RCTs found no differences between cemented and cementless THR. Analysis of registers supported cemented to be superior to cementless THR (Figure 2) Pooled all studies together, the RR was 0.47 (95%CI: 0.45-0.48) with a heterogeneity of 98%. Meta-regression using age group, diagnosis, length of follow-up, starting year, publication type, and type of funding failed to correct the heterogeneity.

Revision of any component due to aseptic loosening: Data regarding revision of any component due to aseptic loosening were available in two RCTs and six registers (Figure 3). Controversy existed between result of analysis of RCTs and registers (RR = 2; 95%CI: 1.2-3.1 and RR = 0.88; 95%CI: 0.83-0.94 respectively). Pooled together, the RR was 0.90 (95%CI: 0.84-0.95) with a heterogeneity of 98%. Meta-regression by age group, diagnosis, length of follow-up, starting year, publication type and funding corrected the heterogeneity into 0%, although none of the factors showed significant influence.

Revision of any component due to infection: One RCT and six registers provided sufficient data for determination of revision of any component due to infection (Figure 4). Analysis of registers favored cementless implant in term of revision of any component due to infection (RR = 1.25; 95%CI: 1.10-1.42). Pooled together, the RR was 1.26 (95%CI: 1.11-1.42) with heterogeneity of 57%.

Table 1 Characteristics of the included studies

Ref.	Age (years old)	Length of follow-up (years)	Diagnosis	Cementing technique (generation)	Comparison		Approach	Comments
Bjørgul *et al*[11]	65 to 66	14	Osteoarthritis (most)	3rd	Cemented (*n* = 120)	Hybrid (*n* = 120)	direct lateral	
Chandran *et al*[12]	64.5 to 65.5	14	primary Osteoarthritis	2nd	Cemented (*n* = 97)	Cementless (*n* = 105)	anterolateral	
Corten *et al*[13]	64 (mean)	19.5	primary Osteoarthritis	2nd	Cemented (*n* = 124)	Cementless (*n* = 126)	direct lateral	
Kim *et al*[14]	43.4 to 46.8	18.4	Avascular necrosis (most)	3rd	Hybrid (*n* = 109)	Cementless (*n* = 110)	ND	May overlap with Kim *et al*[15]
McCombe *et al*[16]	67.3	6.5 to 8	Primary OA (most)	2nd	Cemented (*n* = 84)	Hybric (*n* = 78)	posterolateral	
Berend *et al*[17]	67.1	6.8	Osteoarthritis (most)	ND	Cemented (*n* = 1908)	Cementless (*n* = 623)	anterolateral and posterior	
Clohisy *et al*[18]	61 to 62	10 to 11	Osteoarthritis	2nd	Cemented (*n* = 45)	Hybrid (*n* = 45)	posterolateral	
Emerson *et al*[8]	55 to 70	6.7 to 7.2	Osteoarthritis (most)	3rd	Hybrid (*n* = 113)	Cementless (*n* = 88)	anterolateral	
Hartofilakidis *et al*[19]	39.6 to 45.4	12.4 to 15.4	Osteoarthrosis secondary to congenital hip disease (most)	2nd	Cemented (*n* = 59)	Hybric (*n* = 58)	lateral transtrochanteric	
Kim *et al*[15]	64.6	17.3	Avascular necrosis	3rd	Hybrid (*n* = 50)	Cementless (*n* = 98)	ND	May overlap with *et al*[14]
Pospula *et al*[20]	46.7 to 53.7	3 to 5	Avascular necrosis (most)	ND	Cemented (*n* = 87)	Cementless (*n* = 95)	cemented posterolateral cementless transgluteal	
Van Stralen *et al*[21]	69.5	2.5	Primary OA (most)		Cemented (*n* = 746)	Cementless (*n* = 138)	posterior	
Thomason *et al*[22]	54	7.4	Rheumatoid arthritis	ND	Hybrid (*n* = 47)	Cementless (*n* = 51)	posterior	
Zimmerman *et al*[7]	74.9	1	Osteoarthritis	ND	Hybrid (*n* = 85)	Cementless (*n* = 174)	anterolateral, posterior	
Conroy *et al*[23]	Any	5	Osteoarthritis	ND	Cemented (*n* = 8945); hybrid (*n* = 20445); Cementless (*n* = 28582)		ND	
Dale *et al*[24]	Any	0 to 20	Osteoarthritis (most)	ND	Cemented (*n* = 82996)	Cementless (*n* = 14348)	ND	May overlap with study of *et al*[16]
Engesaeter *et al*[25]	Any	0 to 16	Primary Osteoarthritis	ND	Cemented (*n* = 51016)	Cementless (*n* = 5259)	ND	May overlap with *et al*[15]
Eskelinen *et al*[26]	< 55	0 to 24	Rheumatoid arthritis	ND	Cemented (*n* = 821)	Cementless (*n* = 724)	ND	
Hailer *et al*[27]	Any	15	Osteoarthritis (most)	ND	Cemented (*n* = 161460)	Cementless (*n* = 8593)	ND	
Hooper *et al*[28]	Any	7	ND	ND	Cemented (*n* = 16005); hybrid (*n* = 15189) Cementless (*n* = 10898)		ND	
Lucht *et al*[29]	Any	4		ND	Cemented (*n* = 11671); hybric (*n* = 4491) Cementless (*n* = 2030)		ND	
Mäkelä *et al*[30]	> 55	15	Osteoarthritis	ND	Cemented (*n* = 9549)	Cementless (*n* = 10310)	ND	
Mäkelä *et al*[31]	63 to 69 (> 55)	15	Rheumatoid arthritis	ND	Cemented (*n* = 3440)	Cementless (*n* = 579)	ND	
Mäkelä *et al*[32]	< 55	15	Osteoarthritis	ND	Cemented (*n* = 2342)	Cementless (*n* = 1326)	ND	
Malchau *et al*[33]	All	8	Osteoarthritis (most)	ND	Cemented (*n* = 178762)	Cementless (*n* = 6102)	ND	
Pedersen *et al*[34]	Any	0 to 14	Osteoarthritis (most)	ND	Cemented (*n* = 34656); cementless (*n* = 25571) Hybrid (*n* = 20539)		ND	
Roberts *et al*[35]	All	ND	ND	ND	Cemented (*n* = 92928)	Cementless (*n* = 69882)	ND	

Dislocation of any component: Data from two cohorts and five registers were available to determine dislocation of any component (Figure 5). Analysis of cohorts found no difference in dislocation of any component between any types of THR while analysis of registers favors cemented THR (RR = 0.69; 95%CI: 0.29-1.67 and RR

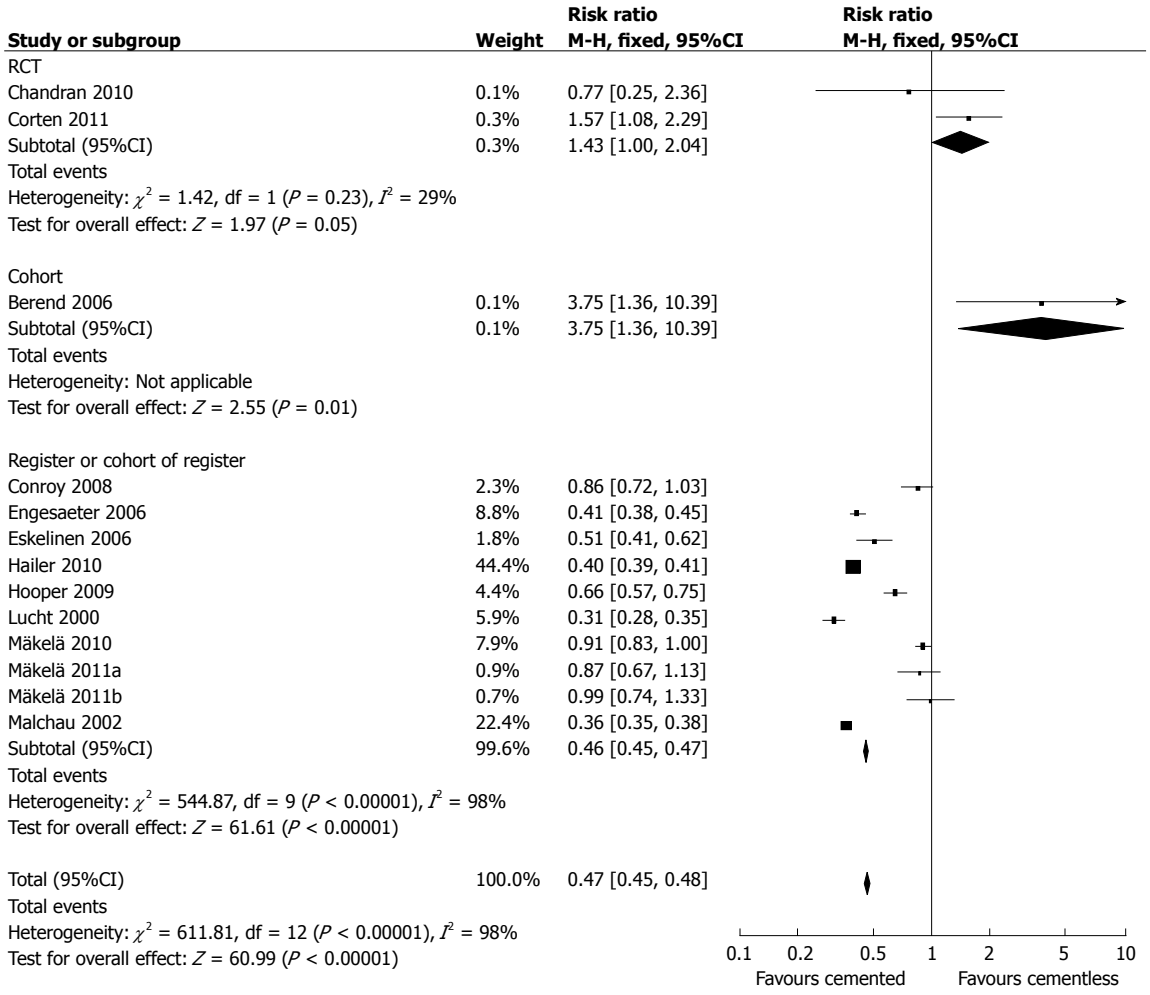

Figure 2 Forest plot of comparison: Cemented *vs* cementless: Revision of any component due to any reason.

