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REVIEW

Return to sports after shoulder arthroplasty

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Abstract

Many patients prioritize the ability to return to sports following shoulder replacement surgeries, including total shoulder arthroplasty (TSA), reverse total shoulder arthroplasty (RTSA), and hemiarthroplasty (HA). While activity levels after hip and knee replacements have been well-established in the literature, studies on this topic in the field of shoulder arthroplasty are relatively limited. A review of the literature regarding athletic activity after shoulder arthroplasty was performed using the PubMed database. All studies relevant to shoulder arthroplasty and return to sport were included. The majority of patients returned to their prior level of activity within six months following TSA, RTSA, and shoulder HA. Noncontact, low demand activities are permitted by most surgeons postoperatively and generally have higher return rates than contact sports or high-demand activities. In some series, patients reported an improvement in their ability to participate in sports following the arthroplasty procedure. The rates of return to sports following TSA (75%-100%) are slightly higher than those reported for HA (67%-76%) and RTSA (75%-85%). Patients undergoing TSA, RTSA, and shoulder HA should be counseled that there is a high probability that they will be able to return to their preoperative activity level within six months postoperatively. TSA has been associated with higher rates of return to sports than RTSA and HA, although this may reflect differences in patient population or surgical indication.

Key words: Total shoulder arthroplasty; Reverse total shoulder arthroplasty; Shoulder replacement; Return to sport; Hemiarthroplasty

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Core tip: Many patients prioritize the ability to return to sports following shoulder replacement surgeries, including total shoulder arthroplasty, reverse total shoulder arthroplasty and hemiarthroplasty. While activity levels after hip and knee replacements have been well-established in the literature, studies on this topic in the field of shoulder arthroplasty are relatively limited. Information about activity levels and the rate of return

to sports following shoulder arthroplasty would help both patients and surgeons more accurately manage expectations. This clinical review examines how return to sport following shoulder arthroplasty has been studied and reported in the literature.

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INTRODUCTION

Over the past decade, shoulder replacement surgeries, including total shoulder arthroplasty (TSA), reverse total shoulder arthroplasty (RTSA), and hemiarthroplasty (HA), have become increasingly more common[1,2]. Technical innovations in shoulder arthroplasty have led to good implant survival and satisfactory long-term outcomes[3-6]. Although most commonly performed in elderly patients for degenerative shoulder conditions[3-5,7], shoulder replacement surgery is also routinely performed in young and active patients[8-11].

As the indications for these procedures expand and life expectancy increases, the goals of shoulder replacement are changing, and many patients are now prioritizing the ability to resume sports postoperatively[12-15]. Frequently during both preoperative and follow-up visits, patients inquire about sports after shoulder arthroplasty[12]. While activity levels after hip and knee replacements have been extensively reported in the literature[16-23], the number of studies on this topic in the field of shoulder arthroplasty are relatively limited[13,14].

Information about activity levels and the rate of return to sports following shoulder arthroplasty would help both patients and surgeons more accurately manage expectations[24]. This clinical review examines how return to sport following shoulder arthroplasty has been studied and reported in the literature[12].

RETURN TO SPORT AFTER TSA

TSA has been shown to be a highly effective treatment for degenerative shoulder disease, and has been shown to have good medium- and long-term outcomes[7,25,26]. The number of total shoulder arthroplasties performed in the Unites States has risen exponentially over the last decade: Since 2004, TSA has increased by approximately 3000 cases each year in the United States compared with an annual increase of fewer than 400 cases each year prior[2]. This trend is only expected to continue[27], and patients have come to have higher expectations of their functions postoperatively. While return to activity has been studied extensively in the lower extremity arthroplasty literature, it is only relatively recently that the same focus has been placed on TSA[12-14].

The largest study by Bülhoff *et al*[28] examined return to sports in 154 TSA patients at an average follow-up of 6.2 years. Their cohort included 105 TSA patients who had participated in sports preoperatively (group 1) and 49 TSA patients who had never participated in sports (group 2). At the time of final follow-up, 60 patients (39%) were participating in sports, and all 60 patients were from the first group (those that had participated in sports preoperatively). The authors concluded that patients who had not recently participated in sports are unlikely to do so after surgery. Among patients who had participated in sports preoperatively, however, the rate to return to sports was 57% in their cohort. Furthermore, of the 45 patients who participated in sports preoperatively and did not resume the activity postoperatively, only 18% cited shoulder problems as the reason[28].

McCarty *et al*[13] reported on 75 patients (86 shoulders) with a minimum follow-up of two years. In their series, 54 patients (61 shoulders) underwent TSA and the other 21 patients (25 shoulders) received a HA. Sixty-four percent of the patients stated that one of the reasons that they were having the surgery was to participate in sports. Overall, 81% of patients resumed at least one sport following the arthroplasty procedure, and 71% of these patients demonstrated an improvement in their ability to play the sport. In their study, fishing (92%), swimming (86%), and golf (77%) were associated with the highest rates of return postoperatively; bowling (40%) and softball (20%) showed the least favorable rates of return. Patients participated in their sport more frequently after surgery (1.7 d/wk compared to 0.7 d/wk previously), and most made a full return to sports by 5.8 mo postoperatively.

Zarkadas *et al*[1] used a mailed questionnaire to assess patient-reported activity after either TSA or HA. With respect to the TSA group, 27 of the 52 respondents (60%) reported having high demand use of their shoulder. The most commonly reported sports that patients were unable to perform due to the arthroplasty procedure were canoeing, biking, and golf[1].

Schmidt-Wiethoff *et al*[29] reported that 62 of 74 patients (84%) were able to return to sport after TSA, but 30% (19 patients) played with limitations. The remaining 12 patients (16%) did not return to sports, but it is not known whether this was due to shoulder problems or comorbid medical conditions[12,29,30].

Schumann *et al*[15] reported on 100 patients who underwent TSA and were followed for a minimum of one year. Eighty-nine percent of patients who participated in sports preoperatively (49 of 55) were able to resume participating in that sport at an average follow-up of 2.8 years; over a third of these patients (36.7%), however, reported persistent restrictions on sports activities due to shoulder issues. Regarding time to return to sports, 67% of the patients that resumed sports were able to do so within 6 mo. Golf was one of the most commonly reported sporting activity in their series (16.3%), and many of the golfers reported an improvement in performance

postoperatively: The golfers in their series increased their maximum drive distance from an average of 110 ± 91.5 m preoperatively to an average of 173.1 ± 51.2 m following the arthroplasty procedure.

Jensen *et al*[14] studied 24 patients (26 shoulders) who played golf prior to TSA (20 shoulders) or HA (6 shoulders). They found that all but 1 patient (96%) had returned to golf by a mean of 4.5 mo postoperatively. Performance improved in most patients, and 18 patients were able to decrease their handicap by an average of five strokes postoperatively. When compared to 76 non-golf playing controls, golfers did not have an increased risk of implant loosening at an average follow-up of 52.4 mo[14].

In summary, these studies demonstrate that patients who participate in sports preoperatively have a high likelihood of returning to sports after TSA. Most are able to return to full activity within six months, and some patients will experience an improvement in their performance. Patients should be cautioned that a small proportion of patients report persistent restrictions on sports activities following TSA.

RETURN TO SPORT AFTER REVERSE TSA

In 2003, the reverse prosthesis, or RTSA, was approved by the Food and Drug Administration for patients with cuff tear arthropathy[31]. Despite the technical challenges it initially presented to surgeons[32], the results of RTSA have been encouraging[31,33], and the indications for RTSA have expanded to include proximal humerus fractures and TSA revisions[24]. The success of the reverse total shoulder prosthesis has been shown to contribute to the large increase in the number of shoulder replacement procedures performed in the United States over the past decade[2,34,35]. Reverse prostheses accounted for nearly half of all total shoulder arthroplasties performed in 2011[36]. Patient satisfaction has been shown to correlate with the resumption of recreational activities[37,38], but only a handful of studies have assessed return to sport and activity following RTSA.

Edwards *et al*[39] reported on postoperative activity levels in a small number (n = 4) of RTSA patients. The authors found that 75% of the patients in this series returned to preoperative sports.

Lawrence *et al*[40] surveyed 78 RTSA patients (81 shoulders) at an average follow-up of 3.6 years, and found that they maintained a high level of activity following RTSA. The most commonly reported low-demand sporting activities were stationary biking (31%) and treadmill (23%), and the most popular medium-demand sports were fishing (23%), dancing (16%), and swimming (16%). The authors concluded that the activities patients participate in after RTSA are similar to those reported after other types of shoulder arthroplasty, including TSA and HA.

In an evaluation of RTSA in a senior athletic population, Simovitch *et al*[41] reported that 60% (40 of 67) patients who participated in a sport preoperatively returned to sports after surgery. Of the patients that resumed sports postoperatively, 12 patients (30%) indicated that they were able to perform their activities at a higher level, and 26 patients (65%) reported no change in performance. The three most popular sports in their series were golf, swimming, and water aerobics. The authors also examined radiographic outcomes in the patients who returned to sports for a minimum of 35 mo (mean 43 mo). At final follow-up, a single zone of lucency was present in 17% of humeral stems and there was one case of early subsidence, but no cases with loosening. The glenoid notching rate was 7% in their cohort, but there were no cases of glenoid subsidence, lucency, or loosening.

Garcia *et al*[24] reported on 76 RTSA patients at an average follow-up of 31.6 mo. All of the patients included in their series participated in sports preoperatively, and the authors found that 85.5% of patients returned to at least one sport following RTSA. The average time to return to full sport was 5.3 mo. The sports with the highest rates of return included fitness sports (81.5%), swimming (66.7%), running (57.1%), cycling (50%), and golf (50%). Nearly half (47.6%) of the patients reported that the duration and intensity of their sporting activities had increased. The most common reasons for not returning to sports in their series were pain (13.1%), shoulder issues related to surgery (11.8%), and loss of interest (9.2%).

Despite no clear consensus in the literature regarding the acceptable activity level after RTSA, the available data demonstrates that most patients are able to return to low-impact sports, such as swimming, biking, jogging, and golf. Further studies are required to determine the mid- and long-term impact of increased activity and load-bearing following RTSA.

RETURN TO SPORT AFTER HA

Despite exponential rises in TSA and RTSA, the rate of HA procedures continues to grow[2]. Glenohumeral HA is well established as a method to treat glenohumeral arthritis and complex three- and four-part proximal humerus fractures[42]. With its low failure rate, HA has traditionally been considered a safer option than total or reverse total shoulder replacements for patients who wish to remain active[41]. Other advantages of HA over these other prostheses include a less technically demanding procedure and shorter operative time[43]. However, others caution against its use in young, active patients, as long-term data shows deteriorating outcomes and worsening glenoid erosion for shoulders that undergo HA for osteoarthritis[44]. Despite a relative indication for HA in patients who wish to resume sporting activities[45], there is limited data on rates of return to sports after HA.

Skutek *et al*[46] evaluated a small series (n = 13) of HA patients and reported a 76% rate of return to

preoperative sport. Swimming (n = 6) and cycling (n = 3) were the most common sports resumed postoperatively, and the average time to return to sport was 33 wk in their series.

Garcia *et al*[45] reported on activity levels following HA in 79 patients at a mean follow-up of 63.1 mo. Of the 58 patients who played a sport preoperatively, the authors found that 67.2% resumed at least one of their previous sports following HA. The average time to return to full sports was 6.5 mo. Among the patients with preoperative sports participation, the sports with the highest rates of return were fitness sports (69%), swimming (65%), running (64%), cycling (63%), and doubles tennis (57%). Of the patients who returned to sports postoperatively, 87% felt that their sports outcome was good or excellent.

Return to sports after HA is considered "safer" than total or reverse shoulder arthroplasty due to its a low risk of component failure or loosening[47]. However, the rates of return to sports following HA (67% to 76%)[45,46] reported in the literature appears slightly lower than those reported for TSA (75%-100%)[13-15] and RTSA (75%-85%)[24,39]. In addition, many studies have shown poor results in long-term follow-up of HA, with one finding that only 25% of HA patients were satisfied with their outcome seventeen years after the operation[44]. Despite these results, HA continues to be a common procedure performed by recent orthopaedic residency graduates, where it is commonly performed on younger, active patients[48].

COMPARISON BETWEEN RETURN TO SPORT IN HA AND TSA

Patients with primary glenohumeral osteoarthritis may be treated with either TSA or HA. The choice is guided primarily by the presence or absence of glenoid arthrosis, but also in part by the patient's age and intended level of activity. TSA has been shown to provide superior pain relief, function, range of motion, and patient satisfaction as compared to HA[49-51]. However, proponents of shoulder HA argue that it provides reliable pain relief in a shorter, less technically demanding, and less costly procedure. Furthermore, many shoulder surgeons permit patients to return to sports with less restrictions following HA as compared to TSA[52,53]. Opposition to TSA in young active patients stems from concerns regarding implant longevity and glenoid loosening[49]. To date, only three studies have compared return to activity following the two procedures[1,13,49].

McCarty *et al*[13] reported on 75 patients who underwent either TSA (n = 54) or HA (n = 21). The authors found an 81% rate of return to sports in both the TSA group (44 of 54 patients) and the HA group (17 of 12 patients) at a minimum follow-up of two years. The authors concluded that there was no difference between TSA and HA in patients' ability to return to sports.

Zarkadas *et al*[1] used a mailed questionnaire to assess patient-reported activity after either TSA or HA. Activities were classified as low-demand (*e.g.,* stationary biking and treadmill use); medium-demand (*e.g.,* fishing, dancing, and swimming); or high-demand (*e.g.,* free weights and hunting). Responses were received from 52 TSA patients and 47 HA patients. The TSA group reported better range of motion and strength than the HA group (P < 0.05). Sixty percent of TSA patients (27 of 52) reported having high demand use of their shoulder as compared to 46% of HA patients (11 of 47); however, this difference was not statistically significant.

Garcia *et al*[49] compared rates of return to sports in a matched cohort of HA and TSA patients. All arthroplasty procedures were performed for glenohumeral arthritis, and patients were followed for a minimum of two years (average 62.0 and 61.1 mo for the HA and TSA groups, respectively). The investigators found significantly higher rates of return to sport in the TSA group as compared to the HA group: Ninety-seven percent of TSA patients (36 of 37) resumed at least one sport postoperatively as compared to 65% of HA patients (19 of 29). The average time to return to full sports was similar in both groups (5.5 mo and 5.4 mo for HA and TSA patients, respectively).

To date, three studies have compared rates of return to athletic activities following HA or TSA[1,13,49].

Only one demonstrated a difference in return to sports between the procedures, concluding that TSA was associated with more favorable rates of return to any sport as compared to HA[49]. All of the studies are limited by their sample sizes, retrospective nature, and follow-up. The mixed results may also reflect differences in patient populations, indication for surgery, and surgeons' postoperative restrictions.

COMPARISON BETWEEN RETURN TO SPORT IN HA AND RTSA

In patients who are not candidates for anatomic TSA due to rotator cuff dysfunction, rheumatoid arthritis, or proximal humerus fracture, the choice between RTSA and HA remains controversial. As compared to HA, RTSA has been associated with improved functional and range of motion outcomes[54-58]. However, HA is generally perceived as the "safer" option in patients who wish to remain active because there is less risk of failure[47]. Consistent with this notion, surveys of surgeons demonstrate that they place fewer postoperative sports restrictions on HA patients than on those undergoing RTSA[52,53]. However, limited literature exists on return to sports following RTSA and HA, and only one study to date has compared rates of return to sport following the two procedures[47].

Liu *et al*[47] reported on 102 RTSA and 71 HA patients with a minimum follow-up of 1 year. All patients participated in sports preoperatively, and had a contraindication for an anatomic TSA, including rotator cuff dysfunction, inflammatory arthritis, or proximal humerus fracture. The authors found significantly higher rates of return

to sport in the RTSA group (85.9%) as compared to the HA (66.7%) group. The RTSA patients also had subjectively higher satisfaction scores regarding their surgery and their ability to return to sports. Female sex, age under 70 years, surgery on the dominant extremity, and a preoperative diagnosis of arthritis with rotator cuff dysfunction predicted a higher likelihood of return to sports for patients undergoing RTSA compared with HA. There were no significant differences in the time to return to full sports between HA (6.2 mo) and RTSA (5.3 mo). No sports-related complications occurred.

Surgeons have been shown to impose much more stringent restrictions on activities following RTSA as compared to HA[52,53], but recent data demonstrates higher rates of return to sports following RTSA than HA[47]. RTSA may be particularly beneficial in certain patient populations, including females, patients under 70 years old, patients with dominant shoulder pathology, and patients with a preoperative diagnosis of arthritis and rotator cuff dysfunction. The conclusions of this study should be interpreted in light of its length of follow-up (31 mo for the RTSA group and 62 mo for the HA group), lack of radiographic outcomes, and differences in the two patient populations.

SURGEONS' PREFERENCES REGARDING RETURN TO SPORTS FOLLOWING SHOULDER ARTHROPLASTY

Several studies have reported on the recommendations of experienced shoulder surgeons regarding return to sport following shoulder arthroplasty[14,52,53,59]. Long-term outcome studies are needed to assess whether these surgeon preferences are clinically supported by patient outcomes or implant survival in patients who participate in sports after shoulder arthroplasty.

Jensen *et al*[14] surveyed 50 surgeons from the American Shoulder and Elbow Society (ASES) on return to golf following TSA; responses were received from 44 (88%) of the surgeons queried. Ninety-one percent of the responding surgeons allowed their patients to resume playing golf at an average of 4.3 mo. However, 29.5% of surgeons surveyed believed that participation in sports following TSA may accelerate component wear[59].

Healy *et al*[60] surveyed 35 surgeons in the ASES regarding participation in 42 different athletic activities following TSA. Surgeons were instructed to rate each activity as one of the following: Recommended/allowed, allowed with experience, not recommended, and no opinion. Not surprisingly, low impact sports such as swimming, dancing, bowling, doubles tennis, and bicycling were recommended and allowed. Activities that were allowed with experience included golf, ice skating, and downhill skiing. The authors determined that only four activities of the list of forty-two were not recommended, including hockey, rock climbing, gymnastics, and football. Activities for which a consensus could not be reached included: Baseball/softball, lacrosse, rowing, soccer, weight lifting, and singles tennis.

Magnussen *et al*[53] queried the members of ASES as well as the European Society for Surgery of the Shoulder and Elbow about return to sports after TSA, RTSA, or HA. The survey contained 37 activities and participants were instructed to classify their postoperative recommendations for each activity as one of the following: Allowed, allowed with experience, not allowed, or undecided. Looking specifically at TSA, almost all of the 94 responding surgeons indicated that they would allow their patients to participate in noncontact activities, such as jogging/running (86%), stationary cycling (91%), and dancing (87%). Although the majority of surgeons would also permit low impact activities following RTSA, other activity restrictions were more conservative than those following TSA or HA. For example, swimming was permitted by the majority surgeons following TSA (82%) and HA (87%), but less than half (45%) would permit participation following RTSA. Similarly, golf was allowed by most surgeons after TSA (75%) or HA (77%), but only 45% of surgeons would permit golf following RTSA; doubles tennis was allowed by about half of surgeons following TSA (48%) or HA (55%), but only permitted by 15% after RTSA. Time to return to sport following RTSA was comparable to that of TSA, with most (56%) of the responding surgeons allowing patients to resume their maximum level of activity 5-7 mo after RTSA. Twenty percent of surgeons, however, required patients to wait at least 8 mo after RTSA to return to this level of activity.

Magnussen *et al*[53] found that recommendations on return to sport following HA were the most lenient. For example, weight-lifting was not recommended following RTSA (82%) or TSA (57%), but permitted or allowed with experience following HA according to 52% of the surgeons surveyed.

Nearly half of surgeons (47%) would allow patients to resume their maximum level of activity earlier following HA, at 2-4 mo postoperatively. Patients were also allowed to return to sports faster following HA, with 48% of surgeons allowing return to maximum level of activity 5-7 mo postoperatively and 47% allowing return to this level earlier, at 2-4 mo postoperatively.

More recently, Golant *et al*[52] surveyed 310 members of the ASES regarding what types of activities they allow their patients to participate in after five different types of shoulder arthroplasty. Responses were received from 94 surgeons (30.3%). Regarding activities after TSA, 59.1% of the surgeons surveyed indicated that they allow their patients to participate in low-impact sports (including golf, bowling, rowing, and swimming) without limitations. About 20% of the surgeons surveyed would permit participation in high-impact sports (including tennis, squash, volleyball, and baseball) without limitations, and 8.2% of the surgeons reported that they would allow participation in contact sports (including football, lacrosse, hockey, and basketball) without limitations.

Consistent with the findings of Magnussen *et al*[53]

restrictions following RTSA were found to be the most stringent of the arthroplasty procedures evaluated. For example, 25.7% of surgeons polled by Golant *et al*[52] would allow their patients to participate in low-impact sports, such as golf and swimming, without restrictions, as compared to 59.1% and 80% of surgeons allowing participation following TSA and HA, respectively. Similar trends were observed with high-impact and contact sports: High-impact sports were allowed with limitations by a greater proportion of surgeons following HA (31.9%) or TSA (39.7%) than RTSA (19.4%); contact sports were allowed with limitations by about one in five surgeons following HA (21.6%) or TSA (18.5%), but only 5.2% of surgeons following RTSA.

In the available literature, there is extensive variation in surgeon recommendations on activity restrictions after joint arthroplasty. The majority of surgeons allow return to noncontact, low-load activities after all types of shoulder arthroplasty. Restrictions on high-impact sports, sports with fall risk, and contact sports were more liberal following HA or TSA as compared to RTSA.

CONCLUSION

The majority of patients are able to return to their preoperative level of activity following TSA, RTSA, and shoulder HA. The rates of return to sports following TSA (75%-100%)[45-46] are slightly higher than those reported for HA (67% to 76%)[45-46] and RTSA (75%-85%)[24,39], although this may reflect differences in patient population or surgical indication. Noncontact, low demand activities are permitted by most surgeons postoperatively and generally have higher return rates than contact sports or high-demand activities. Most patients can expect to return to sports within six months postoperatively, and many will experience an improvement in their ability to participate in sports following the arthroplasty procedure.

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REVIEW

Management of Ewing sarcoma family of tumors: Current scenario and unmet need

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Abstract

Ewing sarcoma family tumors (ESFT) are heterogeneous, aggressive group of disease with peak incidence in adolescent and young adults. The outcome has been improved dramatically from 10% with surgery and radiotherapy alone to 65%-70% now, in localized disease, with the introduction of chemotherapy. Chemotherapy regimen evolved from single agent to multiagent with effort of many cooperative clinical trials over decades. The usual treatment protocol include introduction of multi-agent chemotherapy in neoadjuvant setting to eradicate systemic disease with timely incorporation of surgery and/or radiotherapy as local treatment modality and further adjuvant chemotherapy to prevent recurrence. Risk adapted chemotherapy in neoadjuvant and adjuvant setting along with radiotherapy has been used in many international collaborative trials and has resulted in improved outcome, more so in patients with localized disease. The role of high dose chemotherapy with stem cell rescue is still debatable. The outcome of patients with metastatic disease is dismal with long term outcome ranges from 20%-40% depending on the sites of metastasis and intensity of treatment. There is a huge unmet need to improve outcome further, more so in metastatic setting. Novel therapy targeting the molecular pathways and pathogenesis of ESFT is very much required. Here we have discussed the current standard of management in patients with ESFT, investigational targeted or novel therapies along with future promises.

Key words: Outcome; Review; Chemotherapy; Ewing sarcoma; Targeted therapy; Radiotherapy; Prognostic factors

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Core tip: Ewing sarcoma family tumors are a heterogeneous and aggressive group of disease of bone and soft tissue in childhood. The outcome has improved with introduction of chemotherapy and multimodality management. But, the prognosis of patients with metastatic disease is dismal. Novel targeted therapies

are investigational and may offer some hope in future, especially in metastatic setting. In this review we have discussed current treatment modality, prognostic factors, ongoing trials and novel investigational therapies.

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INTRODUCTION

Ewing sarcoma families of tumors (ESFT) are a heterogeneous and aggressive group of disease of bone and soft tissue that includes classical Ewing sarcoma, peripheral primitive neuroectodermal tumor and Askin tumor. It is the 2nd most common primary malignant bone tumor (34%) after osteosarcoma[1] with peak in 2nd decade of life, though approximately 20% to 30% of all cases occur in 1st decade. Over the last four decades, the survival has been improved from 10% with radiotherapy alone to near 70%, in localized disease, with the introduction of chemotherapy and multimodality approach. This improvement in outcome has been achieved after many international collaborative clinical trials and close liaison between orthopedic surgeons, adult and pediatric oncologists, radiation oncologist, pediatric surgeons, biomedical engineers, pathologists and radiologists as well as invention of better diagnostic imaging, radiotherapy techniques and prosthesis.

With the improvement in outcome and more number of long-term survivors, the focus is now on to minimize toxicities, such as chemotherapy related, radiotherapy related and surgery related long-term complication without compromising the oncological outcomes. The multidisciplinary approach with risk adapted chemotherapy and local treatment (surgery and/or radiotherapy) has been used in recent times in many collaborative trials to minimize the overtreatment and thus treatment related side effects with maintaining high cure rates. This approach is the current standard of care in maximum institutions all over the globe.