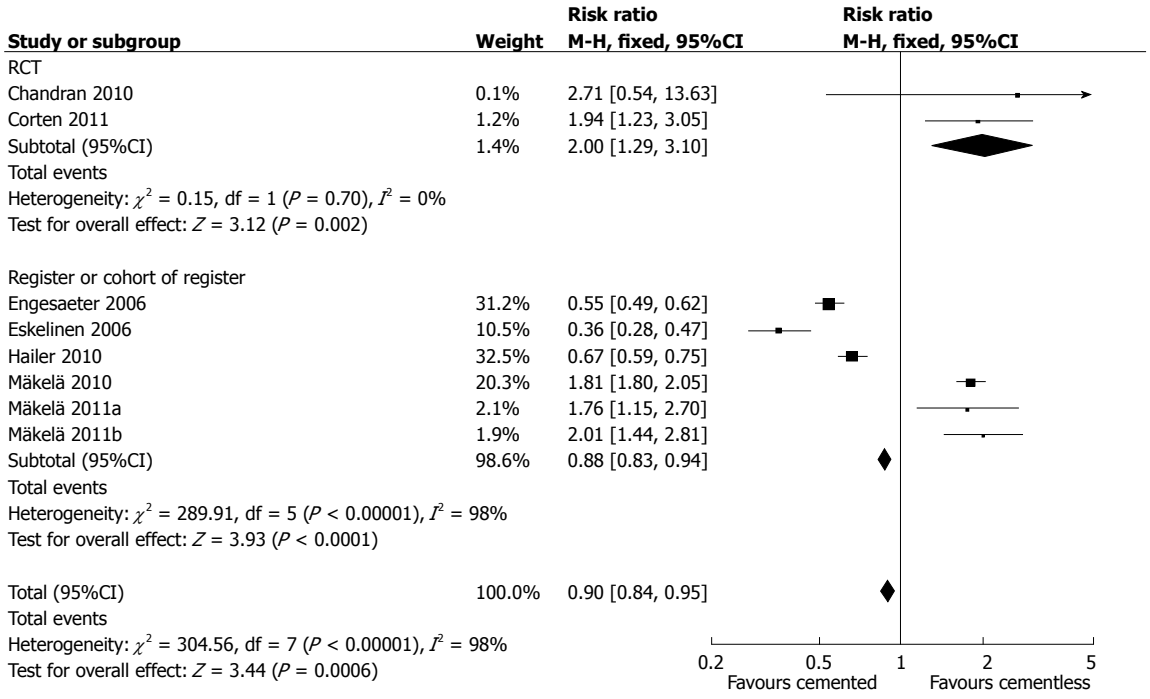

Figure 3 Forest plot of comparison: Cemented *vs* cementless: Revision of any component due to aseptic loosening.

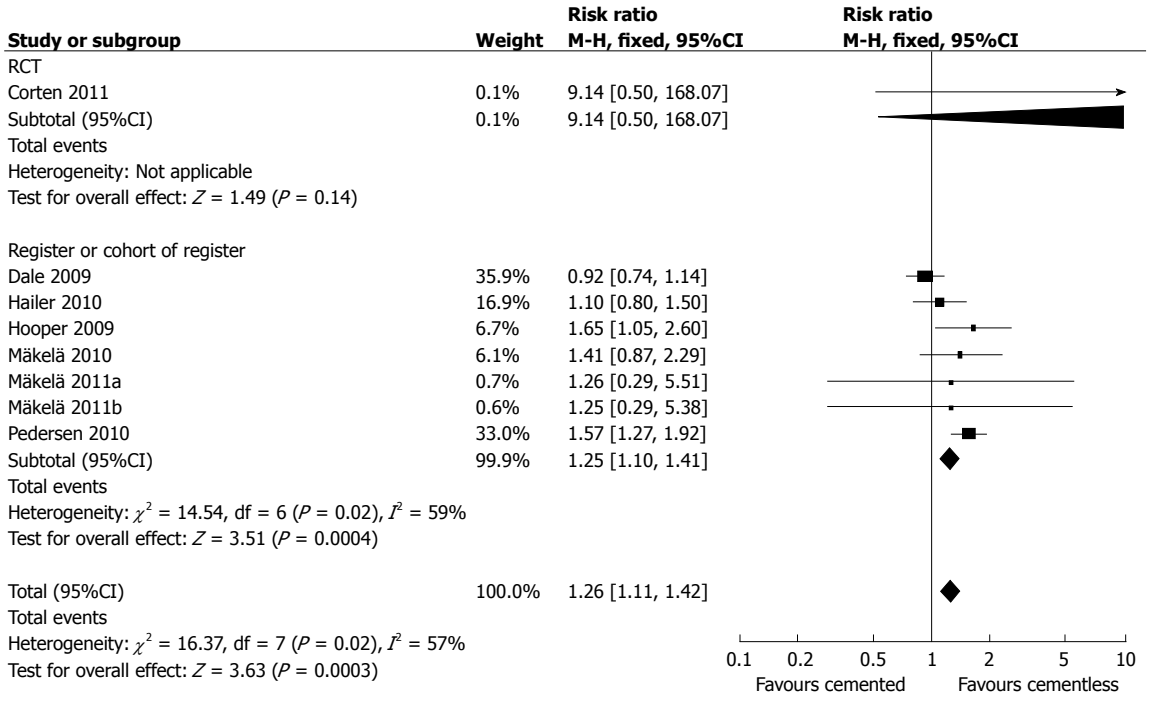

Figure 4 Forest plot of comparison: Cemented *vs* cementless: Revision of any component due to infection.

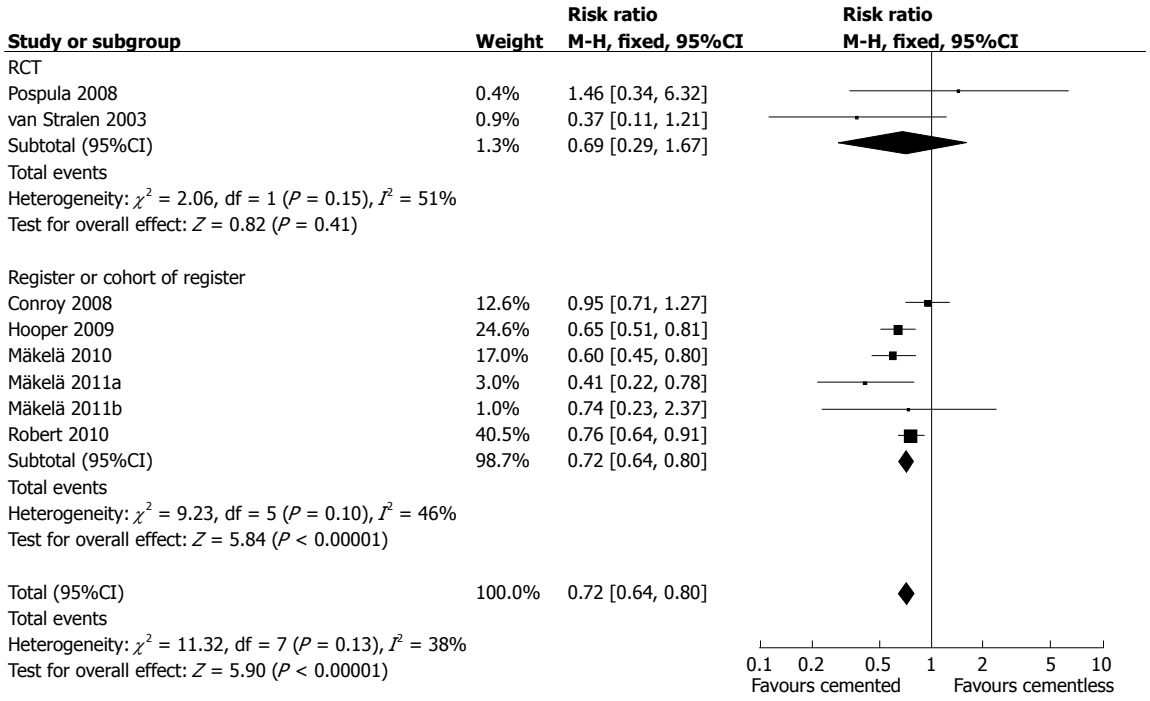

Figure 5 Forest plot of comparison: Cemented *vs* cementless: Dislocation of any component.

= 0.72; 95%CI: 0.64-0.80 respectively). Pooled RR was 0.72 (95%CI: 0.64-0.80) with heterogeneity of 38%.

Cemented vs hybrid THR

Revision of any component due to any reason: Revision of any component due to any reason was addressed by two RCTs, one cohort, and three registers (Figure 6). Analysis of RCTs showed similar risk of revision of any component due to any reason while analysis of registers favored cemented fixation (RR = 0.73; 95%CI: 0.47-1.13 and RR = 0.82; 95%CI: 0.76-0.89 respectively). Pooled all studies together, the RR was 0.82 (95%CI: 0.76-0.89) with a heterogeneity of 41%.

Revision of any component due to aseptic loosening: Only one RCT and one cohort provided information for evaluation of revision of any component

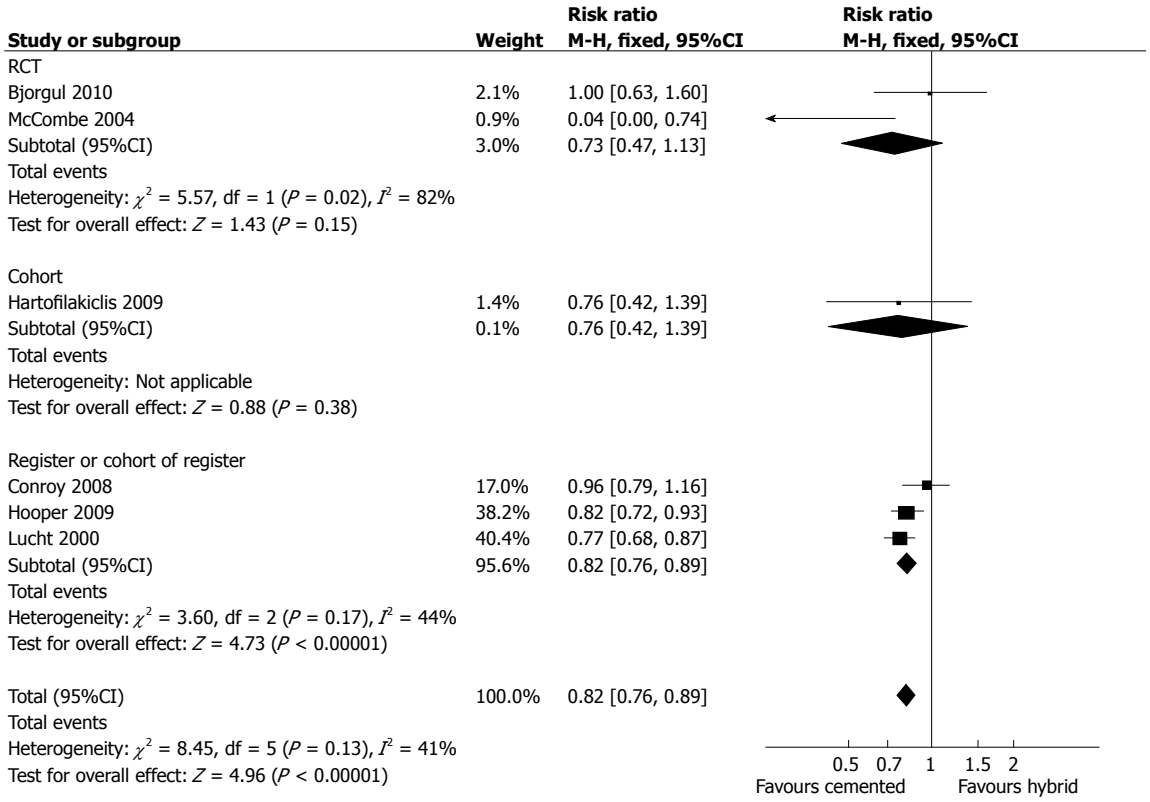

Figure 6 Forest plot of comparison: Cemented *vs* hybrid: Revision of any component due to any reason.

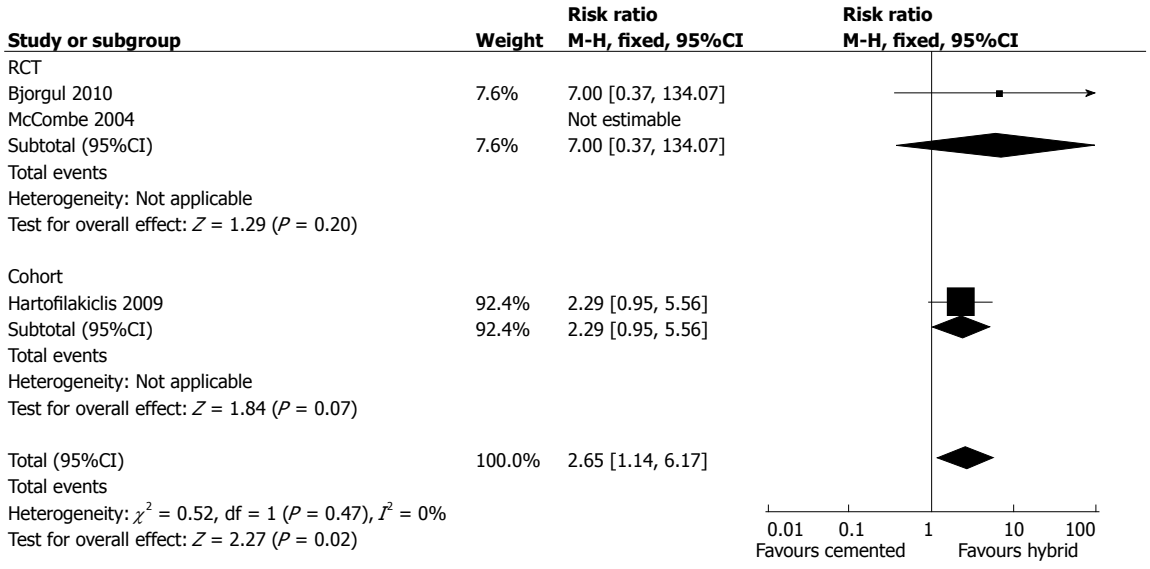

Figure 7 Forest plot of comparison: Cemented *vs* hybrid: Revision of any component due to aseptic loosening.

due to aseptic loosening (Figure 7). When both studies were pooled, the RR was 2.65 (95%CI: 1.14-6.17) and the heterogeneity was 0%.

Revision of any component due to infection: Two RCTs and one cohort and two registers reported revision of any component due to infection (Figure 8). However, one RCT and the cohort encountered zero-event in both arms, so only meta-analysis of registers could be conducted, resulting in RR of 0.94 (95%CI: 0.80-1.11). If all types of study were pooled together, the RR was 0.92 (95%CI: 0.78-1.08) with heterogeneity of 42%.

Dislocation of any component: One RCT and two registers addressed dislocation of any component (Figure 9). Analysis of registers found that risk of dislocation of any component in cemented THR was lower than hybrid THR (RR = 0.11; 95%CI: 0.77-1.59). Pooled together,

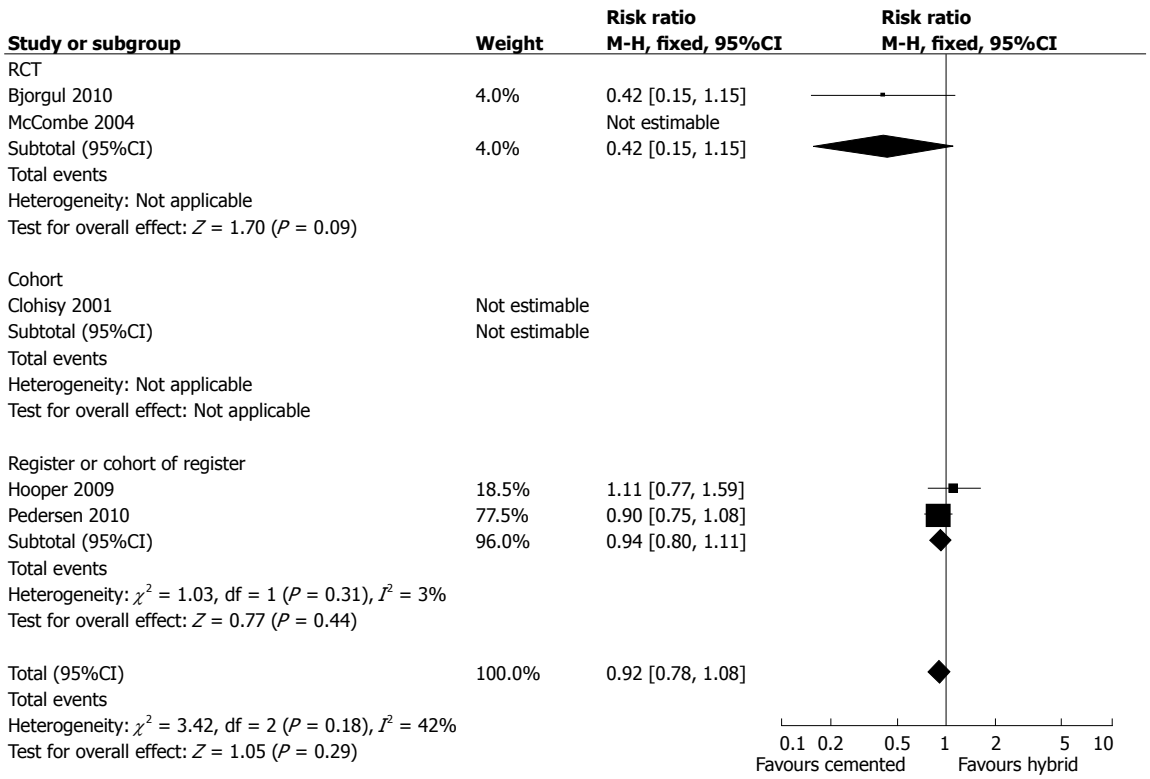

Figure 8 Forest plot of comparison: Cemented *vs* hybrid: Revision of any component due to infection.

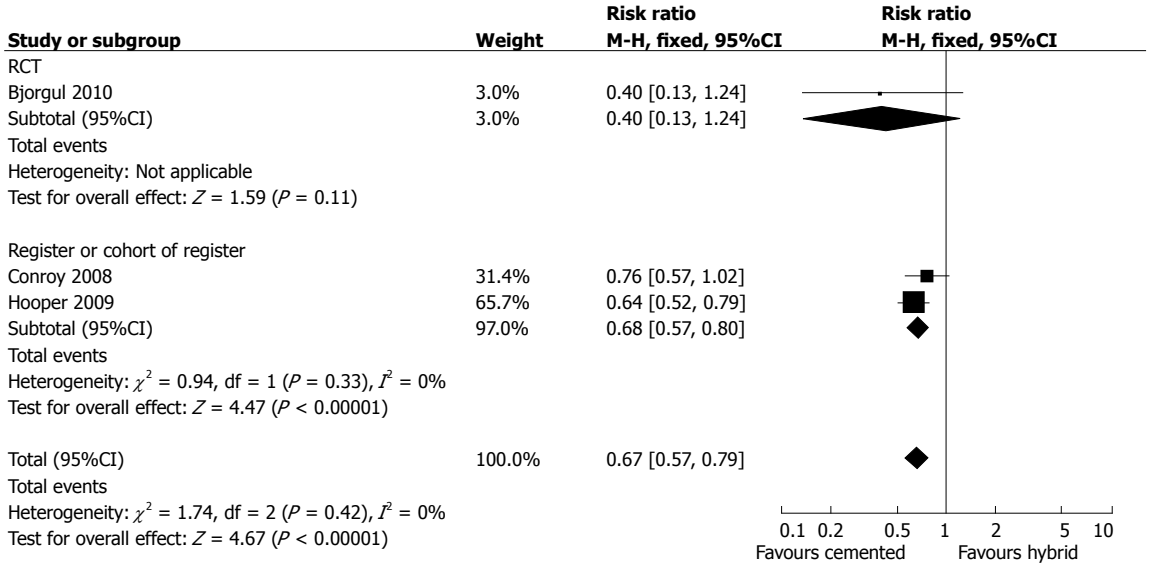

Figure 9 Forest plot of comparison: Cemented *vs* hybrid: Dislocation of any component.

the RR was 0.67 (95%CI: 0.57-0.79) with heterogeneity of 0%.

Cementless vs hybrid THR

Revision of any component due to any reason: One RCT, four cohorts, and three registers investigated revision of any component due to any reason. Analysis of cohorts found similar risk while analysis of registers favored hybrid THR (Figure 10). Meta-regression reduced the heterogeneity into 23.7% but none of the factors analyzed (age group, diagnosis, length of follow-up, starting year, publication type, and funding) showed significant influence.

Revision of any component due to aseptic loosening: One RCT and three cohorts addressed risk of revision of any component due to aseptic loosening (Figure 11). However, one cohorts encountered zero-events in both arms so only two cohorts were eligible for further analysis, which revealed no difference (RR = 0.84;

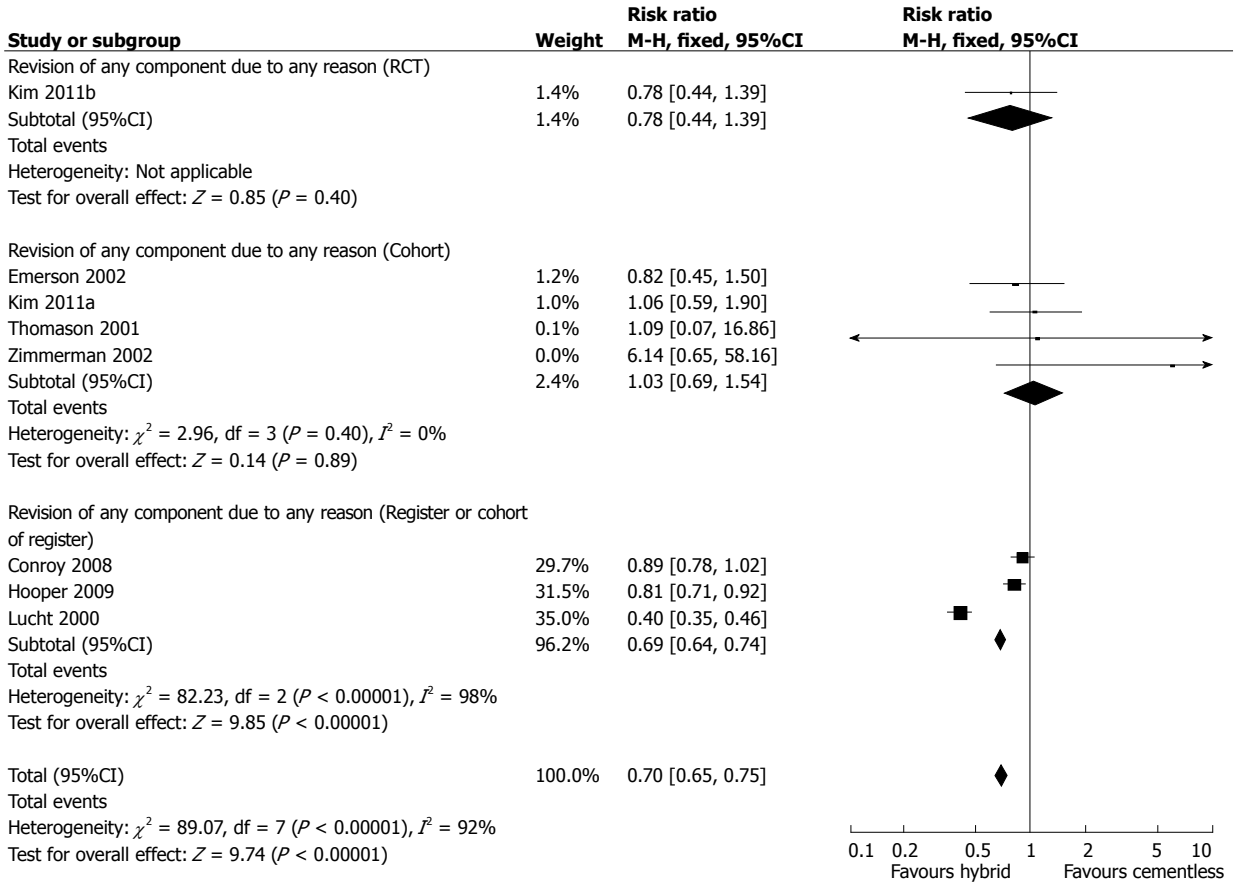

Figure 10 Forest plot of comparison: Cementless *vs* hybrid: Revision of any component due to any reason.