Even with current armamentarium the outcome of ESFT patients with metastatic disease is dismal with cure rate varying between 20%-40%[2,3] and even less in those with recurrent/refractory diseases. The current emphasis is to improve the survival outcome in ESFT patients with metastatic disease and also in the recurrent setting. There is a vacuum in novel and targeted therapies as compared to adult solid tumors, and there lies a huge unmet need to improve the outcome of poor risk ESFTs.

Researchers across the world have tried to understand the pathogenesis of ESFT along with the molecular downstream pathways enhancing the survival of ESFT tumor cells. The primary focus was on *EWS-FLI1* fusion oncogene, and other similar fusions that were thought to drive the oncogenic pathway in ESFT, but targeted therapy by blocking its product has not resulted into any meaningful clinical outcome[4,5]. In this review we have discussed the current standard of treatment-chemotherapy, local treatment modalities, role of high dose chemotherapy, and salvage treatment along with novel targeted therapies under investigation and potential future promises.

WHAT ARE THE CLINICALLY RELEVANT PROGNOSTIC FACTORS?

Many international cooperative trials has been performed over last four decades to improve the outcome of ESFTs and further analysis of those studies revealed many prognostic factors that predicted differential outcomes and successively helped in designing tailored clinical trials to optimize the treatment strategies depending on the risk group and to decrease over treatment and treatment related side effects. Further refinements and validation of those prognostic factors (clinic-pathological and treatment related factors) has been done in further studies and in routine clinical practices. Amongst all the clinic-pathological and treatment related factors, presence of metastasis at baseline is the strongest prognostic factor and has been proven in all clinical studies and routine clinical practices. The prognosis also depends on burden of metastasis and site of metastasis. Spectrum of outcome varies from worst with bone marrow metastasis (3-year EFS of < 10%) with non-pulmonary metastasis in the middle and single pulmonary metastasis having the best outcome (3-year EFS of 40%-50%)[6-10]. No research group or study had prospectively evaluated the prognostic significance of burden of metastasis until recently. Study from our center in ESFT patients with metastatic disease found hypoalbuminemia (< 3.5 g/dL) as a novel and independent poor prognostic factor to affect outcome[2]. The recent EuroEwing 99 (EE99) systematically risk stratified the metastatic group and the 3rd randomized arm (disseminated multifocal ESFT) identified novel prognostic factors, such as - age at diagnosis > 14 years, presence and number of bone metastasis, number of pulmonary metastasis and bone marrow involvement and also developed a prognostic score to predict differential outcome ranging from 8%-40%[10].

Systemic symptom (fever and weight loss) is a poor prognostic factor along with high lactate dehydrogenase level that denotes tumor burden. These two prognostic factors has been used to risk stratify ESFT patients to tailor therapy. Tumor size and tumor volume is well established prognostic across the clinical studies with tumor size > 8 cm[11] and tumor volume > 200 mL[12,13] is poor prognostic and has been used in all clinical trials for risk adapted therapies. Site of primary tumor is also of prognostic significance with axial primary especially pelvic location is poor prognostic. Both tumor size and pelvic primary has been proven as poor prognostic in

our institutional experience[2,14]. But recently histological response to neoadjuvant chemotherapy (poor response has been defined as > 10% viable tumor cells as per Salzer-Kuntschik grading system[13]) has been emerged as the strongest prognostic factor overriding tumor size, tumor volume or tumor location. The recent EE99 study risk stratified ESFT patients in respect to histological response to chemotherapy to tailor therapy[15]. WBC count has been emerged as independent prognostic factor in our experience of ESFT[14,16-18] treated with uniform chemotherapy protocol with high WBC (> 11000/μL) having poor outcome. It may signify micrometastatic disease and inflammatory nature of the disease and will require further validation in a prospective study.

Collaborative efforts have been made to identify potential biomarker in this rare aggressive tumor. Early retrospective studies[19,20] reported prognostic significance of different transcripts (*EWS-ETS* fusion types) but failed to do so in prospective studies[21]. High throughput methods has revealed gene copy number variations[22], such as - 1q-, 18q-, 20-, 16q+ along with mutation in *TP53, CDKN2A* and *STAT2* and concurrent presence of *STAT2* and *TP53* reported as poor prognostic[23]. Detection of disseminated tumor cells in blood and bone marrow[24] in localized patients (up to 20%) found to poor prognostic and its detection after completion of therapy (minimal residual disease) by flow cytometry or other sensitive method can tailor therapy, detect early recurrence and can be of future prognostic significance[20].

WHAT IS THE ROLE OF BIO-IMAGING?

Histological response to neoadjuvant chemotherapy is the strongest prognostic factor in localized ESFT and metastatic disease is the strongest one in whole cohort of ESFT. Efforts have been made to predict metastatic potential of ESFT in view of its aggressive nature and to escalate therapy in case of poor responder before initiation of local therapy. 18F-FDG PET is a relatively non-invasive test that can escape invasive diagnostic metastatic work-up like bone marrow aspiration/biopsy and tissue diagnosis in case of doubtful lung metastasis if it predicts site of metastases, and also post chemotherapy response assessment before the histological response is assessed. Retrospective studies have shown it can predict response to neoadjuvant chemotherapy and have a high concordance rate with the histological response by measuring reduction in standardized uptake value[25,26] and also reduction in metabolic tumor volume[27]. But no prospective study has been done in regards to its predicting power of detecting metastasis and to predict response to chemotherapy before its utilization in routine clinical practice.

LOCALIZED DISEASE

What chemotherapy, what intensity, and how long?

Historically, in early 1970s the outcome of ESFT with radiotherapy and surgery alone was dismal with only < 10% patients surviving and all invariably experienced relapse within 2 years. With the introduction of chemotherapy the outcome have improved drastically to 70% cure rate in localized disease. The evolution of chemotherapy started from single agent vincristine to multiagent chemotherapy (VAC - vincristine, actinomycin D and cyclophosphamide) and from adjuvant to neoadjuvant setting (Table 1). Then comes the role of anthracyclines and addition of doxorubicin resulted in improved survival in 342 localized ESFT along with additional benefit of whole lung irradiation (WLI) in metastasis prevention in Intergroup Ewing's Sarcoma Study 1 (IESS-1)[28]. The value of doxorubicin further potentiated in IESS-Ⅱ which showed that high dose intermittent doxorubicin is better than low dose continuous therapy in 214 non-pelvic localized ESFT[29]. The landmark United States intergroup study (INT0091) by Grier *et al*[6] showed additional benefit of ifosfamide and etoposide (IE) in addition to vincristine, doxorubicin, cyclophosphamide (VDC) in localized patients with ESFT after the beneficial effect of IE has been demonstrated in recurrent setting[30], but the trial failed to demonstrate any benefit of IE in a relatively smaller numbers of patients with metastatic disease. Replacement of ifosfamide with cyclophosphamide has showed conflicting results[31] and EICESS-92 trial showed similar result with four drug chemotherapy regimen in a relatively underpowered study of 155 localized ESFT along with non-significant advantage of addition of etoposide in metastatic disease[7]. In a different strategy to improve outcome by intensifying the alkylator dose and thus reducing the chemotherapy duration to 30 wk as compared to standard 48 wk with VDC-IE failed to improve outcomes in a United States intergroup trial (INT 154)[32]. But subsequent Children Oncology Group (COG) study used dose compressed study of 3-weekly *vs* 2-weekly VDC-IE with use of filgrastim, thus maintaining the dose intensity, and demonstrated superior outcome in 2-weekly arm (5-year EFS of 73% *vs* 65%, P = 0.048)[33] without any increasing toxicity in the experimental arm. The latest and largest trial in ESFT is the ongoing EE99 trial that compared cyclophosphamide with ifosfamide in standard risk ESFT and the early result showed equivalent outcome in both arm with pending long-term toxicity results[15] (Table 2). The role of high dose chemotherapy with autologus stem cell rescue not well studied in localized disease as consolidation in comparison to continuation or maintenance chemotherapy. Two cooperative trials[34,35] used BuMel conditioning regimen with stem cell rescue as consolidation therapy in a non-randomized manner in high risk localized disease (defined as poor histologic response to chemotherapy) and showed improved survival as compared to historical control and similar to that of standard risk patients. Following that result the recent ongoing EE99 trial randomized (arm 2) BuMel based high dose chemotherapy *vs* continuation of standard chemotherapy after VIDE induction chemotherapy in high risk localized patients and the result is still pending (Table 2).

Table 1 Randomized studies of chemotherapy in upfront treatment of Ewing sarcoma family tumors

Study	Patients (*n*)	Intervention[1]	Outcome	*P*	Comments
IESS Ⅰ[78]	Localized (342)		5-yr RFS		Beneficial of doxorubicin and benefit of lung RT
		(1) VAC	24%		
		(2) VACD	60%	--	
		(3) VAC + Lung RT	44%		
IESS Ⅱ[29]	Non-pelvic, localized (214)	VACD	5-yr RFS	0.04	Intermittent, high dose better
		(1) Intermittent, high dose (3 weekly)	73%		
		(2) Continuous, moderate dose (weekly)	56%		
POG-CCSG INT-0091[6]	Localized (398)		5-yr RFS	0.005	IE is beneficial in addition to VDC in localized but not in metastatic disease
		(1) VDC	54%		
		(2) VDC + IE	69%		
	Metastatic (120)	(1) VDC	22%	NS	
		(2) VDC + IE	22%		
POG-CCSG INT-154[32]	Localized (478)		5-yr EFS	NS	Dose intensification not effective
		(1) VDC + IE (standard)	70%		
		(2) VDC + IE (intensified)	72%		
COG AEWS0031[33]	Localized (568)		5-yr EFS	0.05	3-weekly better than 2-weekly with no increase in toxicity
		(1) VDC + IE (3 weekly)	65%		
		(2) VDC + IE (2 weekly)	73%		
EICESS92[7]	*n* = 155	SR (localized and < 100 mL)	3-yr EFS	NS	Cyclophosphamide and ifosfamide is similar in efficacy in SR patients
		4#VAIA → 8# VAIA *vs* 8#VACD	73% *vs* 74%		
	n = 492	HR (metastatic, > 100 mL)	47% *vs* 52%	0.12	No benefit of etoposide in HR patients
		14# VAIA *vs* 14#EVAIA			
Euro-Ewing 99[49]	Detailed in Table 2				

[1]All chemotherapy regimens mentioned in the table is used in neoadjuvant setting followed-by local therapy (in terms of surgery and/or radiotherapy) followed by further adjuvant chemotherapy. EFS: Event free survival; EVAIA: Etoposide, vincristine, dactinomycin, ifosfamide, doxorubicin; HR: High risk; IE: Ifosfamide, etoposide; NS: Not significant; RFS: Relapse free survival; RT: Radiotherapy; SR: Standard risk; VAC: Vincristine, dactinomycin, cyclophosphamide; VACD: Vincristine, dactinomycin, cyclophosphamide, doxorubicin; VAIA: Vincristine, dactinomycin, ifosfamide, doxorubicin; VDC: Vincristine, doxorubicin, cyclophosphamide.

Table 2 Euro-Ewing 99 trial design and details

Randomized arm	Patients	*n*	Randomization	3-yr EFS
Arm 1	SR, Localized (good histologic response, < 200 mL + RT)	856	6#VIDE + 1#VAI f/b 7#VAI *vs* 7#VAC	78% *vs* 75%
Arm 2	HR, Localized (poor histologic response, ⩾ 200 mL and RT alone)	---	6#VIDE + 1#VAI f/b 7# VAI *vs* BuMel (*n* = 281)	45% (BuMel)
	Lung metastasis only	---	6#VIDE + 1#VAI f/b 7# VAI + WLI *vs* BuMel	---
Arm 3	Extrapulmonary metastasis	---	6#VIDE + 1#VAI f/b BuMel/TreoMel *vs* clinical trial	---

BuMel: Busulphan and melphalan; EFS: Event free survival; f/b: Followed-by; HR: High risk; *n*: Number; RT: Radiotherapy; SR: Standard risk; TreoMel: Tresulphan and melphalan; VAC: Vincristine, dactinomycin, cyclophosphamide; VAI: Vincristine, dactinomycin, ifosfamide; VIDE: Vincristine, ifosfamide, doxorubicin, etoposide; WLI: Whole lung irradiation.

What local therapy and when?

The outcome of ESFT with surgery or radiotherapy alone was dismal and with introduction of polychemotherapy regimen improved the outcome dramatically by eradicating systemic micrometastsis in localized disease. But, chemotherapy alone can't eradicate ESF tumor cells and timely incorporation of local therapy either surgery and/or radiotherapy is crucial for optimum management and to produce high cure rate. The approach of local therapy evolved over time with better understanding of the disease biology, better radiation technique, invention of newer engineered prosthesis, better imaging modalities and more information of therapy related complications. The choice of local treatment influenced by multiple factors, such as age of the patients, site and size of the tumor, local extent of the tumor, clinic-radiological response to chemotherapy, expertise and experience of the treating institution and surgeon and patient's choice, *etc.* The different modalities of local treatment include - surgery (amputation, limb salvage or organ sparing surgery) with or without adjuvant radiotherapy, radical radiotherapy, pre-operative radiotherapy, extracorporeal radiotherapy. No prospective formal comparison done between surgery and radiotherapy as local treatment. Across the clinical trials and institutional experience, surgery done better in terms of long term outcome (both local and systemic control), and thus a formal comparison between this two seems not feasible in future.

ESFT is a radiosensitive tumor, but the long term outcome was < 10% with high incidence of local[36] and systemic recurrence. Surgery slowly replaced radiotherapy in view of better local control rate, lesser long-term complication compared to radiotherapy and with invention of better bone replacement materials (endoprosthesis, bone cement, allograft, vascularized autograft) the rate of limb sparing surgery has increased as a norm now-a-days[36,37]. But, the surgery is also associated with long-term complications, such as-post-op infection, limb-length discrepancy, fractures, *etc*. Maintaining limb length is difficult in growing children and expandable endoprosthesis comes handy in this scenario with its increasing uses.

The surgical resection principle depends on the respectability, size and sites the tumor and its operability after chemotherapy. A functional limb or organ is the norm after any local treatment modality. Amputation is rarely indicated and limb salvage or organ sparing surgery should be tried whenever feasible. Surgical resection should be tried whenever a marginal or wide resection is feasible as the outcome seems to be superior to radical radiotherapy as local control[11,32,36,38-42]. Intralesional or debulking surgery should be avoided as the outcome is not superior over radiotherapy alone[41].

Definitive or radical radiotherapy as local treatment modality used where non-mutilating, wide local excision is not feasible with a functional organ, more so in axial primary, such as - head and area, spine, pelvic primary and in very large lesion not amenable to curative surgery even after neoadjuvant chemotherapy, and in case of a metastatic disease, *etc*. The recommended dose varies from 55 to 60 Gy in standard fractionation with 2 cm margin that should include original biopsy scar[39]. Care should be taken to avoid toxicity to adjacent normal organ and newer techniques, such as - intensity modulated radiotherapy, image guided planning or proton therapy, *etc*. should be used in more cases[40]. Data on use of post-operative radiotherapy is mostly debated in view of conflicting results from observational studies[41-43]. The only clear cut indication is that of intralesional surgery[32] where further resection with remaining functional organ is not feasible. Many European institutions use adjuvant radiotherapy in patients with poor histologic response to chemotherapy (> 10% viable tumor cells) and in a soft tissue primary. Recent EE99 study also showed beneficial effect of adjuvant radiotherapy even in good responder and thus broadens its future use, though the risk-benefit ratio to be calculated stringently with long-term radiotherapy related complication. Pre-operative radiation therapy is a good viable future alternative where a complete resection looks not feasible after chemotherapy and thus can sterilize the compartment before reconsideration of surgery after radiotherapy, like in pelvic or spinal primary[40].

What are the current and future studies?

Many collaborative studies are ongoing in ESFT to find out the most appropriate risk-stratified approach for improving outcome with incorporation of high dose chemotherapy (Ewing 2008 and Italian ISG/AIEOP EW-1 study), introduction of metronomic chemotherapy as maintenance (COG AEWS1031 study), role of zoledronic acid (Ewing 2008 and Euro-Ewing 2012 study), optimum use of post-operative radiotherapy along with dose intensified approach (Euro-Ewing 2012 study), and comparison of vincristine, ifosfamide, doxorubicin and etoposide (VIDE) standard therapy in Europe *vs* VAC-IE (Euro-Ewing 2012 study).

METASTATIC DISEASE

Is site of metastasis prognostic?

ESFTs are an aggressive group of disease with high incidence of metastasis at presentation ranging from 20%-40% across different clinical trials and observation studies[2,3,44-47]. Outcome of patients with lung metastasis was better as compared to those with bone metastasis or combined or to those with bone marrow involvement and single metastasis done better as compared to multiple metastases[7]. The recent EE99 trial also revealed the presence and number of bone metastasis, presence and number of lung metastasis and bone marrow involvement as prognostic factors[10]. More prospective studies are needed to define the prognostic nature of site and number of metastasis in a more stringent manner to tailor and intensify therapies.

Is the treatment same as localized disease?

The treatment protocol is similar like in those with localized disease with curative intent - neoadjuvant chemotherapy followed by institution of local therapy (surgery and/or radiotherapy) and further maintenance therapy or consolidation with high dose chemotherapy or an investigation novel agents/targeted therapy. Many agents in combination or with total body irradiation have been used as consolidation in metastatic disease. Definitive radiotherapy used more as compared to surgery in view of high residual disease at metastatic disease after neoadjuvant chemotherapy and a more conservative approach especially in those with disseminated metastases or with bone marrow involvement.

LOCAL TREATMENT: WHAT AND WHEN?

Local treatment usually incorporated after initial 5-6 cycles of chemotherapy and if there is good response to chemotherapy in both local site and metastatic site(s). WLI has been tried in clinical studies in patients with lung only metastasis[48] with 5-year EFS up to 50% along with conventional chemotherapy compared to similar results with high dose chemotherapy without WLI[8]. The EE99 study randomized (arm 2) patients with lung only metastasis VIDE chemotherapy followed by VAI as maintenance plus WLI *vs* BuMel based high dose chemotherapy as consolidation and the result is

pending[49]. Local excision or radiation therapy has been tried in patients with bone metastases in retrospective studies with favorable outcome[50]. Resection of pulmonary metastasis failed to show efficacy in two retrospective studies[51,52] but require validation in a prospective manner especially in those with single lung metastasis.

WHAT IS THE ROLE OF HIGH DOSE CHEMOTHERAPY?

Dose intensity[33] and high dose chemotherapy[34,35] found to be effective and improved outcome in patients with localized disease especially in high risk disease. With the principle of dose intensity and dose density high dose chemotherapy with stem cell rescue has been tried in many randomized and non-randomized study to improve outcome in metastatic disease with mixed results. Single agent high dose melphalan failed to improve outcome[53]. In a single arm study, BuMel conditioning in metastatic patients showed 5-year EFS of 52% in patients with lung metastasis and 36% in those with bone metastases[8]. Subsequently many clinical trials have tried high dose chemotherapy in metastatic patients and showed mixed outcome as compared to conventional chemotherapy only (Table 3). Three large studies using high dose chemotherapy - the EE99 study randomized ling only metastatic group in to BuMel based high dose therapy *vs* WLI along with conventional chemotherapy after initial VIDE chemotherapy and the mature result is pending[49]. The third arm randomized patients with extrapulmonary metastasis in BuMel or TreoMel based high dose chemotherapy *vs* investigational agent after standard VIDE based induction chemotherapy regimen and the early results showed 3-year overall survival[10]. In study by Italian and Scandinavian sarcoma study group used BuMel conditioning with WLI in patients with lung only metastasis or single bone metastasis with 5-year EFS of 43%[9]. The Ewing 2008 trial randomized patients with extrapulmonary metastasis after VAC chemotherapy to TreoMel based high dose chemotherapy *vs* continuation of VAC and the result is pending. On the contrary a study by Children's Cancer Group failed to show any improvement in outcome of patients with extrapulmonary metastases after VAC-IE based chemotherapy followed by high dose chemotherapy with melphalan, etoposide and total body irradiation[54].

RELAPSED AND RECURRENT DISEASE

The progress of improved outcome in ESFT is attenuated by high incidence of recurrence (local and/or systemic) and remains the main challenge in multidisciplinary management of this aggressive malignancy, especially in those with metastatic disease. The incidence of local or distant relapse is approximately 20%-25% in the published literature[45,55] and can reach up to 40% in metastatic setting[2,47]. There is no standard established salvage therapy exist in recurrent disease with dismal outcome of 20% in case of localized relapse[56]. Few chemotherapy agents showed activity in recurrent disease with moderate but short lasting response rate - topotecan and cyclophosphamide[57], ifosfamide in combination with carboplatin and etoposide[58], irinotecan and temozolamide[59]. Gemcitabine and docetaxel[60] combination failed to show any clinically meaningful activity in recurrent ESFT. The mostly studied chemotherapeutic regimen in recurrent ESFT is of irinotecan and temozolamide from a phase 1 trial and from few institutional experiences[61-65], like in other pediatric solid tumors. This combination used protracted course of irinotecan with synergistic activity of temozolamide and produced overall response rate of 25%-60% (Table 4). No prospective study to evaluate role of high dose chemotherapy has been done so far in recurrent ESFT and retrospective institutional data[66,67] is available with modest activity. A well selected prospective trial in needed in this regards. The Euro-Ewing consortium started a randomized phase Ⅱ/Ⅲ four arm study (cyclophosphamide-topotecan *vs* gemcitabine-docetaxel *vs* high dose ifosfamide *vs* irinotecan-temozolamide) in recurrent ESFT and the trial will complete recruitment in 2019. A huge vacuum exist in effective salvage therapy of recurrent/refractory ESFT and novel targeted therapy is very much need to fill that unmet need. Future therapeutic trials will eye on combination of chemotherapy with targeted therapy in recurrent/refractory as well as metastatic disease.

NEW TARGETS AND TARGETED THERAPIES

With the plateau of survival with the current conventional chemotherapy and stem cell transplantation in metastatic and recurrent setting of ESFT the urgent need for novel targeted therapy should match the ongoing research in understanding the biology of ESFT with revelation of more and more oncologic pathways and targets. Various drugs has been discovered and tested in preclinical and clinical studies in ESFT by targeting EWS-FLI 1 fusion protein, the hall mark of ESFT-CD99, angiogenic pathways (VEGF and its receptor), mammalian target of rapamycin (mTOR) and insulin-like growth factor-1 (IGF1) pathways, the osteoclastic-osteoblastic homeostasis and bone microenvironment, enzymatic pathways (poly ADP-ribose polymerase 1 - PARP1), and GD2 ganglioside pathways.

The mostly studied targeted therapy used in ESFT is by inhibiting EWS-FLI1 transcriptional complex. Many agents have been discovered that directly or indirectly inhibit EWS-FLI1 pathways - small-molecule YK-4-279 is in pre-clinical phase that directly inhibit interaction of EWS-FLI1 and RNA helicase A[68], certain chemotherapy agents (doxorubicin, etoposide and cytarabine), midostaurin (broad spectrum protein kinase inhibitor)[69], mithramycin (antibiotic inhibiting RNA synthesis)[70], and the early clinical studies failed to show any clinical benefit of inhibiting EWS-FLI1 pathway in spite of being the

Table 3 Selected studies of high dose chemotherapy with stem cell rescue in Ewing sarcoma family tumors

Study (type)	Disease setting	*n*	Conditioning	Conclusion
CESS (restrospective)[78]	Recurrent or progressive disease (HDC after CR or PR)	73	BuMel (15) TreoMel (38) Other (20)	Early relapse - poor prognostic
Société Française des Cancers de l'Enfant (prospective)[8]	Metastatic at diagnosis	75	BuMel	Beneficial for lung only or bone metastases
Italian Sarcoma Group/Scandinavian Sarcoma Group Ⅳ Protocol (phase Ⅱ)[9]	Metastatic at diagnosis (lung or single bone metastasis)	79	BuMel ± TBI	HDC with WLI is effective
Italian Sarcoma Group/Scandinavian Sarcoma Group Ⅲ Protocol (prospective)[34]	High risk, localized	126	BuMel	Effective and feasible in patients with PR after chemotherapy
Euro-Ewing 99 (prospective)[10]	Metastatic at diagnosis	169	BuMel (123) Mel (15) Others (20)	Effective in Bone and Bone marrow metastases
EBMT registry (retrospective)[79]	Metastatic and HR, localized (*n* = 2411) Recurrent (*n* = 719)	3695	Heterogeneous regimens	Prognostic factors: Age, response to treatment, BuMel regimen

BuMel: Busulphan and melphalan; CR: Complete response; ESFT: Ewing sarcoma family of tumors; HDC: High dose chemotherapy; HR: High risk; *n*: Number; PR: Partial response; TBI: Total body irradiation; TreoMel: Treosulphan and melphalan; WLI: Whole lung irradiation.