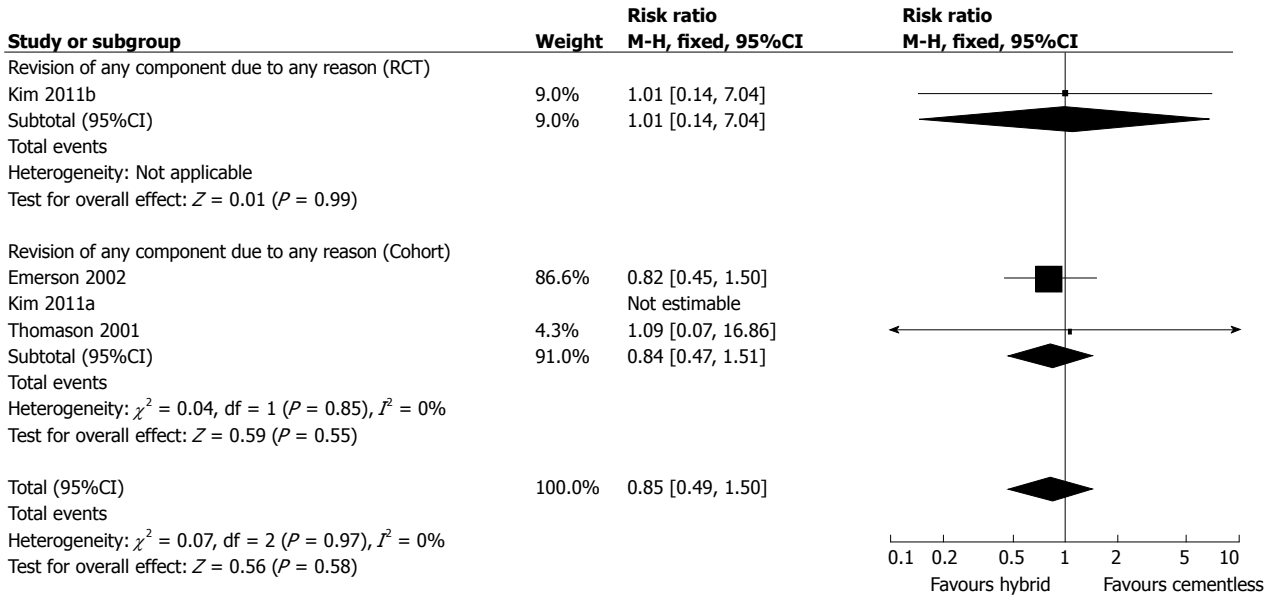

Figure 11 Forest plot of comparison: Cementless *vs* hybrid: Revision of any component due to infection.

95%CI: 0.47-1.51). Pooled all study types together; the RR was 0.85 (95%CI: 0.49-1.50) with heterogeneity of 0%.

Revision of any component due to infection: One RCT, three cohorts, and two registers addressed revision of any component due to infection (Figure 12). However, two cohorts encountered zero events in both arm of studies so insufficient cohort was left for further analysis. Analysis of registers revealed RR of 1.69 (95%CI:

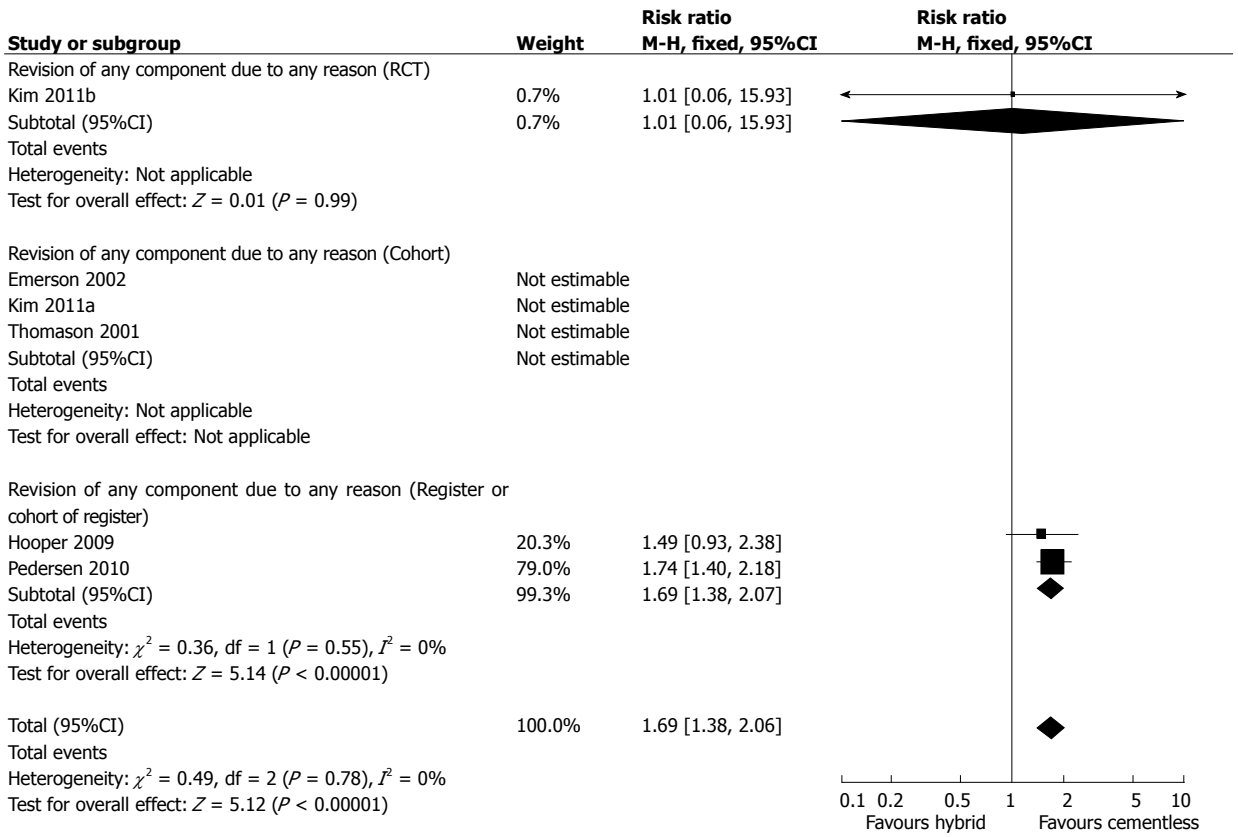

Figure 12 Forest plot of comparison: Cementless *vs* hybrid: Revision of any component due to infection.

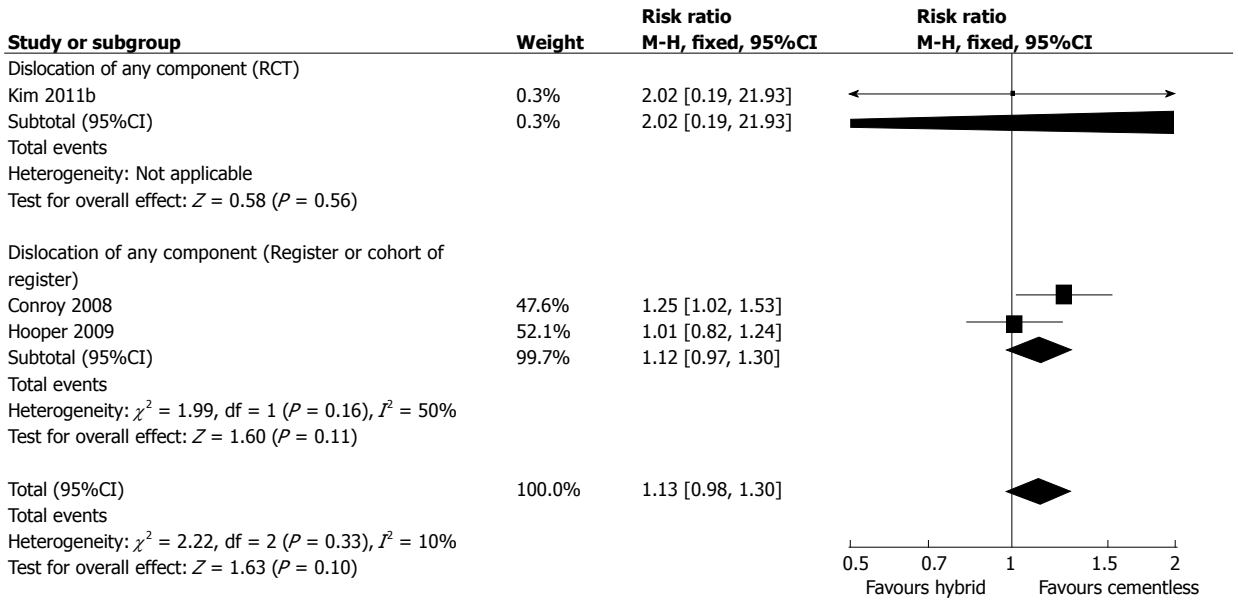

Figure 13 Forest plot of comparison: Cementless *vs* hybrid: Dislocation of any component.

1.38-2.07). If all available studies were put together, the RR was 1.69 (95%CI: 1.38-2.06) and the heterogeneity was 0%.

Dislocation of any component: One RCT and two cohorts evaluated risk of dislocation (Figure 13). Analysis of the registers resulted in insignificant difference between any types of THR (RR = 1.12; 95%CI: 0.97-1.30). Pooled all study types together; the RR was 1.13 (95%CI: 0.98-1.30).

Analysis of publication bias: Figure 14 showed funnel plots based on risk of revision of any component due to any reason between cemented and cementless

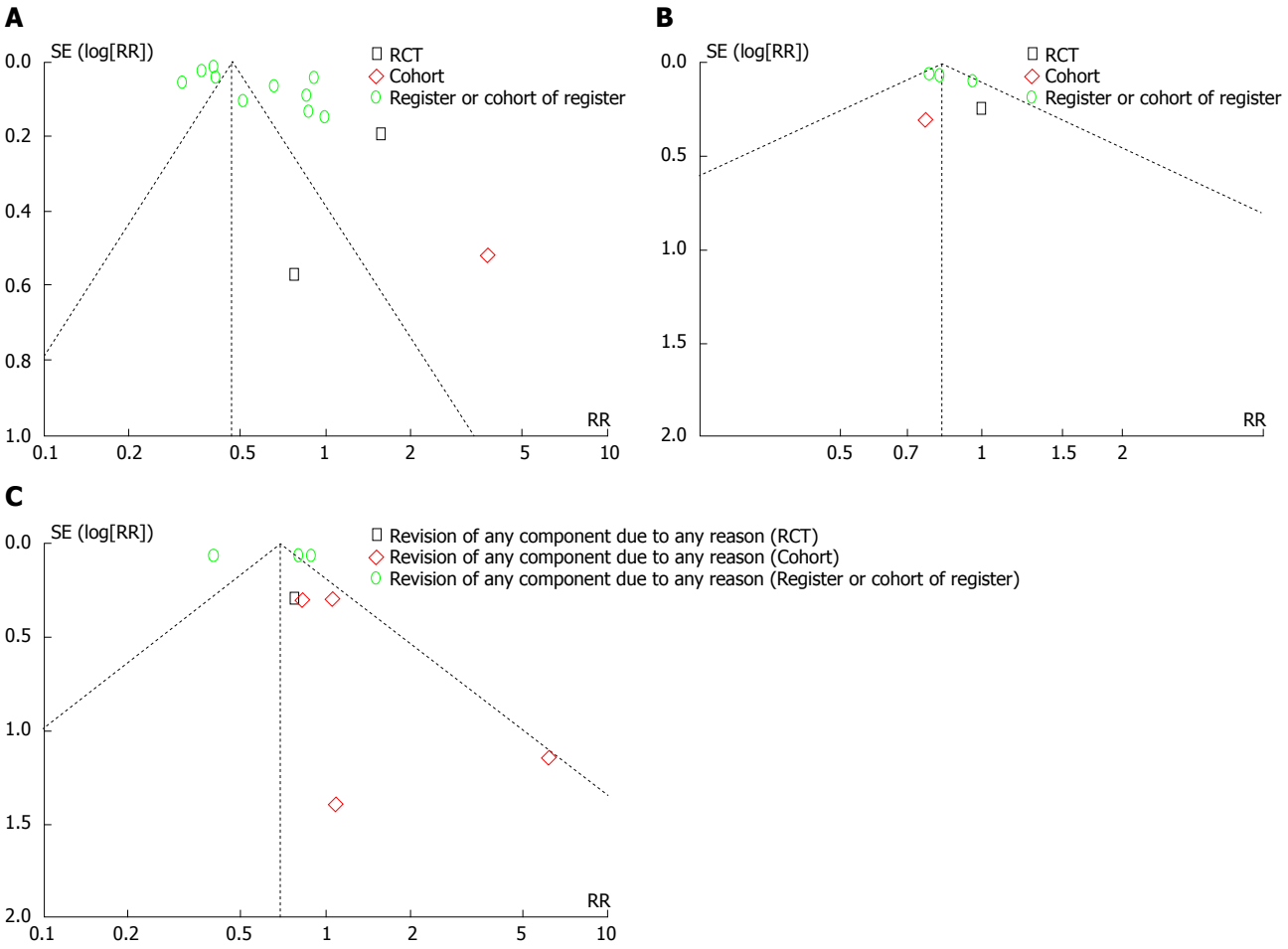

Figure 14 Funnel plot of comparison of revision of any component (A) cementless *vs* cementless; (B) cemented *vs* hybrid; (C) cementless *vs* hybrid.

(a), cemented and hybrid (b), and cementless and hybrid THR (c). Asymmetries were found in these plots suggesting the existence of bias.

Grading of the evidence: Most of the results were of low to very low level of evidence. The summaries of the grading were shown in Tables 2-4.

DISCUSSION

We summarized the evidence from 5 randomized clinical trials, 9 cohorts, and 13 registers or cohorts of register about total hip replacement and found that that cemented THR was superior to cementless THR and hybrid THR in terms of risk of revision due to any reason. Moreover, cemented THR was also more superior compared with cementless THR if revision due to aseptic loosening and revision due to dislocation were used as the endpoint but inferior if revision due to infection was used. Cemented THR was superior to hybrid THR in the risk of revision due to any reason and dislocation. Meanwhile cementless THR was most inferior compared to the others in risk of revision due to any reason.

In our knowledge, Morshed *et al*[9] performed the first metaanalysis reviewing the survival and outcome of cemented and uncemented fixation in total hip replacement in 2007. Although cemented fixation seemed to outperform cementless fixation in large subsets of study population, there was no significant advantages were found for either type of fixation in terms of survival. There was an association between difference in survival and year of publication, with cementless fixation showing relative superiority over time. However, our recent analysis still suggested that cemented fixation continued to outperform uncemented fixation especially in large study populations (registers)[24,26-33].

Recent metaanalysis by Abdulkarim *et al*[37] reviewed 9 RCTs that primarily comparing implants survival between cemented and cementless THR. In their study, no significant differences were found in implant survival especially as measured by the revision rate. By using RCT, which is the gold standard of clinical research, the quality of evidence in GRADE approach should be moderate or even high. However, the average follow up duration were only 4.3 years (2-8 years), which was relatively short to evaluate the implant survival.

In our study, an analysis of 2 RCTs comparing the survival of cemented and cementless implant was performed. As the duration of follow up ranged from 14-19 years, these RCTs would give a better evaluation in terms of implant survival. In this analysis, the relative risk of revision due to any revision was higher in cemented

Table 2 Summary of finding comparing cemented and cementless total hip replacement

	Illustrative comparative risks[7] (95%CI)		Relative effect (95%CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Cementless	Corresponding risk Cemented				
Revision of any component due to any reason - RCT Follow-up: 14 to 19.5 yr	Study population 165 per 1000 Moderate 156 per 1000	 235 per 1000 (165 to 336) 223 per 1000 (156 to 318)	RR 1.43 (1 to 2.04)	452 (2 studies)	++-- low[1,2]	
Revision of any component due to any reason - Register or Cohort of register Follow-up: 0 to 24 yr	Study population 99 per 1000 Moderate 122 per 1000	 46 per 1000 (45 to 47) 56 per 1000 (55 to 57)	RR 0.46 (0.45 to 0.47)	518774 (10 studies)	+--- very low[2,3,4]	
Revision of any component due to any reason - All types of study Follow-up: 0 to 24 yr	Study population 99 per 1000 Moderate 106 per 1000	 46 per 1000 (44 to 47) 50 per 1000 (48 to 51)	RR 0.47 (0.45 to 0.48)	521757 (13 studies)	+--- very low[2,3,5]	
Revision of any component due to aseptic loosening - RCT Follow-up: 14 to 19.5 yr	Study population 104 per 1000 Moderate 97 per 1000	 208 per 1000 (134 to 322) 194 per 1000 (125 to 301)	RR 2 (1.29 to 3.1)	452 (2 studies)	+++- moderate[2]	
Revision of any component due to aseptic loosening - Register or Cohort of register Follow-up: 0 to 24 yr	Study population 47 per 1000 Moderate 48 per 1000	 41 per 1000 (39 to 44) 42 per 1000 (40 to 45)	RR 0.88 (0.83 to 0.94)	255779 (6 studies)	+--- very low[2,3,4]	
Revision of any component due to aseptic loosening - All types of study Follow-up: 0 to 24 yr	Study population 47 per 1000 Moderate 48 per 1000	 43 per 1000 (40 to 45) 43 per 1000 (40 to 46)	RR 0.9 (0.84 to 0.95)	256231 (8 studies)	+--- very low[2,3,5,6]	
Revision of any component due to infection - Register or Cohort of register Follow-up: 0 to 20 yr	Study population 5 per 1000 Moderate 4 per 1000	 6 per 1000 (5 to 7) 5 per 1000 (4 to 6)	RR 1.27 (1.04 to 1.55)	382433 (6 studies)	+--- very low[2,4]	
Revision of any component due to infection - All types of study Follow-up: 0 to 20 yr	Study population 5 per 1000 Moderate 4 per 1000	 6 per 1000 (5 to 7) 5 per 1000 (4 to 6)	RR 1.29 (1.06 to 1.57)	382683 (7 studies)	+--- very low[2,5]	
Dislocation of any component - Cohort Follow-up: 2.5 to 5 yr	Study population 30 per 1000 Moderate 30 per 1000	 21 per 1000 (9 to 50) 21 per 1000 (9 to 50)	RR 0.69 (0.29 to 1.67)	1066 (2 studies)	+--- very low[1,2,3]	
Dislocation of any component - Register or Cohort of register Follow-up: 5 to 15 yr	Study population 6 per 1000 Moderate 13 per 1000	 4 per 1000 (4 to 5) 9 per 1000 (8 to 10)	RR 0.69 (0.59 to 0.8)	254786 (6 studies)	+--- very low[3,4]	
Dislocation of any component - All types of study Follow-up: 2.5 to 15 yr	Study population 6 per 1000 Moderate 14 per 1000	 4 per 1000 (4 to 5) 10 per 1000 Ta(8 to 11)	RR 0.69 (0.6 to 0.79)	255852 (8 studies)	+--- very low[2,5]	

CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect; moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: We are very uncertain about the estimate. [1]95% confidence interval around the pooled or best estimate of effect includes both (1) no effect and (2) appreciable benefit or appreciable harm (> 25%); [2]No explanation was provided; [3]Unexplained heterogeneity; [4]Indirect studies from registers; [5]Overall result from all types of study; [6]High heterogeneity, explained by meta-regression; [7]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

group with RR = 1.43 (1-2.04), which also meant that the cementless implant was superior. But it were pooled together with the cohort studies and registers, the results would be contradictive as it favored the cemented implant with RR = 0.47 (0.46-0.48).

Despite the tendencies of most registers towards cemented implant, there are some studies and even some registries[29,30,33] noted that uncemented implant survived better in the group of younger patients. Malchau *et al*[33] in their Swedish arthroplasty register, found that uncemented implants had better survival in patients with less than 55 years of age. Similar findings were reported by the Lucht *et al*[29] when they evaluated the Danish arthroplasty register. Eskelinen *et al*[26] in the Finnish

Table 3 Summary of finding table comparing cemented to hybrid total hip replacement

Outcomes	Illustrative comparative risks[6] (95%CI)		Relative effect (95%CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Hybrid	Corresponding risk Cemented				
Revision of any component due to any reason - RCT Follow-up: 6.5 to 14 yr	Study population 187 per 1000 Moderate 177 per 1000	 136 per 1000 (88 to 211) 129 per 1000 (83 to 200)	RR 0.73 (0.47 to 1.13)	402 (2 studies)	+--- very low[1,2,3]	
Revision of any component due to any reason - Register or Cohort of register Follow-up: 4 to 7 yr	Study population 30 per 1000 Moderate 31 per 1000	 24 per 1000 (23 to 26) 25 per 1000 (24 to 28)	RR 0.82 (0.76 to 0.89)	76746 (3 studies)	+--- very low[3,4]	
Revision of any component due to any reason - All types of study Follow-up: 4 to 15.4 yr	Study population 31 per 1000 Moderate 104 per 1000	 25 per 1000 (23 to 27) 85 per 1000 (79 to 93)	RR 0.82 (0.76 to 0.89)	77265 (6 studies)	+--- very low[3,5]	
Revision of any component due to aseptic loosening - All types of study Follow-up: 6.5 to 15.4 yr	Study population 23 per 1000 Moderate 0 per 1000	 62 per 1000 (27 to 145) 0 per 1000 (0 to 0)	RR 2.65 (1.14 to 6.17)	519 (3 studies)	+--- very low[3,5]	
Revision of any component due to infection - Register or Cohort of register Follow-up: 0 to 14 yr	Study population 7 per 1000 Moderate	 0 per 1000 (0 to 0)	Not estimable	86389 (2 studies)	+--- very low[3,4]	
Revision of any component due to infection - All types of study Follow-up: 0 to 14 yr	Study population 7 per 1000 Moderate 2 per 1000	 7 per 1000 (5 to 10) 2 per 1000 (1 to 3)	RR 0.98 (0.7 to 1.38)	86881 (5 studies)	+--- very low[1,2,3,5]	
Dislocation of any component - Register of Cohort of register Follow-up: 5 to 7 yr	Study population 11 per 1000 Moderate 11 per 1000	 7 per 1000 (6 to 9) 7 per 1000 (6 to 9)	RR 0.68 (0.57 to 0.8)	60584 (2 studies)	+--- very low[3,4]	
Dislocation of any component - All types of study Follow-up: 5 to 14 yr	Study population 11 per 1000 Moderate 14 per 1000	 7 per 1000 (6 to 9) 9 per 1000 (8 to 11)	RR 0.67 (0.57 to 0.79)	60824 (3 studies)	+--- very low[3,5]	

CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect; moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: We are very uncertain about the estimate. [1]95% confidence interval around the pooled or best estimate of effect includes both (1) no effect and (2) appreciable benefit or appreciable harm (> 25%); [2]No explanation was provided; [3]Unexplained heterogeneity; [4]Indirect studies from registers; [5]Overall result from all types of study; [6]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

arthroplasty register, reported that in age group under 55-years had higher revision rates for aseptic loosening in cemented group compared with proximally coated cementless femoral components. Further analysis of Finnish arthroplasty register in patients aged 55-year and older showed that uncemented femoral stem has better survival in the 55 to 74-year age group while there was no significant difference in 75-year and older patients[30].