Table 4 Data on Irinotecan-temozolamide salvage regimen in recurrent/refractory Ewing sarcoma family tumors

Ref.	*n*	Irinotecan schedule	ORR (*n*)	Toxicity (grade 3 and 4)
Kurucu *et al*[65]	20	20 mg/m^2 (D1-5 and D8-D12)	55% (11)	Diarrhea - 9.2% Neutropenia - 11.3%
McNall-Knapp *et al*[64]	25	15 mg/m^2 *vs* 20 mg/m^2 (D1-5 and D8-D12)[1]	20% (5)	Diarrhea - 5%
Raciborska *et al*[63]	22	50 mg/m^2 (D1-D5)[1]	50% (12)	Diarrhea - 15% Hematological - 10%
Wagner *et al*[62]	16	10-20 mg/m^2 (D1-5 and D8-D12) - 3 weekly *vs* 4 weekly	25% (4)	Diarrhea - 11%
Casey *et al*[61]	20	20 mg/m^2 (D1-5 and D8-D12)	63%	Diarrhea - 4.5% Hematological - 22%

[1]With vincristine. ESFT: Ewing sarcoma family of tumors; *n*: Number; ORR: Overall response rate.

driver in ESFT carcinogenesis.

Anti-angiogenic approach has been used in recurrent tumors and thus inhibiting the tumor growth and its metastatic potential. Bevacizumab (monoclonal antibody against VEGFR) has been tested in phase Ⅱ study by COG in combination with chemotherapy (vincristine, topotecan and cyclophosphamide) in recurrent setting with pending results (NCT00516295). Pazopanib (a small molecule multi-kinase inhibitor including VEGFR) has been tested in a phase Ⅰ trial[71] in refractory pediatric solid tumor and now being tested in a phase Ⅱ study by COG that include ESFT and other sarcomas (NCT01956669). Regorafenib (a small molecule multi-kinase inhibitor like pazopanib) also being tested in refractory sarcomas including ESFT (NCT02048371).

ESFT is characterized by osteolytic bone lesion with extensive soft tissue component which is marked by osteoclastic activity and interaction between RANK and its ligand - RANKL[72]. RANKL facilitates osteoclastic activity, with bone resorption and destruction, and tumor growth. Zoledronic acid, a bisphosphonate inhibit osteoclastic activity and its migration along with inhibition of RANK, showed anti-tumor activity in *in-vivo* model of ESFT and the effect was accentuated by addition of ifosfamide[73]. Ewing 2008 and Euro-Ewing 2012 trial is evaluating the benefit of zoledronic after combining with chemotherapy in localized ESFT.

IGF1 receptor (IGF1R) plays an important role down-stream to EWS-FLI1 for cell survival, angiogenesis and metastasis. But, disappointing results with anti-IGF1R monoclonal antibody let to stoppage of further study of this novel agent due to dramatic but very short lasting response in refractory ESFTs. The cause of this early resistance is not fully understood though up-regulation of IGF1R or mTOR has been postulated[74]. The COG future trial has planned combination of VAC-IE with anti-IGF1R antibody in metastatic disease to overcome this resistance.

The other potential targeted therapies include - PARP1 inhibitor olaparib in combination with temozolamide showed *in-vivo* and *in-vitro* activity[75], anti-GD2 ganglioside (a neuroendocrine marker present in ESFT cells) chimeric antigen[76], and anti-CD99 monoclonal antibody[77] are in preclinical study periods.

FERTILITY ISSUE: A IMPORTANT BUT OFTEN IGNORED ISSUE

ESFT is a disease of young adolescent age group along with many patients in reproductive age group. All three treatment modality in ESFT affects gonadal and reproductive function in these patients. Multi-agent chemotherapy, especially with alkylators and anthracyclines, and radiotherapy are the two major culprits in this scenario due to their goandotoxic effects. Many strategies have been taken to minimize or counter the gonadotoxic effects of cancer treatment especially with chemotherapy and radiotherapy.

Sperm cryopreservation is the standard and effective modality of fertility preservation in case of male patients, whenever indicated. Toxicity to ovarian follicle and embryo is a special scenario especially with pelvic radiotherapy. In a COG study[78], 8.3% of female cancer survivors experienced acute ovarian failure, defined as loss of ovarian function with 5-years of cancer diagnosis. Radiotherapy toxicity to ovary depends on age of the patients, concurrent ovariotoxic chemotherapy, dose and fractionation of radiotherapy and volume of radiation field. Cost, experience, expertise, infrastructure and low success rate are the main logistic issue in female fertility preservation.

Embryo crypreservation is an option for fertility preservation in female patients with a male partner, whereas cryopreservation of mature or immature oocytes is a viable option for those refuse to opt for a sperm donor. Cumulative pregnancy rate up to 40% has been reported with the former technique[79] but with a modest success with the later technique[80]. Cryopreservation of ovarian tissue is the only measures of fertility preservation in very young girls, and recent reports of successful pregnancy have been described in literature[81,82].

Ovarian transposition or ovariopexy is the method to preserve ovarian function in patients receiving pelvic radiotherapy but high rate of permanent cessation of ovarian function has been reported in earlier series[83]. Intensity modulated radiotherapy or 3-D conformal CT planning in radiotherapy can minimize the gonadal toxicity in case of very small pelvic tumor or a tumor distant to ovary.

Protective role of concurrent GnRH-a has been described in literature during combination gonadotoxic chemotherapy. In study of lymphoma patients aged 15-40 years, GnRH-a group resumed menstruation in 93.7% cases within 3-8 mo of chemotherapy as compared to 39% in historical controls of same disease group who didn't received GnRH-a[84]. In important issue remains in fertility preservation where the ovary itself is the primary site of disease in ESFT and rarely ESFT can metastasize to the ovary[85-87].

CONCLUSION

ESFTs are a rare aggressive tumor with high rate of metastasis at presentation and high incidence of recurrence. The outcome of those with localized improved to 70% after multimodality approach mainly by better understanding of disease biology, risk adapted chemotherapeutic approach, timely incorporation of local therapy, and improvement in technology. But, the outcome of those with metastatic and recurrent disease is dismal and no significant advancement has been made in these patients to improve outcome in last four decades. The overall improvement in outcome of ESFT has been made through the tremendous efforts of researcher, clinicians all over the world, better liaison between all the stakeholders of treating team, and collaborative international research in a huge number of cases. The main challenge now remains in preventing recurrence, preventing drug resistance, reducing therapy related long-term toxicities and improving outcome in those with metastatic and relapsed/recurrent disease. No potential biomarker has been identified so far to predict therapeutic efficacy of chemotherapeutic agents and predicting recurrences. The future hope lies in finding useful biomarker, better understanding of disease biology and chemotherapy resistance of ESFT cells, proper designing and execution of targeted therapies currently going under clinical trials, better use of high throughput method to detect novel driver mutations/pathways and potential targets. Better selection of risk group and designing of trials combining chemotherapeutic agents with targeted therapies to bypass drug resistance along with judicious use of high dose chemotherapies, selection of more non-toxic agents with high efficacy and broad therapeutic windows will help to improve future outcomes in expense of decreased treatment related long-term toxicities and good quality of life in survivors.

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MINIREVIEWS

Casting: Pearls and pitfalls learned while caring for children's fractures

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Abstract

Casting is a routine procedure used for fracture care in the pediatric population. The purpose of this review is to provide pearls and pitfalls that our institution has learned from previous literature. When applying the cast, we recommend using cotton padding for the liner and fiberglass or plaster depending on how much swelling is expected. A well-molded cast must be applied in order to prevent further fracture displacement. Cast valving is a valuable technique that allows a decrease in pressure which prevents discomfort and complications like compartment syndrome. Preventing thermal injuries, skin complications, and a wet cast are other important considerations when caring for casts. Appropriate use of a cast saw, avoiding pressure spots, and properly covering the cast are ways to respectively prevent those complications. Lastly, patient education remains one of the most valuable tools in ensuring proper cast maintenance.

Key words: Cast care; Fracture cast; Pediatric casting; Pediatric fractures; Casting; Cast complications

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Core tip: Casting is a routine procedure used for fracture care in the adult and pediatric population. The pediatric population present a unique set of attributes that often making casting difficult. In this article we will review different pearls and pitfalls seen while treating fractures in children which includes cast application, maintenance, and removal.

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INTRODUCTION

Casting is a routine procedure used for fracture care in the pediatric population. Casting may be performed to

immobilize non-displaced fractures, maintain reduction of displaced fractures and protect operatively treated fractures. As commonly as casting is performed, the art of this technique appears to be less emphasized in many orthopaedic training programs, especially with the advancement in methods of surgical fixation of children's fractures. However, their use remains as a mainstay in orthopedics. Orthopaedic providers with a wide range of training background (*i.e*., physician assistants, nurse practitioners, cast technicians) often are the primary applicators of a cast. Despite casting being performed by a wide range of providers, it should not be viewed as a procedure without risks.

Numerous studies, historical and recent, have looked at common complications of casting[1-11]. Many of these have focused on hip spica casts and forearm fractures treated with short or long arm casts[12-16]. These complications can range from skin excoriations to compartment syndrome.

Complications and improper application of casts have contributed a burden of non-emergent patients seen in emergency departments[17]. Sawyer *et al*[17] investigated patients that are seen in emergency departments for problems relative to their cast and found that approximately 29% of the visits were because of a wet cast; 10%, were secondary to a damaged cast; 23%, a tight cast; 13%, a loose cast; and 10%, new or different pain. When casting has been applied correctly, it has the potential to save a significant amount of money when compared to surgical alternatives[17]. According to Newton and Mubarak, the total charges for a hip spica were $494 while the surgical alternative was approximately $21000[18].

The purpose of this article is to review the current literature pertinent to casting and share our own pearls and pitfalls that we have learned while caring for children's fractures with a cast. We also aim to provide various recommendations to safely and effectively place, maintain, and remove casts.

CAST MATERIAL

One of the primary decisions the provider has to make when applying a cast is what material to use. The two types that are traditionally used are plaster and fiberglass. Each of which have benefits and drawbacks that must be considered when choosing one over the other.

Plaster-impregnated cloth's major advantage includes its ability to mold more easily than it's counterpart. This allows the provider to apply a custom mold to a reduced fracture and maintain reduction during the healing process. The drawbacks of plaster is it has a poor resistance to water and low strength-to-weight ratio which make it noticeably heavier than fiberglass[19].

When treating fractures in children primarily with a cast, fiberglass is usually our preferred choice. Since the child on average will wear the cast for 4-6 wk, the lighter and less bulky fit often makes it more comfortable for the child.

CAST APPLICATION

Cast application entails many elements which include the type and amount of material used, type of soft roll, presence or absence of stockinet and the method of rolling the cast as well as the final cast shape and position. The importance of a well-molded cast cannot be over emphasized[12,20]. One of the main tenets of the cast application is to apply a mold based on the fracture pattern to, when applicable, maintain reduction and/or prevent displacement from occurring or at least worsening (Figure 1).

Excessive focused pressure over a small surface area of the cast can lead to decreased areas of perfusion and cause pressure sores. The practitioner should be constantly aware of their hand position in addition to the assistants' so they do not stay in one location for too long. Avoiding wrinkles and uneven ridges throughout the cast are details that will cause even pressure distribution throughout the extremity.

When treating distal radial and ulna fractures calculating the cast index on post application radiographs has been demonstrated to predict fracture displacement after cast application[14,20-22] (Figure 2). The measure is performed at the level of the fracture. The goal is to create a ratio of sagittal width to coronal width to be equal or less than 0.8. If the ratio is equal or less than 0.8 the fracture has approximately 5% of displacement as opposed to 26% chance for an index greater than 0.8. Another radiographic measurement that can be used when treating fractures of the distal radius and ulna is an angle measured by the index finger or second-metacarpal and distal radius[23]. To oppose the pull of the brachioradialis, which is often a deforming force in distal one-third radial fractures, molding a cast in ulnar deviation is recommended. If molded with ulnar deviation (second metacarpal-radius angle > 0 degrees), the outcome was considered to be ideal in 86.7% of cases compared to only 74.4% when it was < 0 degrees[23].

Applying the index layer of fiberglass is crucial to ensuring a proper fit to the child's extremity. It is also important when needing a mold. If the index layer is applied too loosely, the cast will slide on the extremity when applying the mold and ultimately cause displacement of where the mold was originally intended for (Figure 3). However, if the index layer is applied too tightly, the obvious concern is soft tissue and vascular compromise. Our recommendation is that the material, whether plaster or fiberglass, be "un-rolled" onto the extremity to be casted and not pulled onto or wrapped in a fashion that can be constricting.

CAST VALVING AND PADDING

Cast valving and spreading is a technique that is employed in an attempt to alleviate pressure within a cast[9,10,19,24]. A cast valve is performed using a cast

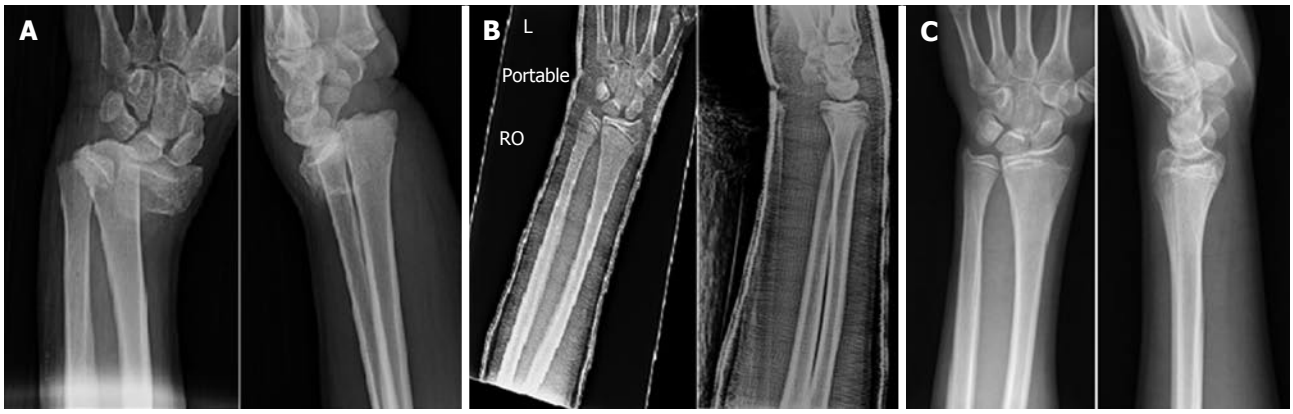

Figure 1 Well-molded cast. A: Pre-reduction X-rays of pediatric forearm demonstrating a completely displaced distal both bone forearm fracture. Immediate post-reduction X-rays; B: Immediate post-reduction X-rays demonstrating adequate reduction with a flexion mold to prevent fracture from dorsal displacement; C: Three-months follow-up X-rays demonstrating completely healed fracture with near-anatomic alignment.

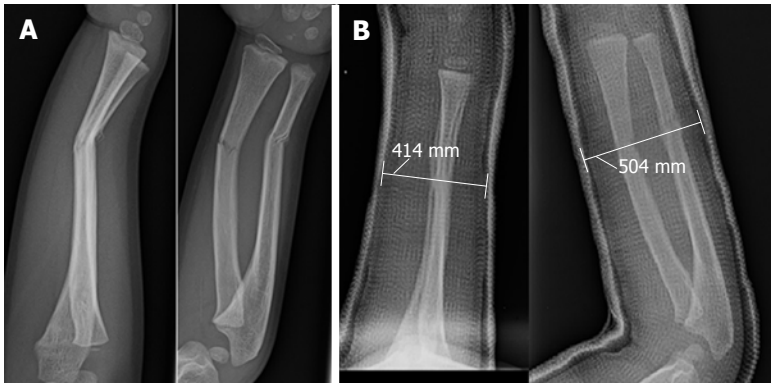

Figure 2 Cast index. A: Initial X-rays of a pediatric forearm fracture with angulation; B: Immediate post-reduction X-rays demonstrating an appropriate cast application based on the cast index (< 0.8). Cast index = Saggital width/coronal width = 41.4 mm/54.4 mm = 0.76.

saw to create a longitudinal linear cut parallel to the long axis of the limb. The cut is either left open with or without a space holder and may be secured by tape. This technique is commonly used after an acute injury, closed reduction, or immediately after surgical fixation all scenarios where the treated limb is at risk for further swelling.

Roberts *et al*[6] performed a biomechanical study that evaluated the amount of pressure reduction after valving a cast in relation to different casting material. They compared effects of cotton, synthetic, and waterproof padding in addition to the effects of overwrapping a valved cast with an elastic bandage. They concluded that valving a cast with cotton padding beneath resulted in the greatest amount pressure reduction when compared to synthetic and waterproof padding and concluded that cotton padding demonstrated the greatest change in pressure within a long-arm cast after undergoing a bivalve. They stated that synthetic and waterproof cast padding should not be used in the setting of an acute fracture to accommodate swelling. Our custom and practice has been to use cotton padding in all instances because of its ease of use, ability to mold and trim in addition to better pressure reduction after valving as shown by Roberts *et al*[6].

In warm climates especially during warmer months waterproof material is also an acceptable option especially when caring for sub-acute or non-displaced fractures. Robert *et al*[25] designed a study that compared casts lined with cotton *vs* water-proof liners and their effectiveness on maintaining pediatric distal forearm fractures. The results showed that there was no significant difference in amount of displacement and angulation at final follow-up between the two groups and that waterproof liners were equally as effective in maintaining reduction.

When considering univalving *vs* bivalving, this decision is based on how much swelling the practitioner expects from the injury. Most low-to-medium energy trauma can be treated with a univalve, however children that have undergone a high-energy mechanism trauma, bivalving should be strongly considered in cases where casting is preferred over splinting. Zaino *et al*[24] performed a study comparing the most effective method in decreasing method in reducing cast pressure in fiberglass casts. Their study concluded that the triple cut method which included bivalving, spreading, and cutting the cotton padding was the most effective in reducing clinically relevant skin pressure[24].

Another useful tool that can be used when valving a

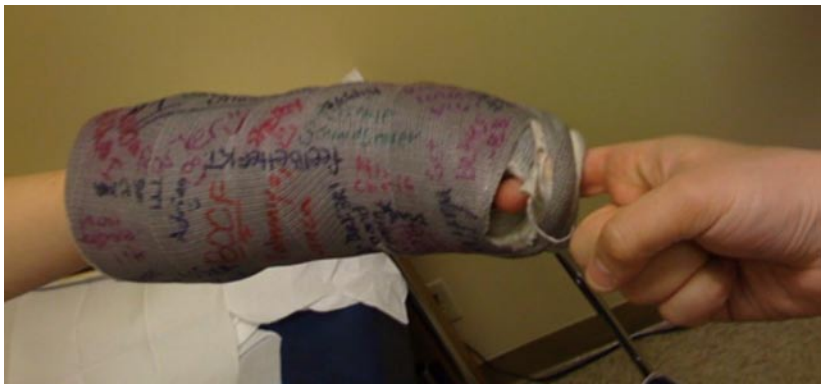

Figure 3 Loose cast. Pediatric cast that was applied too loosely. The physician's hand (right) was able to pull the cast off the child easily.

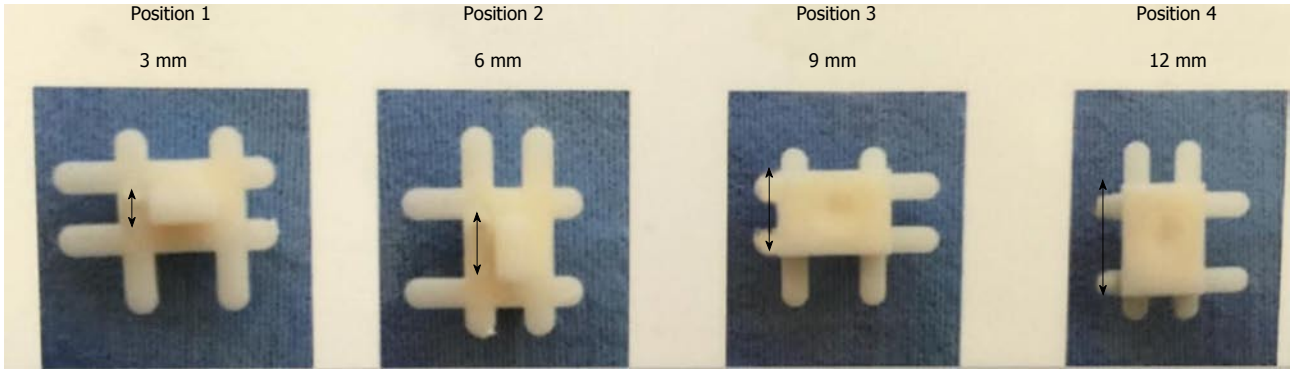

Figure 4 Cast spacers. Cast spacers with four different size settings (3, 6, 9 and 12 mm).

cast are commercially available cast spacers (Figure 4). These cast spacers are inserted in the valved area and are taped circumferentially around the cast. The purpose of the spacer is to maintain a constant spread in the cast material and diminish underlying pressure. The commercially available spacer we typically use has four different inserts that differ in size (3, 6, 9 or 12 mm) in which the provider can adjust the size of the space. Kleis *et al*[26] recently presented their experimental findings after investigating the utility of spacer placement after cast valving. In their study model they reported reduction or pressure by 34% to 95% depending on the setting of the spacer. They recommended using Position #2 for most scenarios as it reduces pressure by an average of 78% but does not weaken the cast. For high energy traumas, Position #3 would be a safer option to prevent excessive compartment pressures.

It is customary for us to use cast spacers in every valved cast most often in the 6 mm position.

THERMAL INJURY

Burns caused after cast application have been studied in recent reports[27,28]. The curing of the cast material itself is exothermic and heat producing. Although the occurrence is not a commonly encountered complication, an unnecessary heat exposure to the child can be uncomfortable and stressful. The risk of thermal injuries may be increased when the temperature of the dip water for the cast material exceeds > 50 ℃ or when the cast is too thick > 24-ply[27,28].

Accurately measuring the dip water immediately prior to each cast application is possible but not highly feasible in most clinical scenarios. Dip water temperature should be warm to the touch similar to the temperature customary when bathing an infant. Although using warmer temperatures will allow the cast to harden at a faster rate, practitioners need to be aware that higher water temperature will increase the risk of thermal injury.

Cast thickness greater than 24-ply is difficult to achieve on most standard casts however the areas that are of concern are located on the concavities and flexion creases of the extremity. A natural surface area discrepancy is present when a cast is placed across a joint that is not in pure extension. These locations include the dorsal aspect of the ankle joint, posterior knee joint, and antecubital fossa of the elbow joint. In these locations a 1:2, concave: Convex ratio is recommended when applying material in these areas. This will prevent excess layers in the areas that are prone to thermal injury.

Another important aspect of preventing thermal injury during casting is to ensure the cast is completely hardened before supporting the extremity on a pillow or soft blanket[27]. If the un-hardened cast is placed on a pillow, the heat generated from the exothermic reaction in the material will be smothered, heat escape limited and the potential for thermal injury is increased.

PREVENTING A WET CAST

When a cast becomes wet, numerous complications can occur, which include skin maceration, infection, and disruption of the structural integrity of the cast[29]. Although educating the patient and family regarding the importance of protecting their cast and keeping it dry is paramount the incidence of a wet cast still continues to be problematic[17]. Currently, there are various methods and products whose purpose is to help prevent casts from becoming wet. These methods include commercially available cast protectors, waterproof liners, and a combination of household products.

McDowell *et al*[30] compared these various methods on their effectiveness in preventing water absorption when applied to a cast. In addition, they also evaluated the most cost effective method. They found that all of the methods provided some level of protection when the cast in their experimental model was exposed to water. They concluded that although abstaining from contact with water is the most prudent approach, if a cast cover is to be used, double plastic bags with duct tape (100% prevention, $10) and the store bought cast protector (100% prevention, $13) were their preferred contemporary methods to prevent a wet cast.

Waterproof padding or cast liners are another option for children to allow bathing or water based activities while in a cast. We have often found that the adding cost of these materials are not covered by most commercial insurers in the United State and often the cost of these materials are transferred to the patient and family.

It is the utmost importance to remind patients and guardians to prevent the cast from becoming wet. Many times the complications from a wet padding can be unnoticed and will not be discovered until the final follow-up when the cast is removed. In order to prevent further skin complications that can lead to significant infection and injury, educating the parents on signs of wound infection such as deterioration of the fiberglass or a strong malodor from the cast must be performed.

SKIN COMPLICATIONS

Skin complications from cast application is a common occurrence that can range from minor skin excoriations to severe pressure ulcers that can eventually require surgical debridement and coverage[31]. There are only several studies published that focused solely on pediatric skin complications associated with casting[12,31].

Many of the skin complications we have encountered in the clinic or emergency department were likely due to poor cast padding. In order to prevent pressure ulcers, it is important to be aware of the locations of the extremity that have notable protuberances (*i.e*., fibular head, heel, femoral epicondyles, *etc*.). At these areas, more padding needs to be placed to prevent excessive pressure. Difazio *et al*[31] published a recent study on reducing the incidence of casted-related skin complications, more specifically heel pad ulcers. Through adding extra padding at the heel area in addition to respective provider education, they decreased the incidence of casted-related skin complications from 17.1 per 1000 lower extremity casts to 6.8.

CAST REMOVAL

The use of cast saws have brought much attention in the orthopedic literature[1-4,7,24,32,33]. These studies have focused mainly on the complications that come with using the saw. Although they are routinely advertised to patients and their families that it is only intended to cut the fiberglass and not the child's skin, cast saws can still result in thermal injuries and abrasions.

Shuler *et al*[4] recently evaluated factors that prevented excessive increase in temperatures when using a cast saw blade. What they found was significant was the amount of cast padding and the relationship with temperature. They recommended four layers, as opposed to two, when applying the padding. This adjustment helped decrease the temperature by 8.0 ℃.

Killian *et al*[3] provided another study that evaluated multiple factors that contribute to thermal injuries from cast saw use. In this study they compared thickness of casts, dullness of blades, and experience of cast saw users. What they concluded was that frequent changes to cast blades, cast thickness to be less than 3/8 inch, and a heightened sense of awareness on the temperature of the blade during cast saw use were important clinical factors that can prevent thermal injuries. They included a tip on how to gauge cast-saw blade temperature which was that if the user is unable to hold the blade with two fingers for longer than 5 s the blade is too hot.

Several articles on cast saw complications have emphasized the importance of the user's experience[2,3,7,32]. Just like any new procedure, it has been studied that an inexperienced user can cause significant harm to the child if not done correctly. Brubacher *et al*[32] developed a cast removal training simulation using a fracture model and experimenting it with various levels of orthopedic attendings and residents. As expected, the more experience surgeons resulted in lower mean peak temperatures after cast removal. What they also discovered was that the beginner and intermediate groups were able to achieve progressively decreasing mean temperatures after they experienced more trials with the simulator. In addition, the study displayed the potential benefits of using a simulation workshop to allow providers of all skill levels to develop experience and comfort when using a cast saw.

At our institution, we strictly emphasize the importance of cast saw use. Our cast-saw blades are routinely checked on a weekly basis and a "blade status/change log" is maintained by our orthopedic technicians.

Using a Saw Stop© protective strip (Figure 5) is another way to further protect the limb from the cast saw during removal. The strip is placed directly over the webril layer on the side that the cast saw will cut. The fiberglass is then layered on top of the protective strip

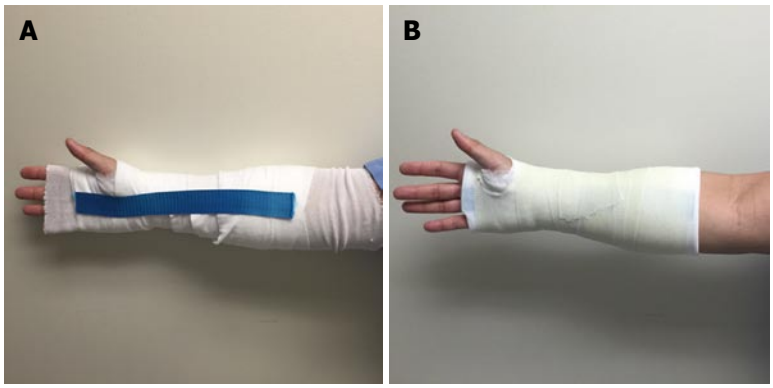

Figure 5 Saw Stop© protective strip (A and B). This protective strip is placed on top of the webril layer before applying the fiberglass cast roll. The strip provides a durable protective layer for the cast saw to cut over.

and the cast saw user is now able to cut through the fiber glass without risk of contacting the skin because of the added protection layer. They are crucial to use if the person removing the cast is unsure of the quality integrity or even the presence of soft roll beneath the cast material. Having a dedicated formal teaching session(s) in place and a practical exam is recommended prior to allowing practitioner in any medical setting use a cast saw to remove a cast in any patient.

PATIENT EDUCATION

Equally as important as all the factors above when applying a cast, is the detailed patient education on how patients and patient's family can maintain this cast. As common as cast application and maintenance is for orthopedic surgeons, it is easily forgotten on how novel this treatment is for the patient and their families. Thus, emphasizing the "do's and don'ts" of cast care is imperative on preventing complications.

DiPaola *et al*[34] designed a prospective study on documenting the incidence and etiology related to unplanned cast changes. What they discovered was that the major reason for unplanned cast changes wasn't because of the technique of the cast application but rather patient non-adherence to instructions or lack of education on maintaining it.

The importance of patient education must be emphasized. After each cast application, the practitioner should have a discussion with the child and family that touches on numerous factors on cast care maintenance that should include how to prevent cast from becoming wet, avoiding inserting objects into the cast and how to handle certain irritating symptoms such as itchiness. Patients are provided with an educational handout on how to best care for their cast and it is translated into their native language when necessary.

CONCLUSION

Casting was one of the first methods of fracture treatment and remains as one of the most common modes of treatment. Perfecting the art of casting remains crucial in ensuring optimal patient outcomes and preventing significant healthcare expenses related to complications.

The ideal cast has a long list of factors that need to be considered to ensure a high quality of patient care. A good cast should immobilize the extremity, remain comfortable, and not cause complications. These factors include the type of cast material and how much padding to apply at certain areas of the extremity. Afterwards, educating the patient and family on how to prevent the cast from getting wet will assist in maintenance, comfort and anxiety. Finally, learning how to properly use a cast saw to prevent thermal injury are just a few notable aspects of providing an optimal cast experience.

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MINIREVIEWS

Implant retention after acute and hematogenous periprosthetic hip and knee infections: Whom, when and how?

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Abstract

Periprosthetic joint infections (PJI) of the hip and the knee are grossly classified as early post-operative, acute hematogenous and late chronic infections. Whereas two-stage exchange arthroplasty is the standard of care in North America for treating chronic infections, irrigation and debridement (I and D) with retention of implants has been used in an attempt to treat the other two types of PJIs. The rationale of this approach is that a PJI may be eradicated without the need of explanting the prostheses, as long as it has not transitioned into a chronic state. With the present paper, we review current evidence regarding the role of I and D with implant retention for treating PJIs of the hip and the knee. While a very wide range of success rates is reported in different studies, a short period of time between initiation of symptoms and intervention seems to play a prominent role with regards to a successful outcome. Moreover, pathogens of higher virulence and resistance to antibiotics are associated with a poorer result. Specific comorbidities have been also correlated with a less favorable outcome. Finally, one should proceed with serial I and Ds only under the condition that a pre-defined, aggressive protocol is applied. In conclusion, when treating a PJI of the hip or the knee, all the above factors should be considered in order to decide whether the patient is likely to benefit from this approach.

Key words: Irrigation and debridement; Periprosthetic infection; Total knee arthroplasty; Implant retention; Total hip arthroplasty

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Core tip: An infected total joint arthroplasty represents a significant burden to patients, as well as to orthopaedic surgeons. Previously, irrigation and debridement with retention of implants has been advocated for certain types of periprosthetic infections. The purpose of the present paper is to review the indications, success rates and factors determining the outcome of this treatment option for periprosthetic infections of the hip and the knee.

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INTRODUCTION

Periprosthetic hip and knee infections: Trends, diagnosis, classification and treatment

Total joint arthroplasty (TJA) is a very useful tool in the hands of orthopaedic surgeons, as it can relieve symptoms and significantly improve the quality of life in patients with end-stage arthritis of the hip and the knee. In the past decades, the use of this modality has known a remarkable growth, which is expected to continue in the future. For example, by the year 2020 the estimated annual number of total hip arthroplasties (THAs) will exceed 500000 procedures[1]. On the other hand, this will also lead to an increase in complications related with TJA, among which periprosthetic joint infection (PJI) is one of the most devastating for the patient. In spite of preventive measures available, the incidence of PJI remains substantial as it ranges from 1% to 3% after primary TJA[2-5], and can be 4 times greater after revision TJA[6].

Implant colonization may occur with either intraoperative contamination, spreading from an adjacent infectious site or hematogenous seeding from a distant site[7], with coagulase-negative staphylococci and *Staphylococcus aureus* species being the most dominant pathogens[8-11]. Diagnosis can be easily made when obvious sequelae of infection are present, such as a draining sinus. However, in many cases such signs are absent and a complex diagnostic evaluation is needed. No single method provides 100% diagnostic specificity and sensitivity. The Musculoskeletal Infection Society introduced specific criteria for the diagnosis of a PJI[12]. The combination of different modalities significantly increase sensitivity and specificity for diagnosing PJI[13,14]. Moreover, synovial biomarkers, including alpha-defensin and leukocyte esterase, have been proven accurate diagnostic tools for PJI with high sensitivity and specificity[15]. Nonetheless, sophisticated methods are expensive and not widely available, and therefore cannot be recommended for routine use.

PJIs of the hip are classified into four types, as proposed by Tsukayama *et al*[16]. Type Ⅰ includes positive intraoperative cultures in patients undergoing revision surgery for non-infectious etiology; Type Ⅱ represents early infections developing within one month postoperatively; late infections presenting within more than one month postoperatively are characterized as Type Ⅲ infections; finally, Type Ⅳ infections are of acute hematogenous nature and are correlated with an identifiable event leading to bacteremia. A similar system has been introduced for PJIs of the knee[17]: Type Ⅰ includes positive intraoperative cultures obtained during a revision surgery for a cause other than infection; Type Ⅱ PJIs are early infections presenting within 4 wk after surgery and include Types ⅡA (superficial) and ⅡB (deep); acute hematogenous deep infections with an onset of more than 4 wk postoperatively are classified as Type Ⅲ infections; lastly, Type Ⅳ PJIs of the knee are late deep infections developing after 4 wk since the index procedure.

The standard of treatment for PJI is a combination of surgical interventions with the goal of reducing microbial load and administration of antibiotics. Two-stage revision is considered to be the gold standard for management of late chronic PJIs in North America[18]. On the other hand, eradicating infection with retention of the prosthesis when possible may be associated with superior functional outcomes. Irrigation and debridement (I and D) with exchange of prosthetic modular parts has been long used with respect to that goal. The purpose of the present paper is to review the indications, success rates and risk factors that determine the outcome of I and D for PJIs of the hip and the knee.

I AND D: PROCEDURE DESCRIPTION

The patient should be off any antibiotics for at least 5 d before the procedure. The affected limb is prepped and draped, the previously healed incision is used and the affected joint is adequately exposed (Figure 1A). A total number of six tissue samples should be obtained and sent for cultures and sensitivity testing. Next, the modular parts, including femoral head and polyethylene liner for a THA and the polyethylene liner for TKA, are removed to gain access to all aspects of the joint and a thorough debridement is performed. All grossly infected and necrotic soft-tissues are meticulously excised (Figure 1B). Great care should be taken to circumferentially debride the articular capsule in both the hip and the knee. After the joint is debrided to macroscopically healthy tissues, the joint is copiously irrigated with antibiotic containing saline. Modular parts are exchanged and the wound is closed. It should be noted that even though exchange of modular parts is advised[18], it may not be always feasible, especially in settings where implant availability is limited. There is no consensus on the duration of intravenous antibiotics administration after the procedure[19]. A common approach is to place the patient on a 6 wk treatment with

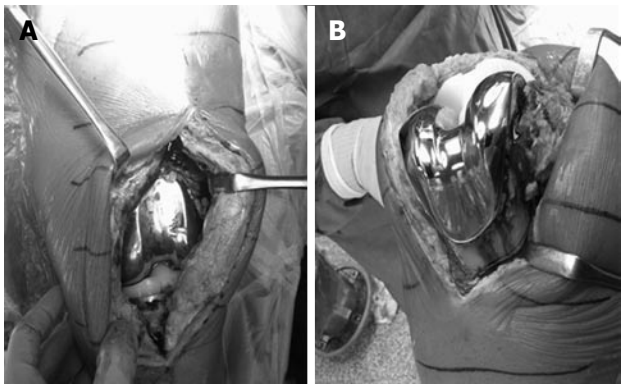

Figure 1 Irrigation and debridement for an infected total knee arthroplasty with retention of implants. A: The joint is exposed through the previously healed incision; B: Note the extensile debridement of the synovium on the anterior aspect of the femur. Debridement of the infected tissues should be carried out throughout the joint, including the posterior capsule.

antibiotics (two weeks of intravenously administered antibiotics followed by another 4 wk of p.o. antibiotics), based on culture and sensitivity results.

The technique described above is the open technique with exchange of modular parts. In the previous years, there was a trend towards performing I and D arthroscopically, especially for periprosthetic infections of the knee[20,21]. However, recently there has been a recommendation against this approach, as it does not allow access to all aspects of the joint and therefore the debridement may be suboptimal[22].

INDICATIONS

Previously, Del Pozo *et al*[23] have outlined the indications of I and D for treating PJIs. According to the authors, these include an infected prosthesis that was implanted within less than 3 mo or a hematogenous infection, with duration of symptoms of less than 3 wk, absence of sinus tract or abscess, stability of implants and a pathogen other than multi-drug resistant microorganisms, Enterococcus species, quinolone-resistant Pseudomonas and fungi.

Recently, the participants of a consensus meeting on periprosthetic infections strongly agreed that I and D may be a viable alternative for patients with early infections that develop within 3 mo post index procedure, as well as with late hematogenous infections; symptoms should have a duration of less than 3 wk[19]. Eradicating infection while avoiding removal of the prostheses may allow for lower morbidity and better function. Published series of patients treated with I and D for PJI of the hip and the knee show great variability in methodology, success rates and identified prognostic factors with regards to outcome.

WHAT IS THE EVIDENCE?

I and D for PJI of the Hip

Implant retention with I and D of the hip for a Type Ⅱ or Ⅳ PJI has been previously reported to be 70% in a previous large series[24]. Westberg *et al*[25] have reported a 71% success rate of I and D in early hip PJIs. In the series of Tsukayama *et al*[16], retention of implants was attained in 70.3% of cases. Barberán *et al*[26] had a success rate of 71.9%, and Vilchez *et al*[27] reported that I and D successfully treated infection with implant retention in 75.5% of patients. On the other hand, other authors have published greatly variable results, with success rates ranging from 14% to 100%[21,28-46] (Table 1).

Symptom duration is a significant factor predicting the outcome of I and D of the hip. When a cut-off point of 5 d of symptom duration was used, it was noted that patients with symptoms of more than 5 d had 95.2% lower odds of success compared to patients with shorter duration of symptoms[24]. Similarly, Sukeik *et al*[36] found that performing I and D more than 5 d after the onset of symptoms led to less favorable outcomes. Others have proposed an even prompter intervention, in as shortly as within 2 d from symptom onset[30]. In other studies, the suggested duration of symptoms within which such an intervention is more probable to be successful ranges from one to four weeks[40,42,45]. Despite this variability, we may conclude that once the diagnosis of a type Ⅱ or IV PJI of the hip is established, action should be prompt from the part of the surgeon when the goal is to retain the implants. The decrease in the probability of successful I and D has been calculated to be 17.7% for each additional day of delay in treatment[24]. A greater duration of symptoms allows formation of the biofilm layer, which provides protection against immune response and resistance against antibiotics. Once this biofilm is formed, I and D with implant retention is less probable to control the infection[43].

The type of pathogen also plays a role in the outcomes of I and D of the hip. Patients with methicillin-resistant staphylococci have been correlated with worse outcomes[24]. Barberán *et al*[26] also reported worse outcomes in patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA). In addition, infections with MRSA, methicillin-resistant *Staphylococcus epidermidis* and vancomycin-resistant Enterococci have been associated with inferior success rates after I and D[40]. Staphylococcal infections have been identified as a negative prognostic factor by other investigators as well[21,29,31,41,42]. In cases of infections with multi-drug resistant pathogens, a more aggressive treatment strategy is warranted and even exchange arthroplasty (either in one or two stages) may be considered.

Other factors that have been found to predict outcomes of I and D of the hip include obesity[24], ASA score and purulence[29], a history of previous infection[40] and elevated inflammatory markers[27,34,40,42]. These factors are associated either with host's impaired immune system response to infection, or with severity of infections and should be considered for decision-making. Additionally, patients with one or more local or systemic compromises according to the Cierny classification have been also correlated with inferior outcomes after I and D for a PJI

Table 1 Reported success rates of irrigation and debridement for treating periprosthetic infections of the hip and the knee

Ref.	Patients	Success rate for PJI of the hip	Success rate for PJI of the knee	Cumulative success rate
Aboltins *et al*[28]	13	92%	85.70%	90%
Azzam *et al*[29]	53	47.83%	45.30%	44.60%
Barberán *et al*[26]	32	71.90%	57.20%	65%
Bradbury *et al*[52]	19	-	16%	-
Brandt *et al*[30]	7	28.60%	38.50%	36.40%
Buller *et al*[40]	62	56.50%	50.60%	51.80%
Burger *et al*[49]	39	-	17.90%	-
Byren *et al*[21]	52	86.50%	74.50%	80.60%
Chiu *et al*[51]	40	-	30%	-
Choi *et al*[31]	92	50%	-	-
Choong *et al*[32]	14	78.60%	-	-
Cierny *et al*[48]	43	-	-	66%
Crockarell *et al*[44]	42	14%	-	-
Engesæter *et al*[46]	180	76%	-	-
Estes *et al*[37]	20	100%	87.50%	90%
Fehring *et al*[43]	86	37.50%	37%	37.20%
Gardner *et al*[50]	44	-	43.20%	-
Geurts *et al*[45]	69	82.60%	85%	83.10%
Klouche *et al*[63]	12	75%	-	-
Konigsberg *et al*[33]	20	80%	77.30%	78.50%
Koyonos *et al*[41]	60	30%	38.50%	35%
Kuiper *et al*[42]	62	61.30%	75.90%	66%
Marculescu *et al*[56]	91	-	-	60%
Martel-Lafarrière *et al*[59]	34	-	-	60%
Martínez-Pastor *et al*[34]	15	73.30%	75%	74.50%
Meehan *et al*[35]	19	66.70%	100%	89.55%
Mont *et al*[53]	24	-	83.30%	-
Peel *et al*[60]	43	71.40%	93%	79.10%
Rasouli *et al*[38]	10	83.30%	0%	50%
Segawa *et al*[55]	28	-	78%	-
Sukeik *et al*[36]	26	77%	-	-
Tattevin *et al*[57]	69	-	-	38.20%
Teeny *et al*[54]	21	-	29%	-
Triantafyllopoulos *et al*[47]	78	-	55.10%	-
Triantafyllopoulos *et al*[24]	60	70%	-	-
Tsukayama *et al*[16]	106	70.30%	-	-
Van Kleunen *et al*[61]	13	-	-	61.50%
Vilchez *et al*[27]	18	88.90%	68.60%	75.50%
Westberg *et al*[25]	38	71%	-	-
Zürcher-Pfund *et al*[20]	21	-	33%	-

PJI: Periprosthetic joint infection.

of the hip[48].

I and D for PJI of the knee

Buller *et al*[40], in their large series of 247 patients with PJI of the knee, reported a success rate of 50.6% for I and D. Similarly, in a series of 78 patients with PJI of the knee treated with I and D, the success rate was found to be 56.3%[47]. A higher success rate (74.5%) was reported by Byren *et al*[21] among 51 patients with PJI of the knee. In contrast, in the study of Koyonos *et al*[41], I and D was successful in only 38.5%. In the literature, there are studies with highly variable success rates, that range from 16% to 100%[20,26-30,33-35,37,42,43,45,49-55] (Table 1). These studies, however, show significant methodological inconsistencies.

Similarly to the hips, duration of symptoms is also identified as a factor predicting the outcomes of I and D. In studies where PJIs of both the hip and the knee were included, favorable outcomes were reported when the intervention was undertaken within an interval ranging from 1-4 wk[40,42,45,56]. In other reports, the suggested timing for a successful outcome is within 5 d since symptom onset[47,57]. Others have proposed an even lower cut-off point of 2 d[30]. For each additional day that treatment delays, a 7.5% decrease in the odds of success has been calculated[47]. This highlights the importance of timely intervention, as the gradual formation of the protective biofilm may prevent eventual eradication of the pathogen without removal of the prosthesis.

The type of pathogen also predicts outcomes of I and D in the setting of a PJI of the knee. As is the case for the hip, MRSA infections have been associated with poorer outcomes[26,40,47]. Treatment failure has been correlated with staphylococcal infections in several previous reports[21,29,33,41,56]. This may be explained by the higher microorganism virulence[58], the formation of biofilm and the increased rates of resistance to antibiotics that characterize staphylococcal strains.

For PJI of the knee, ASA score and joint purulence[29,56,59], preoperative levels of inflammatory markers[34,40,42], and prior infection[40] have been also identified as factors affecting outcomes of I and D. In contrast to the hip, revision surgery[21], as well as thyroid disease[47], has been reported as additional prognostic factors for I and D of a knee PJI.

The role of serial I and Ds

In a previous consensus meeting, the participants recommended against performing serial I and Ds, unless this approach is included in a specific protocol[22]. Studies utilizing a predefined protocol of serial interventions exhibit high success rates. When gentamycin-loaded cement beads were used in combination with a repeat I and D after 2 wk, infection control was established in 83.1% of patients[45]. Kuiper *et al*[42] used a similar protocol, with a success rate of 66.1%. A more aggressive approach was adopted by Peel *et al*[60], which included three I and Ds within 7-10 d; the authors reported an 86% success rate. Estes *et al*[37] performed 2 I and Ds 7 d apart using antibiotic-loaded cement beads and reported a 90% success rate. With a protocol consisting at least 2 I and Ds within 2-3 d, Choong *et al*[32] reported successful outcomes in 78.6% of patients. On the other hand, in studies where no particular protocol for performing serial I and Ds is followed, the results have been more variable and range from 25% to 100%[20,21,25,27-29,31,36,53,61,62].

Time is still a significant factor when the approach of serial I and Ds is chosen. It has been shown that performing a subsequent I and D within more than 20 d after the first procedure is associated with 97.4% lower odds of implant retention[62]. Specific protocols with serial I and Ds involve performing the subsequent procedure in no more than 14 d and, as already described, were associated with superior results. Again, longer duration of symptoms has been also associated with failure of multiple I and Ds[62] as it allows for biofilm formation and transition to infection chronicity, as previously described.

Serial I and Ds have been found less likely to be of success in PJIs of the knee than in hip infections[62]. This may be attributed to differences with regards to the soft-tissue envelope of each joint, as well as to vascular supply. In the same study, patients treated with multiple I and Ds were more likely to have vascular disease[62]. These findings, however, have not been reproduced by other reports and therefore further investigation is needed in order to elucidate their potential impact.

CONCLUSION

I and D with the goal of implant retention is still an important tool in the armamentarium of the orthopaedic surgeon for early postoperative and late acute hematogenous PJIs. In such cases, intervention should be timely and aggressive, as each additional day lowers the odds for a successful outcome. Furthermore, the ideal candidate should have an infection with a low-virulence pathogen and be without comorbidities that have been associated with a less favorable result. Finally, after one failed I and D, the surgeon should be very cautious about repeating the procedure, unless a structured and aggressive protocol incorporating serial I and Ds within a short time interval is applied.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Surgical treatment of Lenke 5 adolescent idiopathic scoliosis: Comparison of anterior *vs* posterior approach

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Abstract

AIM

To compare the posterior *vs* anterior approaches for fusion of Lenke 5 adolescent idiopathic scoliosis curves, matched for curve magnitude and for the distal level of fixation (dLOF) standardized to the third lumbar vertebrae (L3).

METHODS

A prospectively collected multicenter database was used for this retrospective comparative study. Our dependent variables included sagittal and coronal radiographic measurements, number of fused vertebrae, estimated blood loss, length of hospitalization and SRS total and individual domain scores at the two-year follow-up. Subject demographics were similar for all group comparisons. Independent *t*-test was used to compare groups for all analyses at $P < 0.01$.

RESULTS

For all matched cases of Lenke 5 curves, a selective approach was used only 50% of the time in cases undergoing a posterior fusion. When comparing a posterior selective approach to an anterior selective approach, surgeons utilizing a posterior approach fused significantly more levels than surgeons using an anterior approach with no other significant differences in radiographic or SRS outcomes (Ant = 4.8 ± 1.0 levels *vs* post = 6.1 ± 1.0 levels, $P < 0.0001$). When the dLOF was standardized to L3, the anterior approached provided significantly greater lumbar Cobb percent correction than the posterior approach (Ant = 69.1% ± 12.6% *vs* post = 54.6% ± 16.4%, $P = 0.004$), with no other significant radiographic or SRS score differences between approaches.

CONCLUSION
Surgeons treating Lenke 5c curves with a posterior instrumentation and fusion *vs* an anterior approach include more motion segments, even with a selective fusion. When controlled for the distal level of fixation, the anterior approach provides greater correction of the thoracolumbar curve.