This series of studies might explain the reason why contradictive result occurred in our analysis. In their inclusion criteria, both RCTs used 75 years as the upper age limit without any lower age limit, and the average age in both RCTs was around 64 years[12,13]. It was seemed that this fact might play a role in our result.

Hybrid THR was first introduced to address the results of cemented THR in younger patients in whom acetabular failure was the main reason for revision. However, recent studies reported that hybrid THR was the most common THR types to be revised due to dislocation in the first 90 d and even after 90 d after the primary surgery[28]. In their prospective multicenter study about primary total hip arthroplasty revision due to dislocation, Girard *et al*[38] described that, from their revision series, cementless acetabular fixation and cemented femoral stem fixation were involved in a higher number of dislocation which are 63.8% and 53% respectively. However it was not mentioned about the reason why cementless acetabular fixation has a higher chance of dislocation compared to the cemented one. Although there are no supporting data, there was a hypothesis

Table 4 Summary of finding table comparing hybrid and cementless total hip replacement

Outcomes	Illustrative comparative risks[7] (95%CI)		Relative effect (95%CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Cementless	Corresponding risk Hybrid				
Revision of any component due to any reason - Cohort Follow-up: 1 to 17.3 yr	Study population 105 per 1000 Moderate 106 per 1000	 108 per 1000 (72 to 161) 109 per 1000 (73 to 163)	RR 1.03 (0.69 to 1.54)	706 (4 studies)	+--- very low[1,2]	
Revision of any component due to any reason - Register or Cohort of register Follow-up: 4 to 7 yr	Study population 33 per 1000 Moderate 39 per 1000	 23 per 1000 (21 to 25) 27 per 1000 (25 to 29)	RR 0.69 (0.64 to 0.74)	81635 (3 studies)	+--- very low[2,3,4]	
Revision of any component due to any reason - All types of study Follow-up: 1 to 18.4 yr	Study population 34 per 1000 Moderate 116 per 1000	 24 per 1000 (22 to 26) 81 per 1000 (75 to 87)	RR 0.7 (0.65 to 0.75)	82560 (8 studies)	+--- very low[2,5,6]	
Revision of any component due to aseptic loosening - Cohort Follow-up: 6.7 to 17.3 yr	Study population 76 per 1000 Moderate 20 per 1000	 64 per 1000 (36 to 115) 17 per 1000 (9 to 30)	RR 0.84 (0.47 to 1.51)	447 (3 studies)	+--- very low[1,2]	
Revision of any component due to aseptic loosening - All types of study Follow-up: 6.7 to 17.3 yr	Study population 58 per 1000 Moderate 19 per 1000	 49 per 1000 (28 to 86) 16 per 1000 (9 to 28)	RR 0.85 (0.49 to 1.5)	666 (4 studies)	+--- very low[1,2,6]	
Revision of any component due to infection - Register or Cohort of register Follow-up: 0 to 14 yr	Study population 4 per 1000 Moderate	 0 per 1000 (0 to 0)	Not estimable	72197 (2 studies)	+--- very low[2,4]	
Revision of any component due to infection - All types of study Follow-up: 0 to 18.4 yr	Study population 4 per 1000 Moderate 0 per 1000	 6 per 1000 (4 to 10) 0 per 1000 (0 to 0)	RR 1.47 (0.93 to 2.34)	72863 (5 studies)	+--- very low[1,2,6]	
Dislocation of any component - Register or Cohort of register Follow-up: 5 to 7 yr	Study population 9 per 1000 Moderate 10 per 1000	 10 per 1000 (9 to 11) 11 per 1000 (10 to 13)	RR 1.12 (0.97 to 1.3)	75114 (2 studies)	+--- very low[1,2,4]	
Dislocation of any component - All types of study Follow-up: 5 to 18.4 yr	Study population 9 per 1000 Moderate 9 per 1000	 10 per 1000 (9 to 11) 10 per 1000 (9 to 12)	RR 1.13 (0.98 to 1.3)	75333 (3 studies)	+--- very low[1,2,6]	

CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect; moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: We are very uncertain about the estimate. [1]95% confidence interval around the pooled or best estimate of effect includes both (1) no effect and (2) appreciable benefit or appreciable harm (> 25%); [2]No explanation was provided; [3]Unexplained heterogeneity; [4]Indirect studies from registers; [5]Overall result from all types of study; [6]High heterogeneity, explained by meta-regression; [7]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

that positioning of acetabular component may be more accurate in cemented components[23]. Although Parrate and Argenson[39] didn't include cemented acetabular cup in their study, they showed that 57% cementless cup that inserted in conventional way and 20% navigated were outside of the defined safe zone (outliers). While cementing the acetabular component, few adjustments can be made during insertion and while waiting for the cement polymerization. On the other hand, cementless cup has less adjustability and may change their orientation from the most desired position during the final seating of the component. Despite all, from the economic perspective, hybrid prostheses lead to grater gain in mean postoperative quality of life and the most cost effective alternative for most patients according to cost effectiveness analysis model by Pennington *et al*[40].

Clinical trials, cohorts, and register-based studies were included into our meta-analysis. Inclusion of register based studies had certain benefits and limitations[30,36]. Register provided large number of samples for analysis and the population data corresponded to the actual population[36]. Moreover, a poor result in a single center would not have major effect on the result of the study[30]. Despite RCTs is considered the gold standard design for clinical research, one of its disadvantages is that strict inclusion and exclusion criteria might not reflect the condition of real population, as it often narrowed the samples to a highly selected group of patients that is operated by only a

few surgeons. However, the desired outcome was not the main purpose of the registry. Accuracy of the data might be limited due to inconsistencies or errors in data collection inputted to the register[41]. Data available in clinical trials and cohorts might also have been included in the register and therefore were used twice in the analysis.

Various implant designs, surgical approaches and techniques (such as cementing technique), rehabilitation protocols, and activity levels were included in our study. Lack of data prevented us to analyze them separately in subgroup analysis or in meta-regression. Therefore, it was understandable that high heterogeneity existed in our study. We explored the heterogeneity to the greatest degree possible, in to a meta-regression, yet very high heterogeneity remained in some comparison.

Very high heterogeneity indicated that effect size of each study varied greatly[42]. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working group recommended to lower the quality assessment in study with unexplained heterogeneity[41]. Even though the result was obtain by a meta-analysis, interpreting the result must be careful.

In conclusion, despite some limitations in the selected studies especially the low quality assessment and heterogeneity, there was some tendency that cemented fixation was still superior than other types of fixation in terms of implant survival. Future high quality randomized clinical trials, preferably multicenter, to obtain larger sample size, considering all factors that may influent results, are required to give definite recommendations regarding the best type of total hip replacement.

COMMENTS

Background

Controversies still persisted on the optimal method of fixation for primary total hip replacement (THR). Previous meta-analysis found no difference between cemented and cementless implant, but since then, many larger studies with longer duration of follow-up had been conducted. In this meta-analysis, more recent studies were enrolled to determine whether cemented, cementless, or hybrid implant was superior to the other.

Research frontiers

Implant survival analysis in different type of THR fixation is still a controversial debate. Worldwide researches are still focused on which type of implant that suits best on patients to provide better care to the patients.

Innovations and breakthroughs

Despite some limitations in the selected studies especially the low quality assessment and heterogeneity, their study presented a metaanalysis of studies with a long duration of follow up, which would give a better perspective in terms of implant survival. There was some tendency that cemented fixation was still superior than other types of fixation.

Applications

There was some tendency that cemented fixation was still superior to other types of fixation.

Peer-review

It is well presented, well-structured and extensively build up and therefore useful for the readers.

REFERENCES

1 **Ostendorf M**, Johnell O, Malchau H, Dhert WJ, Schrijvers AJ, Verbout AJ. The epidemiology of total hip replacement in The Netherlands and Sweden: present status and future needs. *Acta Orthop Scand* 2002; **73**: 282-286 [PMID: 12143973 DOI: 10.1080/00016470 2320155257]

2 **Merx H**, Dreinhöfer K, Schräder P, Stürmer T, Puhl W, Günther KP, Brenner H. International variation in hip replacement rates. *Ann Rheum Dis* 2003; **62**: 222-226 [PMID: 12594106 DOI: 10.1136/ard.62.3.222]

3 **Felson DT**, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum* 1998; **41**: 1343-1355 [PMID: 9704632 DOI: 10.1002/1529-0131(199808)41: 8<1343: : AID-ART3>3.0.CO; 2-9]

4 **Wroblewski BM**. Cementless versus cemented total hip arthroplasty. A scientific controversy? *Orthop Clin North Am* 1993; **24**: 591-597 [PMID: 8414424]

5 **Rorabeck CH**, Bourne RB, Laupacis A, Feeny D, Wong C, Tugwell P, Leslie K, Bullas R. A double-blind study of 250 cases comparing cemented with cementless total hip arthroplasty. Cost-effectiveness and its impact on health-related quality of life. *Clin Orthop Relat Res* 1994; **(298)**: 156-164 [PMID: 8118970]

6 **Rorabeck CH**, Bourne RB, Mulliken BD, Nayak N, Laupacis A, Tugwell P, Feeney D. The Nicolas Andry award: comparative results of cemented and cementless total hip arthroplasty. *Clin Orthop Relat Res* 1996; **(325)**: 330-344 [PMID: 8998896 DOI: 10.1097/00003086-199604000-00044]

7 **Zimmerma S**, Hawkes WG, Hudson JI, Magaziner J, Hebel JR, Towheed T, Gardner J, Provenzano G, Kenzora JE. Outcomes of surgical management of total HIP replacement in patients aged 65 years and older: cemented versus cementless femoral components and lateral or anterolateral versus posterior anatomical approach. *J Orthop Res* 2002; **20**: 182-191 [PMID: 11918295 DOI: 10.1016/S0736-0266(01)00090-0]

8 **Emerson RH**, Head WC, Emerson CB, Rosenfeldt W, Higgins LL. A comparison of cemented and cementless titanium femoral components used for primary total hip arthroplasty: a radiographic and survivorship study. *J Arthroplasty* 2002; **17**: 584-591 [PMID: 12168174 DOI: 10.1054/arth.2002.32696]

9 **Morshed S**, Bozic KJ, Ries MD, Malchau H, Colford JM. Comparison of cemented and uncemented fixation in total hip replacement: a meta-analysis. *Acta Orthop* 2007; **78**: 315-326 [PMID: 17611843 DOI: 10.1080/17453670710013861]