Key words: Instrumentation; Thoracolumbar curve; Selective fusion

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Core tip: A multicenter database was analyzed to determine the frequency that surgeons performed a selective fusion of the thoracolumbar (TL)/lumbar curve in adolescent idiopathic scoliosis patients with Lenke 5c curves. We found that surgeons treating Lenke 5c curves will include more motion segments when employing a posterior approach. When controlled for the distal level of fixation, the anterior approach provides greater correction of the TL curve.

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INTRODUCTION

Lenke 5 curves are the third most common adolescent idiopathic scoliosis (AIS) curve type[1]. These curves are characterized by a single structural curve in lumbar/thoracolumbar region with non-structural curves (defined as bending to a Cobb angle of less than 25°) in thoracic and low lumbar (lumbosacral) regions of the spine. Common surgical treatment of Lenke 5c curves involves selective fusion (where the proximal level of fixation is distal to the thoracic apex) of the thoracolumbar curve[1] with the expectation that the non-structural thoracic curve will spontaneously correct[1-4]. There appears to be good literature support for selective fusion of thoracolumbar curves[2,4-6]. Ilgenfritz *et al*[4] studied 21 patients undergoing selective fusion of Lenke 5 curves and identified a spontaneous correction of the uninstrumented thoracic curves of 42% at 1 year. Thirty percent was the correction maintained at five years follow-up[4]. These authors and others felt that extension of fusion to include thoracic spine provided no significant advantages[7]. However, there appears to be a state of equipoise in the literature as to whether an anterior or posterior surgical approach is best suited for the selective fusion of Lenke 5 curves.

The anterior approach was initially popularized by Allen Dwyer *et al*[8] and became increasingly popular with advancements in anterior instrumentation[9-11]. The anterior thoracoabdominal approach was reported to be highly efficacious at improving clinical and radiographic measurements of trunk rotation[10,12]. One important potential advantage of anterior approach was the possibility that surgeons could obtain equal or better correction with shorter fusion constructs and consequently preserve more spinal motion[12-17].

The posterior approach, however, is more familiar to spine surgeons and the growing popularity of pedicle screws constructs for posterior spinal segmental instrumentation provided a very viable alternate to anterior approach[18]. Additionally, widespread use of osteotomies[3] has resulted in better coronal and axial correction[19-25]. Geck *et al*[23] compared Lenke 5 AIS correction in 31 patients with posterior pedicle screw instrumented fusion to an equal number of patients undergoing anterior instrumented fusion. The authors[23] reported significantly better curve correction, less loss of correction over time, and shorter hospital stays with the posterior approach. However, this data represented an AIS cohort that underwent an anterior instrumented fusion from a single institution in comparison to an AIS cohort that underwent a posterior pedicle screw instrumented fusion from a different institution, which makes it difficult to know if differences in blood loss, length of hospitalization, and magnitude of correction are due to differences in surgeon skill or management protocols. Bennett *et al*[20] reported maintenance of correction with posterior spinal fusion at five years follow-up for a heterogeneous group of Lenke 3c, 5c, and 6c curve types. However, these results cannot be generalized to Lenke 5 curves, as a systematic review by Helenius[26] suggests that the most appropriate use of the anterior approach is for Lenke 5 curves with a distal level of fixation (dLOF) at third lumbar vertebrae (L3). Evidence suggests that dLOF is significantly correlated with 2-year correction and balance after spinal fusion for Lenke 5 curves[27], however, previous studies have note matched anterior *vs* posterior cases by dLOF.

To effectively compare these two different approaches in regards to the magnitude of correction, the preservation of motion segments, and patient oriented outcomes for Lenke 5 AIS curves, data is required from multiple surgeons (multi-centered study) with careful regard to match cases according to curve magnitude while standardizing the dLOF at L3. Therefore, our purpose was to compare the posterior *vs* anterior approaches for the instrumentation and fusion of Lenke 5 AIS curve types for cases that were matched by curve magnitude, to compare cases where surgeons used a selective posterior approach (where the proximal level of fixation was distal to the thoracic apex) *vs* anterior cases and to compare selective posterior cases to anterior cases where the dLOF was standardized to the L3. We hypothesized that the anterior approach would result in fewer vertebrae fused and would provide better or comparable correction of radiographic curve parameters when the dLOF was standardized to L3.

MATERIALS AND METHODS

Study design

A prospectively collected multicenter database was used for this cohort study and was queried for all surgically treated Lenke 5c patients. Institutional review board approval for the study was obtained locally from each contributing center and consent was obtained from each patient prior to data collection.

Outcome measures

Radiographic and clinical measurements were recorded pre-operatively and at 2 years after surgery. Our dependent variables were thoracic and lumbar Cobb percent correction, lumbosacral take-off angle (LSTOA) (Figure 1), percent correction, absolute change in thoracolumbar (Th-L) apical translation, change in disc angulation below dLOF, change in proximal junctional kyphosis, change in kyphosis (from T5-T12 and from T10-L2), change in lumbar lordosis (T12 to top of the sacrum), number of fused vertebrae, estimated blood loss, length of hospitalization and SRS total and individual domain scores.

Subjects

Patients with Lenke type 5c deformity were included in the analysis if their curve was corrected by either anterior or posterior spinal fusion. Eighty cases (40 anterior and 40 posterior) were identified and matched according to curve magnitude (Table 1). The surgical approach (anterior *vs* posterior), as well as the surgical levels fused, were decided by the operating surgeon.

To compare anterior *vs* posterior surgical approaches, three separate analyses were performed. The first analysis was to compare all matched cases of anterior *vs* posterior approaches (anterior $n = 40$, posterior $n = 40$). The second analysis compared cases where surgeons used a selective posterior approach (meaning the proximal point of fixation was below the apical vertebra of the thoracic cure) *vs* selective anterior approaches (anterior selective $n = 39$, posterior selective $n = 20$). The third analysis was to compare selective posterior cases to selective anterior cases where the dLOF was standardized to the L3 (anterior L3 $n = 25$, posterior L3 $n = 14$) (Figure 1).

Statistical analysis

Independent *t*-tests were used to compare anterior and posterior cases for all outcome measures. Our alpha level was conservatively set a priori at 0.01 to control for multiple comparisons. Cohen's d effect sizes and associated 95%CIs were calculated for our third analysis (dLOF = L3) to estimate the magnitude and precision of the group differences. Clinical interpretation of effect sizes was performed as > 0.80 was a large effect, 0.50 to 0.79 was a moderate effect, 0.20 to 0.49 was a small effect, and < 0.20 was a trivial effect. Data was analyzed using Statistical Package for Social Sciences (SPSS) Version 20.0 (SPSS, Inc, Chicago, IL).

LSTOA reliability

The angulation of the low lumbar segments (L4 and L5) from the sacrum on the standing film was felt to be an important determinant of coronal plane balance[28]. Thus the LSTOA[29], defined from the standing spinal radiograph as the angle between the best-fit line between the spinous processes of L4, L5 and S1 and the vertical, was a radiographic measure developed to assess the influence of instrumentation and fusion on the coronal balance (Figure 2). Four raters of varying experience levels measured pre-operative and 2-year post-operative radiographs for 10 patients on two occasions. Pre-operative and post-operative measurements were separated by at least 24 h and raters were blinded to the first set of measurements during the second measurement occasion. All raters used the same software and all were blinded to one another's measurements until data collection was complete. The reliability of the LSTOA measurement was considered "good" with an intraclass correlation coefficient of 0.829 and Cronbach's alpha value of 0.975.

RESULTS

Demographics and baseline group comparisons

There were no differences in patient demographics for age, height, mass and sex distribution (Ant = 15.1 ± 2.0 years, 163.3 ± 9.6 cm, 56.9 ± 12.1 kg, 8M:32F *vs* post = 15.4 ± 2.0 years, 159.6 ± 20.2 cm, 59.5 ± 14.1 kg, 6M:34F, $P > 0.01$ for all analyses). There were no significant differences between anterior and posterior cohorts for all cases (anterior $n = 40$, posterior $n = 40$, $P > 0.01$ for all analyses), selective fusions (anterior selective $n = 39$, posterior selective $n = 20$, $P > 0.01$ for all analyses), or selective fusions where dLOF was standardized to L3 (anterior L3 $n = 25$, posterior L3 $n = 14$, $P > 0.01$ for all analyses, Table 1).

All matched cases (anterior n = 40, posterior n = 40)

The anterior approach resulted in a significantly less number of fused vertebrae (Ant = 4.9 ± 1.1 *vs* post = 9.0 ± 3.3, $P < 0.0001$). At 2 years follow-up the radiographic correction, estimated blood loss, length of hospitalization and patient reported SRS scores were noted to be similar for both surgical approaches ($P > 0.01$ for all analyses) (Tables 2 and 3).

Selective posterior fusions vs selective anterior fusions (Ant = 39, post = 20)

There were significantly fewer vertebrae included in the fusion construct when surgeons utilized an anterior approach (Ant = 4.8 ± 1.0 *vs* post = 6.1 ± 1.0, $P < 0.0001$). No significant differences were noted between anterior and posterior approaches for measures of radiographic curve parameters, estimated blood loss, length of hospitalization, or SRS scores ($P > 0.01$ for all analyses) (Tables 2 and 3). Representative examples

Table 1 Pre-operative radiographic and self-reported data for anterior and posterior thoraco-lumbar approaches for all cases, selective fusion, and selective fusions where distal level of fixation was the third lumbar vertebra for Lenke 5 curves

	All cases Mean (SD)			Selective fusions only Mean (SD)			Selective fusions where dLOF = L3 Mean (SD)		
	Ant (n = 40)	Post (n = 40)	P-value	Ant (n = 39)	Post (n = 20)	P-value	Ant (n = 25)	Post (n = 14)	P-value
Thoracic Cobb	28.7 (7.2)	29.2 (8.0)	0.759	28.3 (6.7)	26.8 (5.7)	0.395	27.6 (5.9)	25.6 (5.5)	0.313
Lumbar Cobb	46.9 (6.7)	47.1 (6.6)	0.880	46.8 (6.7)	48.0 (6.8)	0.0527	47.5 (7.1)	46.6 (6.8)	0.687
LSTOA	15.8 (4.7)	17.0 (5.7)	0.342	15.7 (4.8)	18.3 (6.3)	0.086	15.8 (4.8)	16.3 (4.8)	0.762
Thoracolumbar apical translation (centimeters)	5.0 (1.6)	5.4 (1.5)	0.241	5.0 (1.6)	5.6 (1.7)	0.214	5.2 (1.7)	5.5 (1.3)	0.521
Disc angulation below dLOF (degrees)	0.7 (6.2)	1.9 (5.4)	0.351	0.8 (6.2)	2.3 (5.4)	0.372	2.8 (6.3)	0.4 (4.5)	0.220
Proximal junctional kyphosis (degrees)	4.1 (5.7)	4.7 (4.6)	0.607	4.0 (5.8)	3.2 (2.6)	0.522	4.2 (6.4)	3.2 (2.7)	0.573
Kyphosis from T5-T12 (degrees)	25.7 (10.4)	24.8 (10.0)	0.719	25.7 (10.5)	24.9 (10.2)	0.756	24.4 (10.9)	25.6 (11.1)	0.743
Kyphosis from T10-L2 (degrees)	5.6 (11.3)	3.8 (8.7)	0.437	6.1 (11.0)	7.5 (7.5)	0.622	8.0 (11.7)	5.9 (7.2)	0.547
Lordosis from T12-top of Sacrum (degrees)	60.0 (12.2)	57.4 (10.8)	0.324	60.1 (12.3)	55.7 (11.5)	0.196	57.8 (12.9)	58.9 (8.0)	0.791
SRS (total)	3.9 (0.5)	4.0 (0.3)	0.463	3.9 (0.5)	4.1 (0.3)	0.371	3.9 (0.4)	4.1 (0.3)	0.305
SRS (self)	3.8 (0.7)	3.7 (0.6)	0.367	3.8 (0.7)	3.5 (0.6)	0.335	3.8 (0.5)	3.5 (0.6)	0.282
SRS (pain)	3.7 (0.7)	3.9 (0.6)	0.269	3.6 (0.7)	4.0 (0.4)	0.139	3.6 (0.6)	4.0 (0.4)	0.087
SRS (function)	4.0 (0.6)	4.1 (0.4)	0.469	4.1 (0.6)	4.2 (0.5)	0.392	4.2 (0.4)	4.2 (0.5)	0.691
SRS (activity)	4.5 (0.7)	4.6 (0.5)	0.576	4.5 (0.7)	4.6 (0.6)	0.572	4.5 (0.5)	4.6 (0.6)	0.496

LSTOA: Lumbo-sacral take-off angle; dLOF: Distal level of fixation; T: Thoracic; L: Lumbar; SD: Standard deviation.

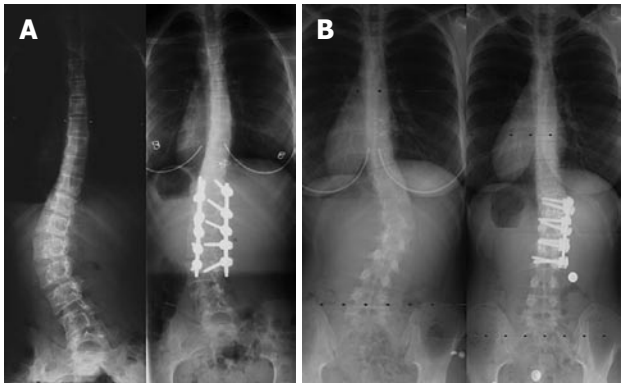

Figure 1 Representative examples for selective posterior (A) and selective anterior (B) spinal fusion.

for selective anterior and posterior approaches are presented in Figure 1.

Selective posterior vs anterior fusions where dLOF = L3 (Ant L3 n = 25, post L3 n = 14)

The anterior approach resulted in a significantly greater lumbar Cobb percent correction (Ant = 69.1% ± 12.6% *vs* post 54.6% ± 16.4%, P = 0.004). No significant differences were noted between anterior and posterior approaches for number of fused vertebrae, radiographic curve parameters, estimated blood loss, length of hospitalization, or SRS scores (P > 0.01 for all analyses) (Tables 2 and 3). We identified large effect sizes in favor of the anterior approach for number of fused vertebrae and lumbar Cobb percent correction. We also identified moderate effect sizes in favor of the anterior approach for LSTOA percent correction, absolute change in Th-L apical translation, and change in disc angulation below the dLOF (L3). All other effect sizes were trivial or small with 95% confidence intervals that were centered around zero, suggesting no meaningful treatment effects for those outcome measures (Figure 3).

DISCUSSION

A primary goal of spinal fusion for idiopathic scoliosis is to maximize correction, while preserving as many motion segments as possible[4]. Lenke 5 curves are unique in having a thoracolumbar or lumbar curve as the dominant curve in association with a flexible, non-structural thoracic curve, which is expected to spontaneously correct with a selective fusion. We have now provided evidence that for matched Lenke 5 cases and for cases where a selective fusion is performed with similar baseline curve parameters, surgeons performing a posterior approach will include more motion segments in the fusion construct when compared to those performing an anterior approach. In our analyses, including more motion segments did not improve radiographic or patient oriented outcomes[30]. These findings are particularly important in the context of current evidence highlighting significant reductions in sagittal, coronal, and transverse planes of motion following instrumented spinal fusion[31]. Furthermore, their results suggest that the more distal the fusion construct goes, the greater reductions in forward flexion post-operatively[31,32], which underscores the importance of standardizing to the dLOF. Surgeons should continue to rigorously evaluate surgical approaches in clearly defined cohorts to elucidate potential options for maximizing curve correction while maintaining spinal mobility. To our knowledge, this is the first study to

Table 2 Independent *t*-test statistical results for surgical outcomes associated with anterior *vs* posterior thoraco-lumbar approaches for all cases, selective fusions, and selective fusions where distal level of fixation was the third lumbar vertebra for Lenke 5 curves

	All cases Mean (SD)			Selective fusions only Mean (SD)			Selective fusions where dLOF = L3 Mean (SD)		
	Ant (n = 40)	Post (n = 40)	P-value	Ant (n = 39)	Post (n = 20)	P-value	Ant (n = 25)	Post (n = 14)	P-value
Thoracic Cobb percent correction	36.7 (23.2)	48.1 (24.3)	0.036	35.9 (22.9)	35 (20.2)	0.890	40.5 (24.6)	37.9 (17.7)	0.732
Lumbar Cobb percent correction	64.5 (14.7)	63.4 (17.0)	0.764	64.7 (14.9)	58.2 (17.1)	0.135	69.1 (12.6)	54.6 (16.4)	0.004[1]
LSTOA percent correction	46.6 (17.0)	44.9 (21.6)	0.688	46.9 (17.2)	46.2 (21.7)	0.900	48.8 (15.6)	37.7 (19.4)	0.058
Absolute change in thoracolumbar apical translation (centimeters)	3.6 (1.4)	3.2 (1.6)	0.293	3.6 (1.4)	3.5 (1.7)	0.669	3.9 (1.4)	3.2 (1.4)	0.157
Change in disc angulation below dLOF (degrees)	5.2 (9.5)	5.8 (5.0)	0.702	5.1 (9.6)	6.0 (5.7)	0.685	9.0 (7.9)	5.1 (5.7)	0.116
Change in proximal junctional Kyphosis (degrees)	3 (5.2)	4.4 (6.1)	0.253	2.7 (5.0)	2.7 (3.8)	0.989	2.7 (5.7)	3.1 (3.7)	0.806
Change in Kyphosis from T5-T12 (degrees)	-2.4 (9.7)	0.2 (10.3)	0.253	-2.3 (9.8)	-4.4 (8.4)	0.424	-3.5 (10.9)	-5.0 (8.2)	0.652
Change in Kyphosis from T10-L2 (degrees)	24.2 (158.1)	9.6 (8.2)	0.562	25.1 (160.1)	12.4 (8.0)	0.725	39.8 (199.7)	11.2 (8.0)	0.597
Change in Lordosis from T12-Top of sacrum (degrees)	25.0 (148.6)	-1.8 (11.6)	0.261	25.9 (150.5)	-6.0 (10.8)	0.350	39.1 (187.9)	-3.3 (11.0)	0.407
No. of fused vertebrae	4.9 (1.1)	9.0 (3.3)	< 0.001[1]	4.8 (1.0)	6.1 (1.0)	< 0.001[1]	5.1 (0.8)	5.8 (1.0)	0.025
Estimated blood loss (mL)	463 (327)	985 (1046)	0.003[1]	457 (329)	396 (166)	0.441	526 (381)	380 (168)	0.185
Length of hospitalization (d)	5.8 (1.5)	6.0 (1.4)	0.593	5.7 (1.4)	5.8 (1.0)	0.926	6.0 (1.2)	5.6 (1.2)	0.378

[1]Denotes significant difference at $P < 0.01$. LSTOA: Lumbo-sacral take-off angle; dLOF: Distal level of fixation; T: Thoracic; L: Lumbar; SD: Standard deviation.

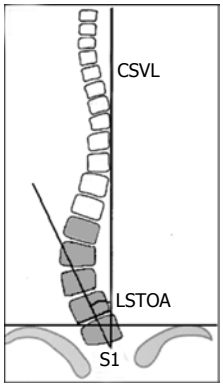

Figure 2 Lumbo-sacral take off angle. LSTOA: Lumbosacral take-off angle; CSVL: Central sacral Vertical Line.

compare selective instrumentation and fusion of matched Lenke 5c curves using either a posterior approach *vs* an anterior approach with the dLOF standardized (as recommended)[26] to the third lumbar level.

In our first analysis, we found that surgeons using a posterior approach to the Lenke 5c deformity included more levels in the instrumentation for comparable curves. This is not a surprising finding given that extension of the posterior exposure and instrumentation is technically easier since the anterior extension requires retraction of the lung, incision of the parietal pleura and control of the segmental vessels proximally or control and mobilization of iliac vessels distally. It should be acknowledged, however, that the relative benefit of complete correction of deformity *vs* the functional loss from fusing more segments has not been fully elucidated. The tendency to fuse more vertebrae with the posterior approach was also demonstrated in our second analysis of selective posterior *vs* selective anterior cases, yet there was no evidence of superior correction with the posterior approach. Interestingly, half (20 of 40 cases) of our original matched posterior cases were not selective spinal fusions, whereas only 1 of the matched anterior cases had a fusion construct that encompassed the thoracic apex. This finding further illustrates the likelihood of surgeons utilizing a posterior approach to include proximal segments that may or may not be required to improve spinal alignment of the thoracic spine. However, we did identify that surgeons that elected to use a selective posterior fusion fused 5-6 fewer levels than those that utilized a non-selective posterior approach. Finally, when the dLOF was standardized in both groups to L3, the anterior approach provides about a 15% greater correction of the lumbar curve. We also identified moderate to large effect sizes in favor of the anterior approach for outcome measures including number of fused vertebrae, lumbar Cobb percent correction, LSTOA percent correction, absolute change in Th-L apical translation, and change in disc angulation below the dLOF (L3). While the clinical importance of differences of this magnitude is not clearly documented, our results illustrate the potential to maximize post-operative spinal motion with equal or greater radiographic correction with an anterior spinal fusion.

Historically, the anterior approach was considered the preferred approach because of its ability to provide

Table 3 Independent *t*-test statistical results for SRS outcomes associated with anterior *vs* posterior thoraco-lumbar approaches for all cases, selective fusions, and selective fusions where distal level of fixation was the third lumbar vertebra for Lenke 5 curves

	All cases Mean (SD)			Selective fusions only Mean (SD)			Selective fusions where dLOF = L3 Mean (SD)		
	Ant (n = 40)	Post (n = 40)	P-value	Ant (n = 39)	Post (n = 20)	P-value	Ant (n = 25)	Post (n = 14)	P-value
Change in SRS (total)	0.15 (0.54)	0.12 (0.53)	0.848	0.19 (0.52)	0.21 (0.31)	0.931	0.14 (0.44)	0.18 (0.32)	0.811
Change in SRS (self)	-0.54 (0.87)	-0.25 (0.93)	0.262	-0.47 (0.83)	-0.14 (0.81)	0.258	-0.40 (0.37)	-0.27 (0.84)	0.632
Change in SRS (pain)	0.49 (0.70)	0.45 (0.83)	0.860	0.55 (0.66)	0.38 (0.56)	0.456	0.48 (0.71)	0.25 (0.53)	0.399
Change in SRS (function)	0.12 (0.66)	-0.09 (0.65)	0.259	0.11 (0.67)	0.05 (0.37)	0.747	-0.03 (0.50)	0.06 (0.42)	0.653
Change in SRS (activity)	0.14 (0.50)	0.06 (0.58)	0.640	0.14 (0.51)	0.17 (0.61)	0.904	0.14 (0.56)	0.21 (0.64)	0.774

T: Thoracic; L: Lumbar; SD: Standard deviation; dLOF: Distal level of fixation.

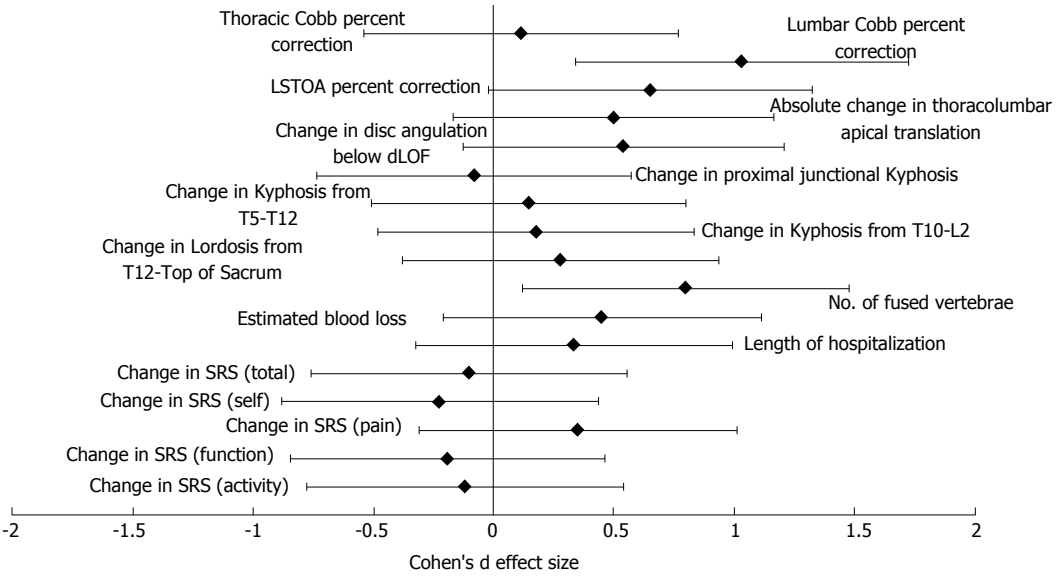

Figure 3 Cohen's d effect sizes and 95%CI for anterior *vs* posterior approach for Lenke 5 adolescent idiopathic scoliosis curves where distal level of fixation is standardized to L3. LSTOA: Lumbo-sacral take-off angle; dLOF: Distal level of fixation; T: Thoracic; L: Lumbar.

excellent coronal curve correction with significant spine derotation and shorter fusion constructs[5-9]. Tao *et al*[14] reported superiority of anterior solid rod-screw instrumentation with shorter fusion segments, better sagittal alignment and quality of life measures (SRS scores) than posterior pedicle screw instrumentation. However, trunk scarring, spine pseudoarthrosis, negative impacts on pulmonary function and reduction of lumbar lordosis were reported to be major disadvantages of the anterior approach[24]. More recent studies with newer techniques and implant designs have reported no significant post-operative kyphosis[12] or pulmonary function changes[33] with the anterior thoracoabdominal approach. Our results are consistent with the recent studies in that there were no differences in patient oriented outcomes as reported on the SRS questionnaires or in EBL or length of hospitalization between anterior or posterior approaches for any of our three analyses.

This study has several limitations. Matching was based on radiographic measures but surgeons may have chosen the surgical approach based on the clinical appearance, extending the fusion to include the thoracic vertebra in cases with a more pronounce right scapular prominence. The sagittal plane alignment of either the lumbar and thoracic curves can also influence the decision on the surgical approach. For instance, increased lumbar kyphosis, excessive thoracic kyphosis or thoracic hyper-lordosis, may prompt the surgeon to use a posterior approach for instrumentation to affect sagittal plane correction and this was not analyzed. An argument could also be made that the magnitude of difference between these two approaches is not meaningful to the patient, as we did not identify significant differences in our SRS outcomes or length of hospitalization between approaches. The relative benefits of complete correction of deformity *vs* the functional lose from fusing more segments has not been objectively studied. However, until we have more objective data on the functional implications of longer fusions or the rate of adjacent level degeneration, we cannot strongly advise an anterior TL approach for the Lenke 5C curve. Given the above considerations, our results do suggest that an anterior approach may be advantageous for severe or rigid deformity where the desired dLOF is the third lumbar level (Figure 1), as it can provide better correction for same levels of fusion with no deleterious effects on patient reported outcomes.

In conclusion, surgeons treating Lenke 5c curves

will include more motion segments when employing a posterior approach; when controlled for the dLOF, the anterior approach provides greater correction of the TL curve.

COMMENTS

Background

Lenke 5 scoliosis can be surgically corrected by either anterior or posterior approach. The purpose of this study purpose was to compare the posterior *vs* anterior approaches for fusion of Lenke 5 adolescent idiopathic scoliosis curves.

Research frontiers

Posterior approach is more popular nowadays because of its ease and universal application. Anterior approach is generating interest again because of its ability to provide excellent coronal curve correction and significant spine derotation with relatively shorter fusion constructs. The current research is also focused on saving fusion levels, which may prove to be an important factor in the long term.

Innovations and breakthroughs

To our knowledge, this is the first study to compare selective instrumentation and fusion of matched Lenke 5c curves with the distal level of fixation (dLOF) standardized to the third lumbar level, in addition to overall surgical outcome of anterior *vs* posterior approaches.

Applications

This study suggests a tendency to fuse more levels with posterior approach for treating Lenke 5c curves and that the anterior approach provides greater correction for similar distal level of fusion. These findings may provide important guidelines with regards to surgical approach if surgeon prefers shorter fusion levels for deformity correction.

Terminology

Distal level of fixation - dLOF.

Peer-review

Interesting paper that compares two different approaches for surgical correction of Lenke 5c scolisois by selective fusion.

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ORIGINAL ARTICLE

Observational Study

Attitudes and diagnostic practice in low back pain: A qualitative study amongst Greek and British physiotherapists

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Abstract

AIM

To explore current diagnostic practice and attitudes of Greek and United Kingdom physiotherapists (PTs) on assessing low back pain (LBP) patients.

METHODS

Three focus groups were undertaken, followed by a structured questionnaire-type survey comprising 23 health professionals and a random stratified sample of 150 PTs, respectively. Twenty-nine themes relating to LBP diagnostic practice emerged. These were then given to 30 British PTs assessing their level of

agreement with their Greek counterparts. Analysis was performed by percentage agreements and χ^2 tests.

RESULTS

The survey was divided into three subsections; PTs' attitudes on LBP assessment, patients' attitudes and diagnostic/healthcare issues, each constituting 14, 7 and 8 statements, respectively. Over half of the statements fell within the 30%-80% agreement between Greece and United Kingdom whereas, 5 statements reported low (< 10%) and 8 statements demonstrated high (> 90%) PT percentage agreement. Similarities across British and Greek PTs were detected in history taking methods and in the way PTs feel patients perceive physiotherapy practice whereas, re-assessment was undertaken less frequently in Greece. Diagnosis according to 91% of the Greek PTs is considered a "privilege" which is exclusive for doctors in Greece (only 17% British PTs agreed) and is accompanied with a great overuse of medical investigations. Forty percent of Greek PTs (compared to 0% of British) consider themselves as "executers", being unable to interfere with treatment plan, possibly implying lack of autonomy.

CONCLUSION

Although similarities on history taking methods and on patients' attitudes were detected across both groups, gross differences were found in re-assessment procedures and diagnostic issues between Greek and British physiotherapists, highlighting differences in service delivery and professional autonomy.

Key words: Diagnostic practice; Low back pain; United Kingdom; Greek; Physiotherapists

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Core tip: This small-scale observational study explored commonalities and differences in low back pain (LBP) perspectives and diagnostic practice between Greek and British physiotherapists (PTs). There was agreement on clinical examination features for targeting treatment; indicating that LBP is a clinical entity whose clinical "expressions" amongst PTs and patients are common across different cultural groups. The differences detected particularly referred to diagnostic issues (*i.e.*, overuse of medical investigations/radiography, *etc.*), reflecting differences in medical and physiotherapy services delivery. Such comparisons contribute to the understanding of the course and/or management of LBP across the two countries.

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INTRODUCTION

Low back pain (LBP) is a highly prevalent problem both within the Greek and British cultural settings, notorious for causing debilitating, economic, psychosocial, and behavioural problems. Within Greece, it is considered ninth in the list of the most common reasons requiring hospital admission[1], first in the list of orthopaedic conditions being encountered in an emergency department[2]. LBP also seems to be the most common musculoskeletal problem amongst the Greek general[3-5] and occupational populations[6-10]; with point and annual prevalence rates ranging between 11%-31.7% amongst adults[3,4]. High prevalence rates are also seen across the general population within Great Britain; point and one-month prevalence rates are estimated between 19%-21% whereas, annual and lifetime prevalence rates range between 29%-43% and 58%-64%, respectively[11-15]. Thus, it is evident that in both countries, LBP is a widespread public health problem, often leading to chronicity as well as disability[4,5,11,16,17].

In terms of the healthcare seeking patterns, one of the first-line health professionals involved in the management of LBP within Greece[7,8], Britain[11,18], as well as internationally[19,20] are physiotherapists (PTs)[2,8,11,13,21,22]. Subsequently, research has turned towards exploring a number of issues dealing with the assessment and treatment aspects of healthcare practice and practitioners, to improve patient care and outcomes.

Clinicians perform a thorough assessment and develop their clinical hypothesis, in order to formulate an objective clinical diagnosis for their patient and determine their intervention plan[23]. However, it has been suggested that their attitudes and beliefs towards assessment issues influence their clinical diagnosis and subsequent treatment decisions. Fullen *et al*[24-26] in a series of studies and systematic reviews explored the factors that impact on doctors' management of LBP patients; they found that, amongst other things, clinicians' attitudes and beliefs influence their management approach. Perreault and Dionne have found discrepancies between PTs' and patients' perceptions of LBP experience, which have been partly attributed to the PTs' attitudes and beliefs regarding pain-related issues[27]. Similar findings were reported in other studies too, relating attitudes and beliefs of a range of health professionals (including PT), to their assessment and treatment strategies for LBP patients[28,29]. Therefore, it appears that, health professionals' attitudes and beliefs are associated to their diagnostic and management practice.

It has been suggested that cultural differences amongst healthcare professionals tend to "shape" particular attitudes, beliefs and perspectives, which subsequently affect the patients' overall management approach. For example, whilst in some European countries such as Great Britain[30] and the Netherlands[31], radiography (X-ray) utilisation was found to be in accordance with current guideline practice, diagnostic

imaging has been reported to be overprescribed across a number of other countries such as Italy[32], Belgium[33], Norway[34], Canada[35], Brazil[36] and the United States[37], thus, highlighting cross-cultural health professionals' differences in LBP diagnostic practice regarding X-ray utilisation.

Skelton *et al*[38] investigated the perceptions of British general practitioners (GPs) regarding their LBP patients, and found that the GPs perception of their patient's psychological constitution, occupation and social class were found to be important factors in determining their clinical approach and behaviour. In another British survey, the attitudes and beliefs of GPs and PTs regarding LBP were explored[30]. A considerable proportion of the health professionals adopted a biomedical (rather than biopsychosocial) approach in their diagnostic practice, thus, taking into account only the pathologic and physical processes of the LBP problem but not the social or psychological influences. Similar conclusions were yielded by a French study exploring the fear-avoidance beliefs of a large GP sample[39]. Fear-avoidance beliefs, which are believed to play a role in chronic disability, are related to pain-related interpretations that activity will cause injury and eventually exacerbate pain. In this study[39], high levels of fear-avoidance beliefs were reported amongst French GPs, which impacted in the recommendations given to patients regarding physical activity and work. Thus, based on the above, there is evidence that health professionals' diagnostic behaviours and management approaches are not exclusively attributed to medical factors but are also influenced by cultural factors and individual perspectives[40].

There is limited research investigating PTs' attitudes and beliefs on LBP assessment and "diagnostic" issues within a number of cultural settings, including the Greek and British ones. Thus, issues linking PTs' perspectives, attitudes, and behaviours to diagnostic practice across the two settings merited further investigation. The aim of this study was to compare current diagnostic practice and attitudes of Greek and British physiotherapists when assessing and treating LBP patients.

MATERIALS AND METHODS

The study was divided into three parts. In the first component, as part of an study described elsewhere[41], a list of issues relating to current diagnostic practice and attitudes of clinicians on LBP assessment within Greece were developed following three focus groups involving 23 health professionals (18 PTs and 5 doctors). In the second component, the issues raised by the PTs (from the focus groups) were given to a wider PT sample in a questionnaire format (Delphi-type survey), to assess their level of agreement with each statement. In the last part, these items were also given to a British PT sample, to assess their level of agreement. Ethical approval was obtained from the Ethical Committees of Technological Educational Institute of Lamia, Greece and University of Manchester, United Kingdom.

Sample

Greek participants, consisted of Greek PTs, randomly selected from data obtained by the Panhellenic Physiotherapy Association (PPA), the official body representing chartered PTs in Greece. Out of the approximately 1500 registered members at the time of the study, 10% (150 PTs) was invited to participate. The sample was further stratified according to geographical location and work status, to obtain greater representation. For geographical location, Greece was divided into 7 areas; 2 urban, representing the 2 biggest cities (Athens and Thessaloniki), and 5 rural ones (North, South, Central, East and West of Greece). For work status, PTs were stratified according to private or public sector, as PPA data revealed a disproportionately high percentage of PTs working in the private compared to the public sector.

The British sample was a convenience sample consisting of 30 Chartered PTs working in the private or public sector, who were at the time involved in another study[42].

Procedure

Overall, 29 statements were collected from the PTs' focus groups, divided into three sections; PTs' attitudes, patients' attitudes and health/diagnostic issues. Generating data by other qualitative means for developing a structured questionnaire is an acceptable, recommended and commonly used method[43-45]. The items were collated into a single list and transformed into a structured questionnaire with 5-point Likert scale answers ("Strongly Agree", "Agree", "Neither Agree or Disagree", "Disagree", "Strongly Disagree"), where PTs were requested to vote on their agreement. For the Greek questionnaire, all questions/statements were reviewed by 2 native (Greek) researchers for clarity and objectivity. Overall, 150 questionnaires were posted to all PTs including the informed consent and a demographic information sheet. For the British questionnaire, each statement was transcribed into the English language by the principal investigator and two native (English) speakers reviewed the questionnaire for grammar, syntax, clarity and comprehensibility. Questionnaires were administered electronically, as electronic surveying is an acceptable and popular method of collecting data across the musculoskeletal field[46-48]. A consent form and a demographic information sheet were also provided.

Additional space was also allocated for further comments in both questionnaires; however, no additional comments were made. Three to five weeks were given for the PTs' replies prior to sending a reminder.

Data analysis

The questionnaires were analysed utilizing percentage agreements for each scored item, utilising SPSS (Version 11.5). Percentage agreement was calculated by utilising the two agreement options ("Strongly Agree" and "Agree") from the Likert scale. The χ^2 test was used to determine associations between Greek and British PTs' as well as differences between survey's responses.

Table 1 Physiotherapists' profile

Characteristics	Greek PTs (n = 125) [% (n)]	British PTs (n = 29) [% (n)]	P value (χ^2 test)
Sex			
Male	57.6 (72)	24.1 (7)	0.053
Female	39.2 (49)	51.7 (15)	
Missing data/not reported	3.2 (4)	24.1 (7)	
LBP clinical experience (yr)			
< 1	3.2 (4)	3.4 (1)	0.002[1]
1-5	28 (35)	3.4 (1)	
6-10	28 (35)	24.1 (7)	
> 11	40.8 (51)	65.2 (19)	
Type of work			
NHS based	35.2 (44)	75.8 (22)	0.671
Private practitioner	49.6 (62)	6.8 (2)	
Community work (private)	10.4 (13)	3.4 (1)	
Other (educational, *etc.*)	4.8 (6)	6.8 (2)	

[1]χ^2 test is statistically significant at the 0.05 level. PTs: Physiotherapists; LBP: Low back pain; NHS: National Health Service.

RESULTS

Overall, 125 Greek and 29 British questionnaires were returned (response rates of 83.3% and 96.6%, respectively). For the Greek PTs, all geographical areas were represented entailing the following number of PTs: For Athens 55 (44%), Thessaloniki 15 (12%), South 10 (8%), North 8 (6.4%), Central 15 (12%), East 11 (8.8%) and West of Greece 10 (8%). Over half of the sample (60%) was working in the private sector compared to 35.2% who were based within a NHS establishment. Over half of the sample (57.6%) was males, and the majority had more than 6 years of clinical experience with LBP patients (68.8%). Most of the convenience British sample had more than 6 years of LBP clinical experience (89.3%) and were NHS-based PTs (75.8%). χ^2 tests across the two PT groups on sex and type of work yielded non-statistically significant results (P > 0.05), indicating similarities (on these variables) across the samples between the two groups, whereas statistically significant differences (P = 0.002) were yielded for clinical experience. The sample's profile is illustrated in Table 1.

The questionnaire consisted of 29 statements which were divided into three subsections (PTs' attitudes, patients' attitudes and diagnostic/healthcare issues), each constituting 14, 7 and 8 statements, respectively. Over half of the statements fell within the 30% to 80% range. Five statements (all from the British PTs) reported low (below 10%) percentage agreement (small history taking, not taking into account psychosocial factors, lack of emphasis in undergraduate assessment, overuse of medical investigations, PTs are "executers", *etc.*).

Whereas, eight statements (5 from Greek and 3 from British PTs) demonstrated agreement for over 90% of the PTs; history guides assessment and paying attention to the medical diagnosis (British PTs), detailed history taking (both groups), alteration of examination for acute/chronic patients, diagnosis as a medical privilege, diagnosing as part of physiotherapy practice and lack of emphasis in undergraduate assessment.

Fifteen out of the 29 statements yielded statistically significant differences across the two PT groups. These, were 7 statements from PT's Attitudes subsection (letting patient talk during assessment, history guides assessment, paying attention to the medical diagnosis and referral card and sequence of re-assessment), two statements from patients' attitudes subsection (sick leave in relation to working on public or private sector and understand patient's psychosocial problems following several treatment sessions) and 6 statements from Diagnostic Issues subsection (diagnosis as a medical privilege, diagnosing as part of physiotherapy practice, lack of emphasis in undergraduate assessment, PTs are executers, overuse of medical investigations and more emphasis on laboratory investigations). Table 2 illustrates percentage agreements and statistical results for each statement amongst the cultural groups.

In summary the data shows that both countries PTs agreed on the need for a thorough clinical examination, including assessment for serious pathology. There was disagreement from the United Kingdom physiotherapists regarding the frequency of reassessment, the right to diagnose, the over-investigation of LBP and the need for more undergraduate training in low back pain.

DISCUSSION

This study explored diagnostic practice and attitudes between Greek and British PTs in assessing LBP patients, utilising a questionnaire-based comparison, the content of which was developed by Greek PTs' focus groups[41].

PTs' attitudes towards assessment

A large number of similarities amongst the two cultural groups were reported in the PTs' assessment section. Both PT groups agreed on taking notes with a detailed history of the patient during the first visit, including the examination of non-musculoskeletal causes (red flags) and including reassessment following every PT session. There was also low agreement that their examina-

Table 2 Percentage agreements amongst the Greek and British physiotherapists

Opinions/statements	Greek PTs (%)	British PTs (%)	*P* value (χ^2 test)
PTs' attitudes towards assessment			
I take a small history the first time (within the first assessment), so as to proceed to the therapy straightaway	15.8	0	0.325
I take a very detailed history the first time trying to locate the patient's problem	91	96.6	0.998
Throughout my formal assessment, I don't take into account the patient's psychosocial status because I believe that the biomedical dimension is the patient's main problem	17.1	3.6	0.476
I let the patient talk (without interruptions) about his problem. This helps the impression I gain about his psychosocial status	72.2	44.8	0.039[1]
I use notes/assessment forms	61.8	79	0.084
The patient's symptoms are what guides history taking and clinical assessment *i.e.*, if symptoms look like a nerve root problem, then the clinical examination will focus more on neurological/ neurodynamic examination	53.7	96.6	0.001[2]
Once doctors have excluded any red flags/serious pathology from their patient, they then are not interested in further distinguishing, diagnosing or sub-classifying the patient's back pain	77.3	58.6	0.562
I believe that physiotherapy assessment should include the assessment of non-musculoskeletal nature of back pain (*i.e.*, red flag type questions and clinical tests)	77	100	0.128
I pay attention to the doctor's medical diagnosis	42.6	96.6	< 0.001[2]
I pay attention to the doctor's referral card	13.8	62.1	< 0.001[2]
I alter my examination based on whether my patient is acute or chronic	97.3	69	< 0.001[2]
I reassess each patient (looking for exacerbation or improvement) before and/or following every treatment procedure (thus, within each treatment session)	44.9	89.7	0.004[1]
I reassess each patient (looking for exacerbation or improvement) following every treatment session only	70	86.2	0.745
I reassess each patient (looking for exacerbation or improvement) following 4-5 treatment sessions only	72	41.4	0.011[1]
Patients' attitudes towards assessment			
You start getting a feel of the patient's psychosocial problems, after you start develop a relationship with the patient (that is, following several treatment sessions)	58.1	13.8	0.002[1]
All patients' have the attitude that the PT should follow exactly what is written on the referral card	21	20.7	0.867
A large proportion of our patients from Mediterranean cultures "hurt everywhere" (and nowhere very specifically), compared to other cultures who are much more precise with the site of their pain	39.5	10.3	0.092
The type of job the patient has (whether he works in the private or public sector) seems to be important in terms of the amount of "sick leave" taken for episodes of LBP	81.5	34.5	< 0.001[2]
I feel patients have a very "passive" attitude regarding physiotherapy treatment	37.8	44.8	0.407
There is a poor understanding among patients about what physiotherapy is and what it entails	57.7	34.5	0.066
There a difference in concordance between rural and urban LBP patients	50.5	65.5	0.476
Diagnostic issues			
Diagnosis in a medical privilege exclusively and doesn't form part of physiotherapy at all	90.9	17.2	< 0.001[2]
I believe diagnosing a condition should be part of physiotherapy practice	90.9	10.3	< 0.001[2]
Formal assessment of the patient prior to commencement of treatment is not performed by a large number of PTs	75.6	89.7	0.441
I believe more emphasis should be given in assessment at undergraduate level than in treatment techniques	92.7	6.9	< 0.001[2]
Performing an X-ray on a patient with LBP is obligatory	57	72.4	0.291
Legally, physiotherapists are "executers" and they cannot interfere greatly in treatment planning (alter it)	40.3	0	0.002[1]
In general there is an overuse of medical investigations	60.9	3.4	< 0.001[2]
In general there is more emphasis on laboratory investigations at the expense of the clinical investigations	77.4	58.6	0.024[1]

[1]χ^2 test is statistically significant at the 0.05 level; [2]χ^2 test is statistically significant at the 0.001 level. PT: Physiotherapist; LBP: Low back pain; X-ray: Radiograph.

tion focussed only on the biomedical dimension of the patient's problem, indicating that both countries take into consideration the patient's psychosocial status in their assessment. Despite evidence that biomedically orientated diagnostic practice[49-51] is still the dominant paradigm[30,52], it is worth noting the adherence that most of these statements (relating to history taking) have with current guideline practice for LBP[53,54]. It is also interesting to note that psychosocial features were considered important prognostic indicators in LBP recovery and management by both groups[55-57].

Two statements from the assessment section highlighted significant differences between populations. Whilst the majority of the British PTs stated that they pay attention to the doctor's medical diagnosis and referral card, most Greek PTs did not seem to agree. This low agreement in the Greek cohort conforms with what was noted during the focus group discussions, in that little credence is afforded to the doctors' medical diagnosis and subsequent referral card[41].

In terms of re-assessment procedures the majority of the British PTs re-assess within each treatment session (*i.e.*, test-retest following an interventional procedure) as well as following each treatment session whereas, Greek

PTs re-assess following 4-5 treatment sessions. This could reflect the lack of autonomy in decision-making that has been prevalent in Greece for many years.

Patients' attitudes towards assessment

Interestingly, over half of the Greek PTs agreed that following several treatment sessions they start to acknowledge the patients' psychosocial problems. However their British counterparts did not agree with that. This Greek "perspective" is in agreement with the longer gap between re-evaluations (4-5 treatment sessions, as previously indicated) compared to only one for the British PTs, and could possibly imply a longer term management plan and a slower recovery expectation rate compared to the British ones.

Both PT groups disagreed that patients have a passive attitude towards physiotherapy, thus agreeing with a recent British study exploring patients' attitudes and beliefs following physiotherapy, which reported that active patient involvement with their LBP problem was considered essential[58]. It is interesting to note that over half of the Greek PTs believe that patients have a poor understanding of the role of physiotherapy, compared to only a third of the British PTs, which could reflect the more medically-orientated status existing within Greece. There was also significant disagreement between the PT groups about the association of the working sector with sick leave; Greek PTs agreed that the amount of sick leave a patient takes is associated with his working sector (public or private) compared to a lower agreement range by the British PTs. This could reflect differences in security of employment for the different sectors; *i.e.,* as the Greek public sector entails mostly permanent contracting employees, it could be the case that sick leave can more easily be asked for. However, this is conjecture.

Diagnostic issues

This final section demonstrated with the largest differences between the PT groups (6 out of 8 statements yielded statistically significant results). Most British PTs did not agree with the "Greek notion" that diagnosis is considered a medical privilege and does not form part of physiotherapy. This is to be expected considering that the healthcare infrastructure in Great Britain has moved away from a medically-centred model of care and has adopted a more multidisciplinary approach[11,18]. Something similar however, has not been detected within Greece yet[4,8,41]; in Greece medical referrals, dictating (by the doctor) which particular method should the PT follow, are obligatory prior to seeing a physiotherapist and it is anticipated that the PT will follow the exact referral (treatment instructions). Furthermore, 40.3% of the Greek PTs as opposed to none of the British PTs still consider themselves as "executers", not being able to interfere with treatment planning. This barrier to autonomous practice and diagnosis has not been reported in other cultural settings[23,59,60], probably because autonomy within physiotherapy is not an issue in other developed countries.

Over 90% of the Greek PTs (compared to less than 11% of United Kingdom ones) felt strongly that physiotherapy assessment should be more actively included in undergraduate physiotherapy programmes and diagnosis should also form an official part of physiotherapy practice. The British sample did not agree that there is an overuse of medical investigations in clinical practice in their country. This again, reflects their current guideline practice[30,61]. Based on the focus group data[41], X-rays in Greece are used as a means of reassuring and helping patients to recover as well as building upon the doctor-patient relationship. Interestingly, patient reassurance[62,63], perceived recovery[34] and enhancement of doctor-patient relationships[63] were reasons for ordering an X-ray in other cultural settings.

In terms of this study's clinical implications, this cross-cultural report appeared to be beneficial in clarifying commonalities and differences in perspectives and diagnostic practice in LBP between Greek and British PTs. Of particular interest is the fact that both cultural groups appeared to agree on the importance of clinical and psychosocial features during the examination (for targeting treatment), thus, indicating that LBP is a clinical entity whose "somatic expressions" amongst health professionals and patients are common even across different cultural groups. Similarities across the methods utilised in history taking and in the way PTs feel patients perceive physiotherapy practice, also indicate that LBP clinical diagnosis is similar in approach, beyond each country's borders.