10 **Moher D**, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336-341 [PMID: 20171303 DOI: 10.1016/j.ijsu.2010.02.007]

11 **Bjørgul K**, Novicoff WM, Andersen ST, Brevig K, Thu F, Wiig M, Ahlund O. No differences in outcomes between cemented and uncemented acetabular components after 12-14 years: results from a randomized controlled trial comparing Duraloc with Charnley cups. *J Orthop Traumatol* 2010; **11**: 37-45 [PMID: 20198405 DOI: 10.1007/s10195-010-0082-2]

12 **Chandran P**, Azzabi M, Miles J, Andrews M, Bradley J. Furlong hydroxyapatite-coated hip prosthesis vs the Charnley cemented hip prosthesis. *J Arthroplasty* 2010; **25**: 52-57 [PMID: 19056219 DOI: 10.1016/j.arth.2008.10.009]

13 **Corten K**, Bourne RB, Charron KD, Au K, Rorabeck CH. Comparison of total hip arthroplasty performed with and without cement: a randomized trial. A concise follow-up, at twenty years, of previous reports. *J Bone Joint Surg Am* 2011; **93**: 1335-1338 [PMID: 21792500 DOI: 10.2106/JBJS.J.00448]

14 **Kim YH**, Kim JS, Park JW, Joo JH. Comparison of total hip replacement with and without cement in patients younger than 50 years of age: the results at 18 years. *J Bone Joint Surg Br* 2011; **93**: 449-455 [PMID: 21464481 DOI: 10.1302/0301-620X.93B4.26149]

15 **Kim YH**, Kim JS, Park JW, Joo JH. Contemporary total hip arthroplasty with and without cement in patients with osteonecrosis

of the femoral head: a concise follow-up, at an average of seventeen years, of a previous report. *J Bone Joint Surg Am* 2011; **93**: 1806-1810 [PMID: 22005866 DOI: 10.2106/JBJS.J.01312]
16 **McCombe P**, Williams SA. A comparison of polyethylene wear rates between cemented and cementless cups. A prospective, randomised trial. *J Bone Joint Surg Br* 2004; **86**: 344-349 [PMID: 15125120]
17 **Berend ME**, Smith A, Meding JB, Ritter MA, Lynch T, Davis K. Long-term outcome and risk factors of proximal femoral fracture in uncemented and cemented total hip arthroplasty in 2551 hips. *J Arthroplasty* 2006; **21**: 53-59 [PMID: 16950062 DOI: 10.1016/j.arth.2006.05.014]
18 **Clohisy JC**, Harris WH. Matched-pair analysis of cemented and cementless acetabular reconstruction in primary total hip arthroplasty. *J Arthroplasty* 2001; **16**: 697-705 [PMID: 11547367 DOI: 10.1054/arth.2001.24447]
19 **Hartofilakidis G**, Georgiades G, Babis GC. A comparison of the outcome of cemented all-polyethylene and cementless metal-backed acetabular sockets in primary total hip arthroplasty. *J Arthroplasty* 2009; **24**: 217-225 [PMID: 18534419 DOI: 10.1016/j.arth.2007.11.010]
20 **Pospula W**, Abu Noor T, Roshdy T, Al Mukaimi A. Cemented and cementless total hip replacement. Critical analysis and comparison of clinical and radiological results of 182 cases operated in Al Razi Hospital, Kuwait. *Med Princ Pract* 2008; **17**: 239-243 [PMID: 18408394 DOI: 10.1159/000117799]
21 **van Stralen GM**, Struben PJ, van Loon CJ. The incidence of dislocation after primary total hip arthroplasty using posterior approach with posterior soft-tissue repair. *Arch Orthop Trauma Surg* 2003; **123**: 219-222 [PMID: 12684831 DOI: 10.1007/s00402-003-0482-3]
22 **Thomason HC**, Lachiewicz PF. The influence of technique on fixation of primary total hip arthroplasty in patients with rheumatoid arthritis. *J Arthroplasty* 2001; **16**: 628-634 [PMID: 11503123 DOI: 10.1054/arth.2001.23720]
23 **Conroy JL**, Whitehouse SL, Graves SE, Pratt NL, Ryan P, Crawford RW. Risk factors for revision for early dislocation in total hip arthroplasty. *J Arthroplasty* 2008; **23**: 867-872 [PMID: 18534522 DOI: 10.1016/j.arth.2007.07.009]
24 **Dale H**, Hallan G, Hallan G, Espehaug B, Havelin LI, Engesaeter LB. Increasing risk of revision due to deep infection after hip arthroplasty. *Acta Orthop* 2009; **80**: 639-645 [PMID: 19995313 DOI: 10.3109/17453670903506658]
25 **Engesaeter LB**, Espehaug B, Lie SA, Furnes O, Havelin LI. Does cement increase the risk of infection in primary total hip arthroplasty? Revision rates in 56,275 cemented and uncemented primary THAs followed for 0-16 years in the Norwegian Arthroplasty Register. *Acta Orthop* 2006; **77**: 351-358 [PMID: 16819671 DOI: 10.1080/17453670610046253]
26 **Eskelinen A**, Paavolainen P, Helenius I, Pulkkinen P, Remes V. Total hip arthroplasty for rheumatoid arthritis in younger patients: 2,557 replacements in the Finnish Arthroplasty Register followed for 0-24 years. *Acta Orthop* 2006; **77**: 853-865 [PMID: 17260192 DOI: 10.1080/17453670610013132]
27 **Hailer NP**, Garellick G, Kärrholm J. Uncemented and cemented primary total hip arthroplasty in the Swedish Hip Arthroplasty Register. *Acta Orthop* 2010; **81**: 34-41 [PMID: 20180715 DOI: 10.3109/17453671003685400]
28 **Hooper GJ**, Rothwell AG, Stringer M, Frampton C. Revision following cemented and uncemented primary total hip replacement: a seven-year analysis from the New Zealand Joint Registry. *J Bone Joint Surg Br* 2009; **91**: 451-458 [PMID: 19336803 DOI: 10.1302/0301-620X.91B4.21363]
29 **Lucht U**. The Danish Hip Arthroplasty Register. *Acta Orthop Scand* 2000; **71**: 433-439 [PMID: 11186396 DOI: 10.1080/000164700317381081]
30 **Mäkelä KT**, Eskelinen A, Paavolainen P, Pulkkinen P, Remes V. Cementless total hip arthroplasty for primary osteoarthritis in patients aged 55 years and older. *Acta Orthop* 2010; **81**: 42-52 [PMID: 20180718 DOI: 10.3109/17453671003635900]
31 **Mäkelä KT**, Eskelinen A, Pulkkinen P, Virolainen P, Paavolainen P, Remes V. Cemented versus cementless total hip replacements in patients fifty-five years of age or older with rheumatoid arthritis. *J Bone Joint Surg Am* 2011; **93**: 178-186 [PMID: 21248215 DOI: 10.2106/JBJS.I.01283]
32 **Mäkelä KT**, Eskelinen A, Pulkkinen P, Paavolainen P, Remes V. Results of 3,668 primary total hip replacements for primary osteoarthritis in patients under the age of 55 years. *Acta Orthop* 2011; **82**: 521-529 [PMID: 21992084 DOI: 10.3109/17453674.2011.618908]
33 **Malchau H**, Herberts P, Eisler T, Garellick G, Söderman P. The Swedish Total Hip Replacement Register. *J Bone Joint Surg Am* 2002; **84-A** Suppl 2: 2-20 [PMID: 12479335]
34 **Pedersen AB**, Svendsson JE, Johnsen SP, Riis A, Overgaard S. Risk factors for revision due to infection after primary total hip arthroplasty. A population-based study of 80,756 primary procedures in the Danish Hip Arthroplasty Registry. *Acta Orthop* 2010; **81**: 542-547 [PMID: 20860453 DOI: 10.3109/17453674.2010.519908]
35 **Roberts DJS**, Garlick NI. Increased rate of dislocation of total hip arthroplasty with cementless implants: accuracy of acetabular inclination. *Internet J Orthop Surg* 2010; **17**: 1 [DOI: 10.5580/68e]
36 **Skyttä ET**, Jarkko L, Antti E, Huhtala H, Ville R. Increasing incidence of hip arthroplasty for primary osteoarthritis in 30- to 59-year-old patients. *Acta Orthop* 2011; **82**: 1-5 [PMID: 21189098 DOI: 10.3109/17453674.2010.548029]
37 **Abdulkarim A**, Ellanti P, Motterlini N, Fahey T, O'Byrne JM. Cemented versus uncemented fixation in total hip replacement: a systematic review and meta-analysis of randomized controlled trials. *Orthop Rev* (Pavia) 2013; **5**: e8 [PMID: 23705066 DOI: 10.4081/or.2013.e8]
38 **Girard J**, Kern G, Migaud H, Delaunay C, Ramdane N, Hamadouche M. Primary total hip arthroplasty revision due to dislocation: prospective French multicenter study. *Orthop Traumatol Surg Res* 2013; **99**: 549-553 [PMID: 23890966 DOI: 10.1016/j.otsr.2013.03.026]
39 **Parratte S**, Argenson JN. Validation and usefulness of a computer-assisted cup-positioning system in total hip arthroplasty. A prospective, randomized, controlled study. *J Bone Joint Surg Am* 2007; **89**: 494-499 [PMID: 17332097 DOI: 10.2106/JBJS.F.00529]
40 **Pennington M**, Grieve R, Sekhon JS, Gregg P, Black N, van der Meulen JH. Cemented, cementless, and hybrid prostheses for total hip replacement: cost effectiveness analysis. *BMJ* 2013; **346**: f1026 [PMID: 23447338 DOI: 10.1136/bmj.f1026]
41 **Guyatt GH**, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008; **336**: 995-998 [PMID: 18456631 DOI: 10.1136/bmj.39490.551019.BE]
42 **Thompson SG**, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002; **21**: 1559-1573 [PMID: 12111920 DOI: 10.1002/sim.1187]

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CASE REPORT

Novel technique for a symptomatic subscapularis herniation through a scapular defect

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Abstract

Fractures of the scapula are rare and have been reported to account for only 1% of all fractures and 3%-5% of upper extremity fractures. Several studies have reported successful outcomes with non-operative treatment of scapula fractures. Although non-operative treatments are successful in a very high percentage of patients, very few cases of non-union of scapular body fractures have been reported. In our review of the literature, we found two case reports of scapular body fractures developed into non-unions. In both of these cases, open reduction and internal fixation with reconstruction plates and bone graft was successful at eliminating pain and restoring function. This is a case report of a patient with a symptomatic, extra-articular scapular body defect from a non-union that was treated successfully with an acellular dermal extracellular matrix and bone graft using a novel technique

Key words: Scapular fractures; Mesh repair; Non-union; Bone graft; Acellular dermal extracellular matrix

Core tip: Scapular fracture complicated by non-union requiring surgical intervention is extremely rare and seldom reported in the literature. This study demonstrates successful surgical treatement of a symptomatic scapular body defect using a novel technique that has never been described for this condition.

Grau L, Chen K, Alhandi AA, Goldberg B. Novel technique for a symptomatic subscapularis herniation through a scapular defect. *World J Orthop* 2017; 8(2): 208-211 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i2/208.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i2.208

INTRODUCTION

Several studies have reported successful outcomes with non-operative treatment of scapula fractures[1-3]. In reviewing the literature, we found only two case reports of scapular body fractures that developed into non-unions[4,5]. In both of these cases, open reduction and internal fixation with reconstruction plates and bone graft was successful at eliminating pain and restoring function. This is a case report of a patient with symptomatic, extra-articular scapular body defect from a non-union, which was treated successfully with acellular dermal extracellular matrix and bone graft using a novel technique.