However, a number of differences were detected particularly in diagnostic issues raised, such as the utilisation of radiology. Additionally, of the items identified that were culturally distinct these related more to re-assessment procedures and diagnostic practice issues, possibly highlighting the multi-disciplinary approach of the British healthcare system compared to a more unimodal and medically-centred one of the Greek system (*i.e.,* over utilisation of medical investigations, PTs seen as "executers", *etc.*).

However, in view of the qualitative nature of this study and the relatively smaller British sample, these findings cannot be generalised beyond the samples and cultural groups utilised until further work is undertaken. To the authors' knowledge, this is the only study exploring such perspectives and issues relating to LBP practice in two different cultural contexts, and it is believed that these findings in their wider sense reflect cultural variables which may contribute to the understanding of the course and/or management of a given clinical entity in these two countries.

In conclusion, this study aimed to explore current diagnostic practice and attitudes of Greek and United Kingdom physiotherapists on assessing LBP patients *via* a structured questionnaire-type survey. A number of similarities were detected predominantly in history taking methods and in the way patients seem to perceive physiotherapy practice thus, indicating that LBP is similar in approach across different cultural groups. However,

several differences were apparent, particularly in re-assessment procedures as well as in general diagnostic issues regarding the value of the medical diagnosis, overuse of medical investigations, autonomy within physiotherapists, *etc.* These differences may reflect the different evolutionary stages in the healthcare delivery service provided across the two cultural settings; from the more unimodal and medically-centred Greek healthcare system to a more holistic and multi-modal British one.

COMMENTS

Background

It is suggested that cultural differences amongst healthcare professionals: (1) in diagnostic practice of low back pain (LBP); and (2) in terms of attitudes towards their patients care and clinical decision-making tend to "shape" particular attitudes, beliefs and perspectives, which subsequently, have an effect on their overall LBP management approach.

Research frontiers

This study's research hotspots are to compare the current diagnostic practice and the associated attitudes of Greek and United Kingdom physiotherapists on assessing LBP patients.

Innovations and breakthroughs

In terms of conducting the LBP assessment (history taking procedures, *etc.*) both cultural groups presented with similarities, indicating that LBP is similar in approach across the two physiotherapy (PT) cultural groups. It was interesting to note that general diagnostic issues regarding the value of the medical diagnosis, overuse of medical investigations as well as autonomy within physiotherapists, *etc.*, were different, possibly reflecting different evolutionary stages in the healthcare delivery service provided across the two cultural settings (from the more unimodal and medically-centred Greek healthcare system to a more holistic and multi-modal British one).

Applications

This cross-cultural report appeared to be beneficial in clarifying commonalities and differences in perspectives and diagnostic practice in LBP between Greek and British PTs. Similarities indicate that LBP clinical diagnosis is similar in approach, beyond each country's borders. Culturally distinct themes (which related more to re-diagnostic practice issues), possibly highlight the multi-disciplinary approach of the British healthcare system compared to a more unimodal and medically-centred Greek one.

Terminology

LBP refers to any pain in the back region, between the lower rib and the gluteal folds. It is one of the most highly prevalent musculoskeletal disorders with extremely high recurrent rates. In most LBP episodes, a specific underlying cause is not accurately identified and quite often the impact of psychosocial factors (instead of mechanical ones) is believed to be of great importance. As a result, the health professionals' perspectives are important in enhancing or contributing to the management of the patients' psychosocial profile.

Peer-review

In this manuscript, the authors conducted a cross-cultural survey to observe current diagnostic practice and attitudes of Greek and United Kingdom physiotherapists (PTs) on assessing low back pain (LBP) patients. Author's conclusions were that although similarities on history taking methods were detected across both Greek and United Kingdom groups, gross differences were found in re-assessment procedures and diagnostic issues between Greek and British physiotherapists.This topic is small, but informative one for those who are involved in this area.

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ORIGINAL ARTICLE

Observational Study

Epidemiology of isolated hand injuries in the United Arab Emirates

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Abstract

AIM

To provide suggestions for hand injury prevention by study the demography and risk factors of casualties suffering from isolated hand injuries.

METHODS

All trauma patients with isolated hand injuries who were admitted to Al Ain Hospital for more than 24 h during a period of 3 years were studied. Patient demographics, location, mechanism/time of injury, and length of hospital stay were all analyzed.

RESULTS

Two hundred and ten patients were studied. Their mean age was 29.7 years. Males constituted 92%. Sixty-five point one percent of all cases were from the Indian subcontinent. The workplace was the most common location of injury (67.1%), followed by the home (17.1%) and road (6.2%). Machinery caused 36.2% of all injuries, followed by heavy object (20.5%) and fall (11%). Cases injured at home were young ($P < 0.0001$) with an associated higher incidence of females ($P < 0.0001$).

CONCLUSION
Male workers in Al Ain city are at greater risk of sustaining hand injuries, predominantly from machinery. Safety education, personal protection, and the enforcement of safety standards are essential to the prevention and avoidance of hand injury.

Key words: United Arab Emirates; Occupational safety; Hand injury; Injury prevention

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Core tip: Two hundred and ten hospitalized patients with isolated hand injuries were prospectively studied in Al Ain Hospital, United Arab Emirates. Males were in greater danger of sustaining work-related hand injuries especially from machinery. Safety education, personal protection, and enforcement of safety standards are essential for hand injury prevention.

Grivna M, Eid HO, Abu-Zidan FM. Epidemiology of isolated hand injuries in the United Arab Emirates. *World J Orthop* 2016; 7(9): 570-576 Available from: URL: http://www.wjgnet.com/2218-5836/full/v7/i9/570.htm DOI: http://dx.doi.org/10.5312/wjo.v7.i9.570

INTRODUCTION

Hand injuries are common in young men[1,2]. They constitute 7%-28% of all injuries[3,4], and account for about one fifth of all emergencies presenting to hospital emergency departments[5]. Although the outcome of hand injuries is seldom fatal, patients may suffer substantial disability[6]. Types of injuries vary from soft tissue injuries and lacerations to burns, fractures, and amputations[7]. The costs of treatment are high as some patients may require hand reconstruction[7]. Many of these injuries affect the dominant hand[8] and can cause considerable physical disability and psychological stress[9,10].

The United Arab Emirates (UAE) is a country experiencing a rapid economic development. The population, reportedly circa 4 million in 2003, consisted of a high proportion of expatriate workers[11]. Injury remains the second main cause of fatalities at 27.3 per 100000 persons per year[12]. Data on isolated hand injuries are lacking in this region. There is a need for information on risk factors for hand injuries related to the individual, the environment and the equipment in order to allow the development of efficient injury prevention and safety promotion[12]. To reduce the effect of associated injuries it was decided to study only patients with isolated hand injuries who had been admitted to Al Ain hospital.

The purpose of the study was to evaluate the risk factors of inpatients with isolated hand injuries so that recommendations for hand injury prevention in the UAE could be advocated.

MATERIALS AND METHODS

Ethical approval

Ethical approval for this study was obtained from Al Ain Health District Ethics Committee (ethical approval No: RECA/02/44). All patients who are admitted to Al Ain Hospital, or their legal guardian, sign a general consent form permitting the use of their anonymous data for audit and research.

Data collection and setting

Data of all patients with isolated hand injuries and who were hospitalized more than 24 h were retrieved from Al Ain Hospital Trauma Registry. During a 36-mo period (March 2003-March 2006), data from the Registry were prospectively collected by a full time Trauma Research Fellow. Al Ain Hospital is a major specialized acute care hospital with a capacity of more than 400 beds[13]. The hospital cared for approximately 80% of trauma cases in Al Ain during the study period. The hospital is located in Al Ain City which had a population of 460000 during that period. Twenty-two percent of cases were UAE nationals while the remainder came from the expatriate work force[11]. Nationalities were categorized as Indian subcontinent and others as it had been previously shown that risks of injury for these two groups in Al Ain differed. There is a significantly higher proportion of manual laborers in Al Ain from the Indian subcontinent[14,15].

Studied variables included gender, age, nationality, mechanism and anatomical location of hand injury, time/date of injury, and length of hospital stay.

Calculations and statistics

We used Kruskall Wallis test to compare continuous and ordinal data and Fisher's exact text to compare categorical data. A *P*-value of less than 0.05 was considered significant. Data were analyzed using Statistical Package for the Social Sciences (IBM-SPSS version 21, Chicago, Il, United States).

RESULTS

Out of 2573 patients in the Trauma Registry, 210 patients sustained isolated hand injuries (8.2%). The majority of patients were male (91.9%, n = 193). The average (SD) age of cases was 29.7 (12.6) years. There were two peaks, in children < 5 years old injured mostly at home, and younger adults 20-30 years injured at work (Figure 1). Seventy-two point seven percent of patients (n = 152) were in the age group of 20-44; children and youth < 20 years constituted 14.7% (n = 31) (Figure 1). In respect of nationality, the majority of patients came from India, Pakistan, Bangladesh and Sri Lanka (65.1%, n = 136), then other Arabs (21.1%, n = 44), UAE nationals (7.6%, n = 16) and other nationalities (6.2%, n = 13). Patients from the Indian subcontinent were significantly older than UAE-nationals and others (P = 0.002).

Machinery and heavy objects caused more than half

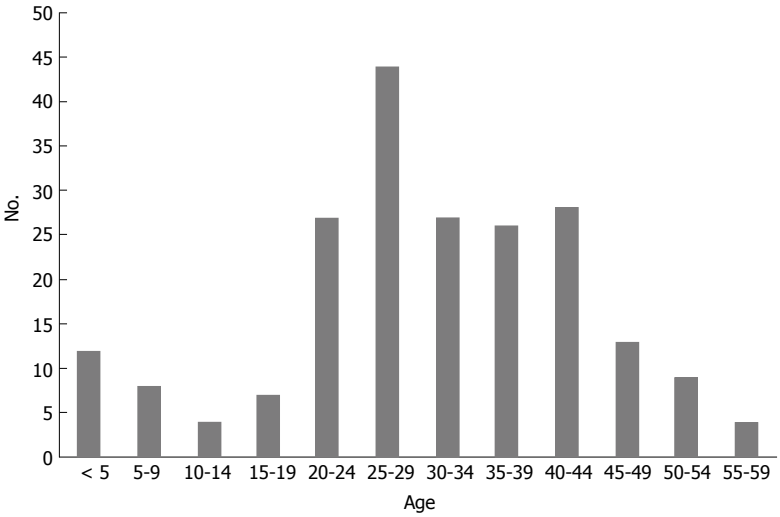

Figure 1 A histogram showing the age distribution of hospitalized patients having isolated hand injuries, Al Ain Hospital, 2003-2006 (*n* = 210).

Table 1 Isolated hand injury hospitalization by age group and mechanism, Al Ain Hospital, 2003-2006 (*n* = 210) *n* (%)

Variable	Age groups			
	0-14	15-29	30-59	Total
Machinery	1 (4.2)	32 (41)	43 (40.2)	76 (36.4)
Heavy object	3 (12.5)	12 (15.4)	28 (26.2)	43 (20.6)
Fall	5 (20.8)	9 (11.5)	9 (8.4)	23 (11)
Cut	6 (25)	9 (11.5)	5 (4.7)	20 (9.6)
Traffic	3 (12.5)	6 (7.7)	7 (6.5)	16 (7.6)
Burn	4 (16.7)	4 (5.1)	7 (6.5)	15 (7.2)
Crush	1 (4.2)	2 (2.6)	2 (1.9)	5 (2.4)
Animal	1 (4.2)	0	3 (2.8)	4 (1.9)
Other	0	4 (5.1)	3 (2.8)	7 (3.3)
Total	24 (100)[1]	78 (100)[1]	107 (100)	209 (100)[1]

[1]The percentage may not add to 100 due to rounding; age of 1 patient was unknown.

Table 2 Isolated hand injury hospitalization by location and mechanism, Al Ain Hospital, 2003-2006 (*n* = 210) *n* (%)

Variable	Location of injury				
	Work	Road	Home	Other	Total
Machinery	72 (51.1)	0	2 (5.6)	2 (10)	76 (36.2)
Heavy object	39 (27.7)	0	4 (11.1)	0	43 (20.5)
Fall	8 (5.7)	1 (7.7)	9 (25)	5 (25)	23 (11)
Cut	8 (5.7)	0	10 (27.8)	2 (10)	20 (9.5)
Burn	9 (6.4)	0	6 (16.7)	1 (5)	16 (7.6)
Traffic	0	12 (92.3)	1 (2.8)	3 (15)	16 (7.6)
Crush	3 (2.1)	0	2 (5.6)	0	5 (2.4)
Animal	0	0	0	4 (20)	4 (1.9)
Other	2 (1.4)	0	2 (5.6)	3 (15)	7 (3.3)
Total	141 (100)[1]	13 (100)	36 (100)[1]	20 (100)	210 (100)[1]

[1]The percentage may not add to 100 due to rounding.

of all injuries (Table 1). Children < 15 years were mainly injured by cuts, followed by falls and burns (Table 1). In the productive age (15-59 years), the most common mechanisms of injury were machinery and heavy object (Table 1). Two injuries were caused by assault (1%), and all other were unintentional.

Table 3 Demography and hospital stay of isolated hand injury by location of injury, Al Ain Hospital, 2003-2006 (*n* = 210)

Variable	Work	Road	Home	*P*-value
	n = 141	*n* = 13	*n* = 36	
Age	32 (18-55)	40 (14-45)	11.5 (1-57)	< 0.0001
Gender				
Males	98.6% (139)	100% (13)	61.1% (22)	< 0.0001
Females	1.4% (2)	0	38.9% (14)	
Nationality				
UAE	1.4% (2)	7.7% (1)	27.8% (10)	< 0.0001
Indian Subcontinent	76.6% (108)	46.2% (6)	30.6% (11)	
Others	21.3% (30)	46.2% (6)	41.7% (15)	
Hospital days	6 (1-110)	6 (2-17)	3.5 (2-22)	0.008

Twenty-six patients injured in other locations were not included; Data are presented as median (range) or number (%) as appropriate; *P* = Kruskall Wallis test or Fisher's Exact test as appropriate. UAE: United Arab Emirates.

Work was the most common location for isolated hand injury (67.1%), followed by home (17.1%) and road (6.2%) (Table 2). The most common cause of injury at work was machinery (51.1%) followed by heavy object (27.7%); while at home it was cuts (27.8%) followed by fall (25%) and burn (16.7%) (Table 2). Home cases were significantly younger ($P < 0.0001$) (Table 3). More males than females were significantly injured at work and road ($P < 0.0001$) (Table 3). More females than males sustained injury at home ($P < 0.0001$) (Table 3). Nationals from the Indian subcontinent were more often injured at work (76.6%), while UAE nationals were more often injured at home (27.8%) (Table 3).

During the day there were three peaks: In the morning at around 9 o'clock, at lunch time at around noon, in the evening at around 5 o'clock (Figure 2A). During the week, injuries occurred most often on Saturdays, which was, during the study period, the first working day of the week (Figure 2B). There was a peak of injuries during

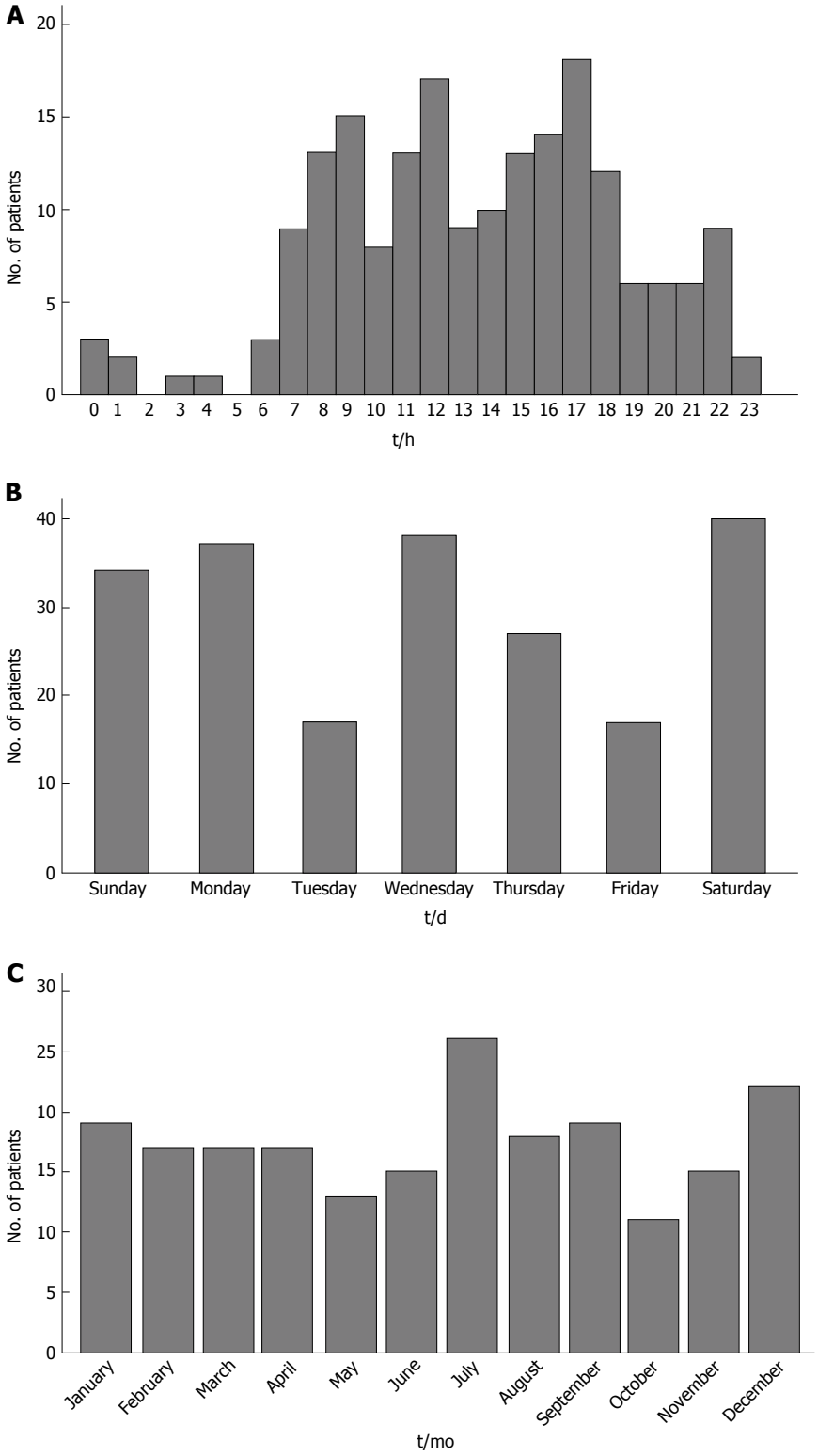

Figure 2 Distribution of hospitalized patients having isolated hand injuries by the hour of the day (A), day of the week (B), and the month of the year (C), Al Ain Hospital, 2003-2006 (*n* = 210).

summer in July (Figure 2C).

The length of hospital stay ranged from 1 to 110 d (mean 7.9; median 5). Those who were injured at home had a significantly shorter hospital stay ($P < 0.0001$) (Table 3). Forty-eight/two hundred and ten (22.9%) patients sustained an amputation of one finger or more. There were no deaths of studied patients during the study period.

DISCUSSION

The highest risk group for hand injuries in our setting was young male adults. Males from the Indian subcontinent were commonly injured at work, while UAE nationals

were more commonly injured at home.

The proportion of hand injuries (8.2%) in all injured patients and the proportion of males (91.9%) in those with hand injuries in our study was higher compared with studies in Sweden, Poland and Nigeria[1,2,8]. As indicated in other studies, it was found that young males sustained injury mainly at work[16,17]. Immigrant construction workers, mainly from the Indian subcontinent, were found to be at a higher risk of isolated hand injury[18]. If injured, workers may lose their employment, income, and jeopardize both their socio-economic status and family life. The majority of women in this study sustained injury at home, where they stay most of their time due to cultural factors. This finding exemplifies the importance of home safety in the UAE setting.

The mean age in our study (29.7 years) was similar to that found in other studies[16,19]. In this study, 14.7% were children and youth < 20 years. The hand is one of the most commonly injured body regions in children[20], which may be explained by their lack of appreciation of risk. The majority of pediatric injuries in our study were sustained at home, similar to findings in a recent study in the United States[21].

Machinery caused the most often hand injury in this study, followed by heavy objects, both of which are common causes of hand injury in industrialized countries[2,16]. These injuries occur as a result of inattention, tiredness, stress, doing an unusual task, being rushed, and the use of poorly maintained or defective machinery[10,22]. Hand injuries caused by machinery are usually more severe and can lead to permanent loss of hand function or even amputation[2]. Adopting the use of gloves can decrease the risk of lacerations and punctures, but not crushing, fractures, avulsions, amputations or dislocations[23]. Other preventive measures, including engineering control and safety training, are necessary to reduce the incidence of more severe injuries[23].

Violence-related injuries are uncommon in this community compared to other countries. Violence constituted only 1% in this study. In a report from Nigeria, the high level of violence was associated with a high incidence of gunshot injuries to the hand[8]. Although the percentage of burns in this study was similar to those in other reports, the burn hazards differed[8]. It has been previously reported that scalds from hot liquids were the major hazard at home, compared with gas and flames at work[24]. Sport-related hand injuries were not seen in our study compared with a European study that indicated a high prevalence of these injuries[25]. It is possible that the majority of people in this community do not participate in outdoor sport activities because of hot weather and long working hours.

Animal-related hand injuries were not common in this study (1.9%), and were mainly caused by camels[26]. Many farm workers in the UAE take care of camels, a large animal with a powerful, incisive bite[27].

Twenty-two point nine percent of patients in this study sustained finger amputations, similar to findings in other studies[8,16]. The identification of the object causing amputation was not possible in this study. Usually these amputations in adults are caused by press machines and powered wood cutters[28], and, in children, by doors, furniture, and machinery[29]. These amputations are particularly devastating to the patients and cause distress due to the physical loss and a need for body image adjustment[30].

Similar to findings in other studies, it was found that the peak time of injury in the morning was around 9 o'clock[31]. Workers in the UAE tend to work long hours with an associated reduced time for sleep. It has been reported elsewhere that sleep deprivation decreases alertness, adversely affects work performance and constitutes a serious work hazard[32].

It was also found that injuries were sustained most often on Saturdays, the first day of work in the UAE after the weekend. The first working day of the week usually had the highest incidence of hand injuries[19]. Similar to findings in other studies, the incidence of injuries was high during summer. It is possible that hot outdoor temperatures in the UAE cause a decrease in the vigilance of outdoor workers[19].

Hospital stays of patients with hand injuries are usually longer in the UAE than for other injuries because of the greater need for rehabilitation[2]. It is believed that the longer hospital stays among those injured at work were the result of the social circumstances of UAE expatriate workers. Many of them live alone and without support in crowded accommodation and so prefer to remain as long as possible in the more congenial and supportive environment of the hospital.

It should be emphasized that this study is an epidemiological study and not a clinical outcome study. Injury prevention remains an important duty of trauma surgeons, whose responsibility it is to define risk factors pertaining to injury, to carry out studies on interventional injury prevention and their effects, and to support health promotion through in-depth research on injury prevention[33-35].

Limitations

This study has certain limitations that require to be highlighted. Patients with minor hand injuries were managed at the Emergency Department. Those who stayed in the hospital for less than 24 h were not included. The Trauma Registry was based in Al Ain hospital, therefore the results of this study may not be generalized for the whole UAE population. This study was for a limited time which was funded by the National University. It is a unique and important source of data for GCC countries. Although these data are a decade old, we think that they still reflect the present situation as isolated hand injury risk factors have not changed in the working environment during this period. Manual laborers still normally do not wear gloves, the electrical saw machines still usually do not have in-built safety, and safety precautions are still not properly followed by labourers. Finally, some important variables were missing like details of occupation, information about injury of dominant hand, absence of functional outcome, occupational experience, length of working

shifts, the causal activity of the person during the injury (smoking or consumption of alcohol), inadequate training, deployment of safety equipment and protective gear, as well as socio-economic variables. There is a need for additional research on causal factors in hand injuries and the importance of transferring these research findings into safety practice in the UAE.

Isolated hand injuries constitute a major proportion of admitted trauma patients in Al Ain city with lengthy hospital stays. Males are at greater risk of sustaining isolated hand injuries especially at work, the majority from machinery. Safety education, personal protection and the enforcement of safety standards could reduce both the need for hospitalization and the incidence of disability in relation to hand injuries.

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COMMENTS

Background

Hand injuries are common in young men. They rarely lead to death, but may cause serious physical disability and psychological stress. Some may require hand reconstruction with associated high cost of treatment. There is a lack of information on personal, environmental and product/equipment risk factors for hand injuries.

Research frontiers

The aim of the study was to investigate demographics and risk factors of hospitalized patients with isolated hand injuries in order to give recommendations for hand injury prevention.

Innovations and breakthroughs

The majority of patients with isolated hand injuries in this study were males. The most common location was work, followed by home and road. Females were injured more at home. Patients injured at home were younger. The most common mechanism was injury from machinery, followed by heavy object and fall. Children < 15 years were mainly injured by cuts, followed by falls and burns.