CASE REPORT

Presentation

A 52-year-old female sustained a right scapular body and right clavicle fracture in a motorcycle accident 14 mo prior to presenting to our clinic. She was treated non-operatively for the scapular body fracture and with open reduction and internal fixation of the clavicle fracture at an outside hospital. The patient complained that she continued to have constant, posterior shoulder pain along her right scapula after the accident. She came to our clinic because her pain was preventing her from sleeping at night and affecting her activities of daily living. A computed tomography (CT) scan showed a 4 cm × 2 cm elliptical defect of the inferior scapular body with herniation of the subscapularis muscle through the defect (Figures 1 and 2).

Physical exam

On physical exam the patient had tenderness to palpation over the inferior aspect of the scapular body on her right side. Her range of motion was intact with forward flexion of 180 degrees, abduction of 180 degrees, internal rotation of 90 degrees and external rotation of 55 degrees. She was neurologically intact in the axillary, median and ulnar nerve distributions. Her strength was 5/5 in all planes of motion in her upper extremity.

Surgery

After the nonunion site was marked (Figure 3), an oblique 10 cm incision was made just inferior to the scapular spine running from medial to lateral (Figure 4). A portion of the deltoid was incised in a longitudinal manner to help expose the scapular spine. The infraspinatus muscle was peeled off to expose the nonunion site that was approximately 4 cm in length and 2 cm in width (Figure 5). A herniation of the subscapularis muscle through the defect was noted.

Several drill holes around the edge of the defect were made circumferentially with K-wires and two #2 FiberWires were passed through each of these holes. An Arthroflex jacket (Arthrex, Naples, Florida), which is an acellular dermal extracellular matrix, was sewn into the undersurface of the scapula using #2 FiberWires. Approximately 7 cc of Graft-on bone product was placed on top of the jacket into the defect. The jacket was then folded onto the Grafton and sewn onto the posterior aspect of the scapular creating a pouch and barrier between the anterior and posterior aspects of the scapula (Figure 6). The infraspinatus was then attached back to its origin using O Vicryl and repair the deltoid muscle was performed with O Vicryl sutures in a figure of eight fashion. The dermis and epidermis was closed in standard fashion and dressings were applied. There were no complications postoperatively.

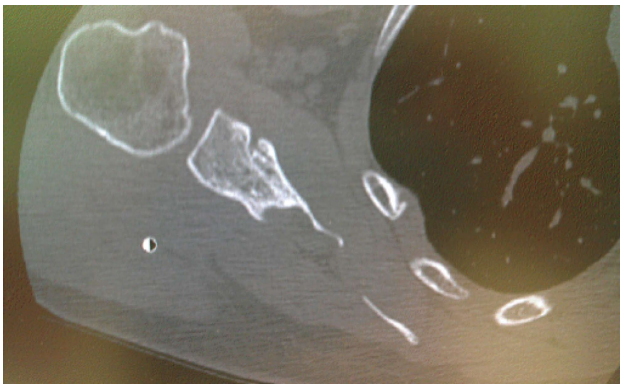

Figure 1 Axial computed tomography showing defect of scapular body.

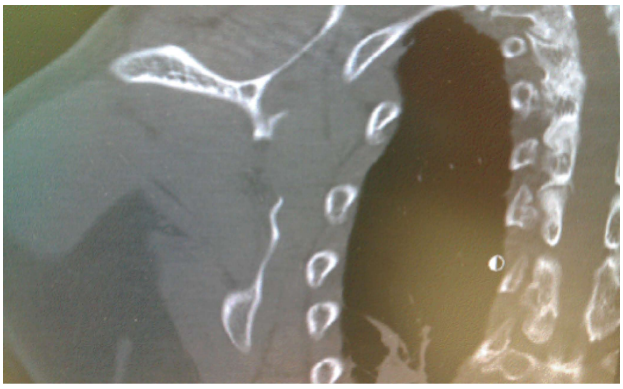

Figure 2 Coronal computed tomography showing defect of scapular body.

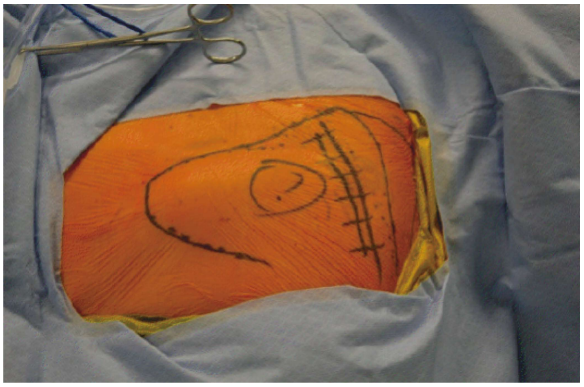

Figure 3 Borders of scapula, scapular spine, incision site (dashed line) and area over defect were marked.

Outcome

At 2 wk follow up, the patient could sleep through the

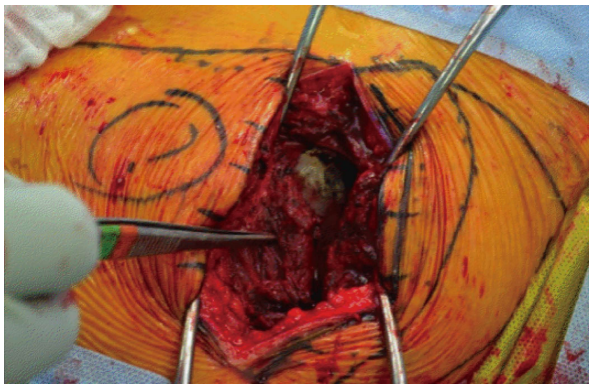

Figure 4 The 10 cm incision made just inferior to scapula spine, running from medial to lateral.

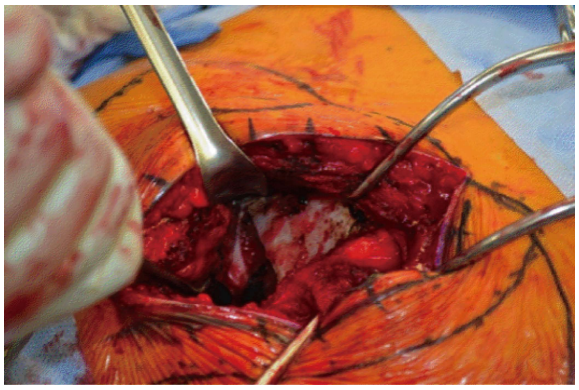

Figure 5 The 4 cm × 2 cm scapular defect exposed.

night, which she could not do prior to the operation. At her two month follow up visit the patient no longer complained of any right shoulder pain. She was also able to get back to doing activities such working out and riding her motorcycle. Her range of motion, strength, and sensation of the right shoulder were fully intact.

DISCUSSION

In our review of the literature, we found two case reports on scapular nonunion, Gupta *et al*[5] and Ferraz *et al*[4] both had excellent results with open reduction and internal fixation using reconstruction plates and bone graft. In both cases the patients had a fracture pattern that was unstable and causing functional limitations. Ferraz *et al*[4] reported that their patient had pain and decreased range of motion of the shoulder joint secondary to intra-articular involvement of the fracture and cartilage damage. In the case reported by Gupta *et al*[5] the patient had a transverse comminuted fracture with displacement and overlap of the fracture fragments that was causing winging with forward flexion and decreased range of motion.

Non-union is rare in patients treated conservatively for scapular body fractures and it is perhaps even rarer for these to be symptomatic. Persistent pain following injury requires further work up and possible surgical intervention.

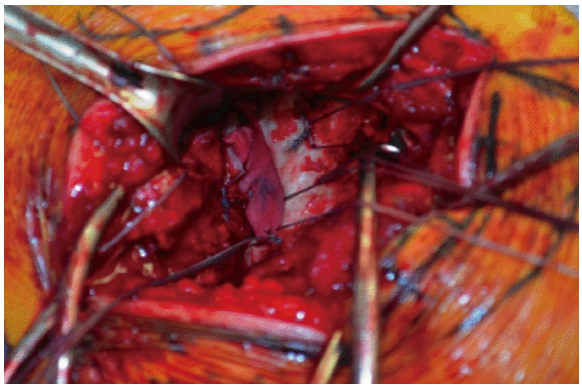

Figure 6 The dermal jacket is sewn into the defect.

Herniation of the subscapularis muscle through the scapular defect was likely the cause of our patient's pain. This could be seen on the pre-operative CT scan (Figures 1 and 2). The patient had excellent preoperative function because the defect was not unstable and the scapula remained functioning as a unit and there was no involvement of the joint. For these reasons the authors believed that mechanical stabilization with plates and screws was not necessary. Similar to mesh that is used for intestinal herniation in general surgery the use of the extracellular dermal matrix with bone graft was successful at preventing herniation of the subscapularis, which was likely the patient's source of pain. This was confirmed by the success of our surgery in providing relief for the patient as early as 2 wk after the procedure and at later follow-up. We believe this to be rare case of scapular nonunion with a unique etiology for pain that was treated with a novel technique.

COMMENTS

Case characteristics

A 52-year-old women, 14 mo status post non-operative treatment of scapular fracture, presented with constant pain that interrupted her sleep and daily activities.

Clinical diagnosis

Intact range of motion and neurovascular exam, with tenderness to palpation over the inferior aspect of the scapular body on her right side.

Differential diagnosis

Subscapularis herniation, painful scapula non-union, rotator cuff pathology, and scapula dyskinesia.

Laboratory diagnosis

Within normal limits.

Imaging diagnosis

Computed tomography scan showed a 4 cm × 2 cm elliptical defect of the inferior scapular body with herniation of the subscapularis muscle through the defect.

Pathological diagnosis

Pathological samples were not taken.

Treatment

Surgical intervention by acellular dermal extracellular matrix and bone graft.

Related reports
Other reports in the literature have mentioned decreased range of motion associated with the injury. The lack of decreased range of motion does not exclude the injury.

Term explanation
Scapular fracture healed in non-union are not a common result of non-operative treatment.

Experiences and lessons
The use of the extracellular dermal matrix with bone graft was successful at preventing herniation of the subscapularis and alleviating the patient's symptoms.

Peer-review
It is a well-written case.

REFERENCES

1 **Dimitroulias A**, Molinero KG, Krenk DE, Muffly MT, Altman DT, Altman GT. Outcomes of nonoperatively treated displaced scapular body fractures. *Clin Orthop Relat Res* 2011; **469**: 1459-1465 [PMID: 21161746 DOI: 10.1007/s11999-010-1670-4]

2 **Jones CB**, Sietsema DL. Analysis of operative versus nonoperative treatment of displaced scapular fractures. *Clin Orthop Relat Res* 2011; **469**: 3379-3389 [PMID: 21830167 DOI: 10.1007/s11999-011-2016-6]

3 **McGahan JP**, Rab GT, Dublin A. Fractures of the scapula. *J Trauma* 1980; **20**: 880-883 [PMID: 6252325 DOI: 10.1097/00005373-198010000-00011]

4 **Ferraz IC**, Papadimitriou NG, Sotereanos DG. Scapular body nonunion: a case report. *J Shoulder Elbow Surg* 2002; **11**: 98-100 [PMID: 11845159 DOI: 10.1067/mse.2002.118479]

5 **Gupta R**, Sher J, Williams GR, Iannotti JP. Non-union of the scapular body. A case report. *J Bone Joint Surg Am* 1998; **80**: 428-430 [PMID: 9531212]

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