Applications

Male workers are in higher risk for isolated hand injury, especially from machinery. Safety education, the use of personal protective equipment, and the proper enforcement of safety guidelines are essential.

Terminology

UAE: United Arab Emirates; GCC: Gulf Cooperation Council is a political and economic union consisting of Arab countries - Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates; IBM-SPSS: Statistical Package for the Social Sciences.

Peer-review

The paper describes an epidemiological study concerning isolated hand injuries supported by solid references. This study is definitely worth publishing.

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ORIGINAL ARTICLE

Prospective Study

Risk assessment instruments for screening bone mineral density in a Mediterranean population

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Abstract

AIM

To evaluate the power of six osteoporosis-screening instruments in women in a Mediterranean country.

METHODS

Data concerning several osteoporosis risk factors were prospectively collected from 1000 postmenopausal women aged 42-87 years who underwent dual-energy X-ray absorptiometry (DEXA) screening. Six osteoporosis risk factor screening tools were applied to this sample to evaluate their performance and choose the most appropriate tool for the study population.

RESULTS

The most important screening tool for osteoporosis status was the Simple Calculated Osteoporosis Risk Estimation, which had an area under the curve (AUC) of 0.678, a sensitivity of 72%, and a specificity of 72%, with a cut-off point of 20.75. The most important screening tool for osteoporosis risk was the Osteoporosis Self-assessment Tool, which had an AUC of 0.643, a sensitivity of 77%, and a specificity of 46%,

with a cut-off point of -2.9.

CONCLUSION
Some commonly used clinical risk instruments demonstrate high sensitivity for distinguishing individuals with DEXA-ascertained osteoporosis or reduced bone mineral density.

Key words: Osteoporosis; Bone mineral density; Risk assessment; Dual X-ray absorptiometry; Osteopenia

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Core tip: Bone mineral density (BMD) measurement using dual-energy X-ray absorptiometry (DEXA) is currently the most widely used method for osteoporosis screening, treatment and patient monitoring. Nevertheless, performing routine BMD measurements of all women is not feasible for most populations, and at present there is no universally accepted policy for population screening in Europe to identify patients with osteoporosis or those at high risk of fracture. Osteoporosis risk factor screening tools have been developed to identify postmenopausal women in need of DEXA screening and possible intervention for osteoporosis.

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INTRODUCTION

Osteoporosis is the most common bone disease, characterized by low bone mass and microarchitecture deterioration, which increase bone fragility and susceptibility to fracture[1]. Distal forearm fractures, vertebra fractures and proximal femoral (hip) fractures are typical osteoporotic fractures. However, patients with low bone mineral density (BMD) are at high risk for all types of fractures, irrespective of fracture site[2].

An estimated 50% of Caucasian women and 20% of Caucasian men older than 50 years will experience a fragility fracture in their lifetime[3]. This is an important public health issue because many of these fractures are associated with increased mortality, morbidity or permanent disability, as well as high societal and personal costs[4]. Identification and treatment of patients, particularly women, at risk for osteoporosis is of great importance for the prevention of osteoporotic fractures[5].

BMD measurement using dual-energy X-ray absorptiometry (DEXA) is currently the most widely used method to diagnose osteoporosis (*i.e.*, provide criteria for fracture risk), to guide treatment decisions and to monitor patient course after receiving or not receiving treatment[6]. Nevertheless, routine BMD measurement of all women is not feasible for most populations because of lack of scanners, lack of awareness or lack of widely accepted guidelines. At present, there is no universally accepted policy for population screening in Europe to identify patients with osteoporosis or those at high risk of fracture.

Additionally, the various osteoporosis-screening instruments that exist to help clinicians identify women at increased risk for osteoporosis who should undergo further testing in combination with DEXA screening[7].

The aim of this survey was to evaluate the power of six osteoporosis-screening instruments[8-13] in identifying postmenopausal women at risk of developing osteoporosis in a Mediterranean country. More specifically, our aim was to evaluate these clinical risk estimation instruments in distinguishing individuals with DEXA-identified osteoporosis or reduced BMD while sustaining specific levels of sensitivity and specificity for select cut-off values to identify individuals with BMD T-scores beneath a defined DEXA score.

MATERIALS AND METHODS

Patients

This cross-sectional study utilized prospectively collected data from the Bone Density Measurement Unit of the Department of Orthopaedic Surgery at University General Hospital of Alexandroupolis, a tertiary hospital. The study was approved by the Ethics Committee of the hospital, and informed consent was obtained from all participants.

The study included postmenopausal women (> 12 mo since last menstrual period). Women receiving medication for either the prevention or treatment of diagnosed osteoporosis were excluded.

All the study subjects underwent DEXA screening between October 1, 2012 and October 1, 2014. Confirmation of osteoporosis occurred through BMD measurements, which were compared with the results of the other analytical tools used.

Additionally, the following information was obtained from each patient: Age, weight, height, various osteoporosis risk factors (*i.e.*, a history of fragility fractures of the spine or hip that occurred after age 50 years), parental hip fracture, ever or current long-term use of steroids (> 3 mo use), current smoking, small stature (body mass index < 21 kg/m^2), medical history of rheumatoid arthritis, other medical causes of bone loss (*i.e.*, hyperthyroidism, hyperparathyroidism, kidney failure, or anorexia), use of long-term therapy with medications known to adversely affect BMD (*i.e.*, heparin or anticonvulsants), use of arms to stand up (as an indicator of physical activity), ever or current hormonal therapy, concomitant medications, and family and personal medical histories. The results from each DEXA screen were obtained and incorporated into the database.

Screening tools

In this study, six screening tools[8-13] were applied to

Table 1 Criteria for clinical decision rules and osteoporotic risk factors

SCORE	Age, body weight (kg), race, hormone therapy use, fracture history, history of rheumatoid arthritis
ORAI	Age, body weight (kg), hormone therapy use
OST	Age, body weight (kg)
BW	Body weight (kg)
OSIRIS	Age, body weight (kg), hormone therapy use, fracture history
ABONE	Age, body size, lack of estrogen

SCORE: Simple calculated osteoporosis risk estimation; ORAI: Osteoporosis risk assessment instrument; OST: Osteoporosis self-assessment tool; BW: Body weight; OSIRIS: Osteoporosis index of risk; ABONE: Age, body size, no estrogen.

evaluate a sample of Greek postmenopausal women. The performance of the tools was compared to select the most suitable instrument for this population.

The simple calculated osteoporosis risk estimation (SCORE) was formulated by Lydick *et al*[8] and accounts for 6 risk factors (Table 1). The SCORE possesses a sensitivity ranging from 0.80 to 1.00 and a specificity ranging from 0.40 to 0.50.

The osteoporosis risk assessment instrument (ORAI) was formulated by Cadarette *et al*[9] and accounts for 3 risk factors (Table 1). The ORAI has a sensitivity of 0.90 and a specificity of 0.45.

The osteoporosis self-assessment tool (OST) was formulated by Geusens *et al*[10] for evaluation of Asian and Caucasian women. It utilizes 2 factors (Table 1) and shows a sensitivity of 0.88 and a specificity of 0.52.

The body weight criterion (BW) was formulated by Michaëlsson *et al*[11] and accounts for only one factor (Table 1). It has a sensitivity of 0.94 and a specificity of 0.36.

The osteoporosis index of risk (OSIRIS) was formulated by Sedrine *et al*[12] using four factors (Table 1). It has a sensitivity of 0.79 and a specificity of 0.51.

Weinstein and Ullery[13] formulated the Age, Body size, No Estrogen tool (ABONE) (Table 1), which has a high specificity of 0.84 but a low sensitivity of 0.56.

Statistical analysis

Data are expressed as the mean ± SD or the median (IQR) for quantitative data and as percentages for qualitative data. The Kolmogorov-Smirnov test was utilized for normality analyses of the parameters. A receiver operating curve (ROC) analysis was conducted to determine the diagnostic abilities and obtain the cut-off levels of the various osteoporosis-screening tools in classifying patients as osteoporotic or at high osteoporotic risk. This was accomplished according to T-score classification by calculating the areas under the curve (AUC) and their standard errors and 95%CIs. To evaluate the internal credibility of the indices, sensitivity was delineated as the proportion of the population with reduced BMD who were correctly categorized by the risk index (true positive fraction), and specificity was delineated as the proportion of the population with normal BMD who were correctly categorized by the risk index (true negative fraction).

We also measured the positive predictive value (PPV) and negative predictive value (NPV) of each instrument to measure their external credibility. The PPV and NPV corresponded to the average numbers of women who were deemed as positive or negative (as compared by the four instruments), respectively, who truly had or did not have BMD values beneath the T-score cut-off.

The ROC curves were used to provide a graphical interpretation of the general quality of each test by plotting sensitivity against (1-specificity) for all thresholds, while the AUC values were used to indicate test quality. Multiple logistic regression analysis using the enter method was performed with the dependent variables (T-score $\leqslant$ -2.5 *vs* T-score > -2.5) and (T-score $\leqslant$ -2 *vs* T-score > -2) and the osteoporosis-screening indices as the independent variables. All the tests were two-sided, and statistical significance was set at $P < 0.05$. All analyses were carried out using SPSS ver 17.00 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, Ill., United States).

RESULTS

One thousand women with a mean age of 63.41 years (minimum 42 years and maximum 87 years) were included in this study. The mean age at menarche was 13.2 years (minimum 8 years and maximum 18 years), and the mean weight and height were 73.52 kg (minimum 40 kg and maximum 120 kg) and 1.59 m (minimum 1.42 m and maximum 1.80 m). The mean number of pregnancies was 2.3 (0-12 pregnancies), the mean alcohol consumption was 0.37 drinks weekly (0-7 drinks), and the mean coffee consumption was 1.60 cups daily (0-6 cups). Additionally, 12.1% of the population were smokers, 64.5% had previously experienced a graduated fracture, 20% regularly exercised, 20% had kyphosis, 2.7% had rheumatoid arthritis, 3.8% had received hormone therapy, and 3.2% had received cortisone.

The following indicator values were obtained: BW: 73.52 ± 11.32, OST: -2.02 ± 2.94, ORAI: 10.05 ± 5.02, SCORE: 20.54 ± 3.70, OSIRIS: 0.68 ± 3.14 and ABONE: 1.54 ± 0.66. The AUC ratios and the sensitivities and specificities of the instruments for identifying high osteoporotic risk and osteoporosis were assessed using cut-off points from the literature. The tool with the highest AUC value was the ABONE (AUC: 0.628), followed by the ORAI (AUC: 0.608).

The highest levels of sensitivity and accuracy in identifying patients at high risk of osteoporosis were obtained by the ORAI (72%) and the ABONE (65%). The highest levels of sensitivity and accuracy in diagnosing osteoporosis were obtained by the OSIRIS (63%) and the BW (67%). The sensitivity for the OSIRIS was 0.631, and the specificity was 0.570. The sensitivity for the BW was 0.40, and the specificity was 0.667. These values are listed in Table 2.

Table 2 Receiver operating curve analysis using international guidelines

	AUC	95%CI		Sensitivity	Specificity	*P*-value
SCORE[1]	---	---	---	---	---	---
ORAI[1]	0.608	0.57	0.65	0.716	0.498	< 0.0005
ABONE[1]	0.628	0.59	0.67	0.650	0.610	< 0.0005
BW[2]	0.535	0.49	0.58	0.400	0.667	0.109
OST[2]	0.586	0.54	0.63	0.515	0.312	< 0.0005
OSIRIS[2]	0.600	0.56	0.64	0.631	0.570	< 0.0005

[1]Osteoporosis risk T-score < -2; [2]Osteoporosis status T-score < -2.5. AUC: Area under the curve; SCORE: Simple calculated osteoporosis risk estimation; ORAI: Osteoporosis risk assessment instrument; ABONE: Age, body size, no estrogen; BW: Body weight; OST: Osteoporosis self-assessment tool; OSIRIS: Osteoporosis index of risk.

The AUC, sensitivity, and specificity values and the cut-off points for the indicators of osteoporosis risk are presented in Table 3. The clinical tool with the highest AUC value was the OST (AUC: 0.643), followed by the ORAI (AUC: 0.640) and the ABONE (AUC: 0.631). The highest sensitivity in identifying patients at high risk for osteoporosis was obtained with the OST (77%), followed by the ORAI (72%) and the ABONE (65%). The highest accuracy for identifying individuals at high osteoporotic risk was obtained by the BW (61%), followed by the SCORE (60%). The sensitivity of the BW was 51%, and its specificity was 61%. The sensitivity and specificity for the SCORE were 61% and 60%, respectively.

The AUC, sensitivity, and specificity values and the cut-off points for the indicators of osteoporotic condition are shown in Table 4. The clinical tool with the highest AUC value was the SCORE (AUC: 0.678), followed by the OST (AUC: 0.644) and the OSIRIS (AUC: 0.641). The highest sensitivity in diagnosing osteoporosis was obtained with the OST (80%), followed by the OSIRIS (76%) and the SCORE (65%). The highest accuracy for assessing osteoporotic status was obtained with the ORAI (60%) and the SCORE (60%).

The sensitivity for the OST was 80%, and its specificity was 43%. The sensitivity and specificity for the OSIRIS were 76% and 44%, respectively. For the SCORE, the sensitivity and specificity were 72% and 60%, respectively. For the ORAI, the specificity and sensitivity were 65% and 60%, respectively.

The results from the multiple logistic regression analysis for the variable high osteoporotic risk are presented in Table 5. For this analysis, we introduced each of the variables into a multiple linear regression model (known as the enter method) to identify the independent effects of each instrument on the variable high osteoporotic risk. We found that the OST (P = 0.012), ABONE (P = 0.051) and SCORE (P = 0.081) each had a statistically significant effect on this variable.

The results from the multiple logistic regression analysis for the variable osteoporosis are presented in Table 6. Similar to the above, we used the enter method to identify the independent effects of each instrument on the variable osteoporosis. Only the SCORE (P < 0.0005) had a statistically significant effect on this variable.

DISCUSSION

In this survey, we assessed the performance of six osteoporosis pre-screening models in evaluating a sample of Greek postmenopausal women and selected the most suitable instrument for that population. Our results exhibited that, assuming a -2.5 cut-off for T-score in three areas of concern, the OST and the OSIRIS had equal predictive precision (AUCs between 0.586 and 0.6). Additionally, assuming a -2 cut-off for T-score in three areas of concern, the ORAI and the ABONE had equal predictive precision (AUCs between 0.608 and 0.628). The least suitable and least useful model based on AUC was the BW, which had only 40% sensitivity. The ABONE and the ORAI were more suitable models, each with an AUC of approximately 0.628.

When considering the AUCs, sensitivities, specificities and cut-off points for the indicators of patients at high-risk of osteoporosis, the clinical tool with the highest AUC value was the OST (AUC: 0.643), followed by the ORAI (AUC: 0.640) and the ABONE (AUC: 0.631).

With regard to the AUCs, sensitivities, specificities and cut-off points for osteoporosis, the clinical tool with the highest AUC value was the SCORE (AUC: 0.678), followed by the OST (AUC: 0.644) and the OSIRIS (AUC: 0.641).

Combining the above criteria, in the Greek postmenopausal population, the most important screening tool for osteoporosis status is the SCORE, and for osteoporotic risk, it is the OST. In our study, the SCORE had an AUC of 0.678, a sensitivity of 72%, and a specificity of 72%, with a cut-off point of 20.75, for osteoporosis status. Additionally, the screening tool most important for osteoporosis risk was the OST. The OST had an AUC of 0.643, a sensitivity of 77%, and a specificity of 46%, with a cut-off point of -2.9.

These results must be interpreted with caution, as they are based on a sample of only 1000 patients and may not represent the entire Greek population.

As clinical decision tools, instruments used to predict osteoporosis risk and to identify osteoporosis should be straightforward and convenient to apply in clinical practice in addition to being accurate. Nevertheless, when applying such instruments to different countries or populations, their reported utility has varied amongst different studies. It has been found that they perform well in classifying the risk of osteoporosis and that applying them is more prudent than the use of the BMD[14]. However, clinical decision-making tools were found to have limited utility for predicting osteoporosis in patients with rheumatoid arthritis[15]. Wallace *et al*[16] reported sensitivities of 83% for the SCORE and 65% for the ORAI. Martínez-Aguilà *et al*[17] found sensitivities of 64% for the ORAI and 83% for the BW in Spanish women, while Cass *et al*[18] reported sensitivities of 66% for the SCORE and 68% for the ORAI in a group of Caucasian (non-Hispanic and Hispanic) and African-

Table 3 Receiver operating curve analysis using Greek population values for osteoporosis risk

	Area	95%CI		Cut-off	Sensitivity	Specificity	PPV	NPV	*P*-value
SCORE[1]	0.613	0.576	0.650	20.75 >	61%	60%	46%	73%	< 0.0005
ORAI[1]	0.640	0.603	0.676	9.5 >	72%	52%	46%	76%	< 0.0005
				10.5 >	62%	62%	48%	74%	
ABONE[1]	0.631	0.595	0.668	1.5 >	65%	41%	32%	85%	< 0.0005
OST[1]	0.643	0.607	0.678	-2.9 >	77%	46%	45%	78%	< 0.0005
BW[1]	0.592	0.555	0.630	70.5 <	51%	61%	42%	68%	< 0.0005
OSIRIS[1]	0.609	0.572	0.645	0.5 <	59%	59%	44%	71%	< 0.0005

[1]High risk for osteoporosis: T-score ⩽ -2. SCORE: Simple calculated osteoporosis risk estimation; ORAI: Osteoporosis risk assessment instrument; ABONE: Age, body size, no estrogen; OST: Osteoporosis self-assessment tool; BW: Body weight; OSIRIS: Osteoporosis index of risk; PPV: Positive predictive value; NPV: Negative predictive value.

Table 4 Receiver operating curve analysis using Greek population values for osteoporosis status

	Area	95%CI		Cut-off	Sensitivity	Specificity	PPV	NPV	*P*-value
SCORE[1]	0.678	0.640	0.717	20.75 >	72%	60%	36%	87%	< 0.0005
ORAI[1]	0.632	0.591	0.673	10.5 >	65%	60%	33%	85%	< 0.0005
ABONE[1]	0.618	0.576	0.659	1.5 >	66%	60%	48%	75%	< 0.0005
OST[1]	0.644	0.604	0.684	-2.9 >	80%	43%	30%	87%	< 0.0005
BW[1]	0.591	0.549	0.633	75.5 <	69%	41%	26%	81%	< 0.0005
OSIRIS[1]	0.641	0.601	0.681	0.5 <	63%	57%	31%	83%	< 0.0005
				1.5 <	76%	44%	30%	86%	< 0.0005

[1]Osteoporosis status: T-score ⩽ -2.5. SCORE: Simple calculated osteoporosis risk estimation; ORAI: Osteoporosis risk assessment instrument; ABONE: Age, body size, no estrogen; OST: Osteoporosis self-assessment tool; BW: Body weight; OSIRIS: Osteoporosis index of risk; PPV: Positive predictive value; NPV: Negative predictive value.

Table 5 Multiple logistic regression model (T-score ⩽ -2)

	Reference category	Odds ratio	95%CI		*P*-value
SCORE	20.75 <	1.36	0.96	1.91	0.081
ORAI	10.5 <	1.30	0.8	2.09	0.287
ABONE	1.5 <	1.64	1.00	2.70	0.051
OST	-2.9 <	1.81	1.14	2.88	0.012
BW	70.5 >	1.05	0.75	1.47	0.772
OSIRIS	0.5 >	0.78	0.52	1.16	0.214

SCORE: Simple calculated osteoporosis risk estimation; ORAI: Osteoporosis risk assessment instrument; ABONE: Age, body size, no estrogen; OST: Osteoporosis self-assessment tool; BW: Body weight; OSIRIS: Osteoporosis index of risk.

Table 6 Multiple logistic regression model (T-score ⩽ -2.5)

	Reference category	Odds ratio	95%CI		*P*-value
SCORE	20.75 <	2.87	1.92	4.29	< 0.0005
ORAI	10.5 <	1.42	0.81	2.48	0.215
ABONE	1.5 <	0.95	0.53	1.70	0.865
OST	-2.9 <	1.55	0.90	2.65	0.115
BW	70.5 >	1.10	0.76	1.60	0.600
OSIRIS	0.5 >	0.88	0.56	1.39	0.586

SCORE: Simple calculated osteoporosis risk estimation; ORAI: Osteoporosis risk assessment instrument; ABONE: Age, body size, no estrogen; OST: Osteoporosis self-assessment tool; BW: Body weight; OSIRIS: Osteoporosis index of risk.

American women. A recent systematic review concerning the performance of the OST found that this tool may be of clinical value in ruling out low BMD[19], while another systematic review focused on accuracy that compared the OST to the SCORE and the ORAI produced similar results[20].

When comparing the different studies that have focused on the performance of these instruments, two notable points arise. The first concerns the threshold for defining osteoporosis; in particular, some tools (such as the ORAI and the ABONE) were developed using as a T-score ⩽ -2.0 as a threshold, while other tools (such as the BW and the OSIRIS) use a T-score ⩽ -2.5 as a threshold. A lower threshold provides more robust and defined segmentation for prophylactic strategies and helps in assigning screening intervals[21]. The second point concerns the skeletal site that is tested for BMD, as different BMD values have been measured at different anatomic sites within the same patient. It has been suggested that a value beneath the determined threshold at any site (lumbar spine or hip) is sufficient[22].

Study limitation

The main limitation of our study is the small population evaluated. The information we gathered specifically pertains to women who were seen at university hospital in Alexandroupolis, Eastern-Macedonia and Thrace. However, as a notable strength, our study is the most inclusive evaluation of clinical risk assessment instruments for distinguishing Greek postmenopausal women with osteoporosis or reduced BMD.

In conclusion, our study identified clinical risk instruments that showed high sensitivity for identifying individuals with DEXA-determined osteoporosis or low BMD.

We believe that further studies from other centers in our region concerning the effectiveness of these instruments are required.

COMMENTS

Background

Osteoporosis is the most common bone disease, characterized by low bone mass and microarchitecture deterioration, which increase bone fragility and susceptibility to fracture. Dual-energy X-ray absorptiometry (DEXA) is currently the most widely used method to diagnose low bone mass, but routine bone mineral density (BMD) measurement of all women is not feasible for most populations, and universally accepted guidelines do not exist.

Research frontiers

Clinical risk assessment instruments for distinguishing individuals with osteoporosis or reduced BMD have been formulated to identify postmenopausal women who should undergo DEXA measurement for osteoporosis. Nevertheless, applying these instruments in different countries or populations has shown varied utility amongst previous studies.

Innovations and breakthroughs

In the current study, the authors utilized six osteoporosis pre-screening instruments on a sample of Greek postmenopausal women to standardize their interpretation and select the most suitable instrument for that population. With consideration of the factors identified in other instrument validations, we showed that using -2.5 as a cut-off T-score in three areas of interest for the studied osteoporosis self-assessment tools and osteoporosis index of risk produced the highest precision [area under the curve (AUC) between 0.586 and 0.6]. At the same time, using -2 as a cut-off T-score in three areas of interest in the studied osteoporosis risk assessment instruments while accounting for age, body size, and lack of estrogen produced the highest precision (AUC between 0.608 and 0.628).

Applications

The purpose of this study was to measure the performance of a panel of clinical risk instruments in identifying individuals with DEXA-determined osteoporosis or reduced BMD in a Mediterranean population. Specifically, the authors measured the sensitivity and specificity associated with different cut-off values to identify individuals with BMD T-scores beneath a nominal DEXA threshold.

Terminology

Osteoporosis is a skeletal disease characterized by low bone mass and microarchitecture deterioration, which increase bone fragility and susceptibility to fracture. BMD measurement using DEXA is currently the most widely used method to diagnose osteoporosis (*i.e.*, provide criteria for fracture risk), guide its treatment and monitor patient course after receiving or not receiving treatment. Osteoporosis risk factor clinical risk assessment instruments for distinguishing individuals with osteoporosis or reduced BMD were formulated to identify postmenopausal women who should undergo DEXA measurement for osteoporosis.

Peer-review

This is an interesting paper with regards to the argument of screening tools for osteoporosis and identification of the patients that need to have DEXA measurement. Furthermore, it adds information missing in this area of the Mediterranean Sea.

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Total knee arthroplasty for treatment of post-traumatic arthritis: Systematic review

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Abstract

AIM

To review and report functional outcomes, complications, and survivorship associated with total knee arthroplasty (TKA) in the treatment of post-traumatic arthritis (PTA).

METHODS

We conducted a systematic review according to the PRISMA guidelines. We searched PubMed, Cochrane Library, and SCOPUS in December 2015 for English-language clinical research studies, both prospective and retrospective, examining the use of TKA for the treatment of PTA. All relevant articles were accessed in full. The manual search included references of retrieved articles. We extracted data on patients' demographics and clinical outcomes, including preoperative diagnosis and pre- and post-operative functional scores. We summarized the data and reported the results in tables and text.

RESULTS

Sixteen studies, four prospective and ten retrospective, examined patients who underwent TKA for PTA due to fractures of the proximal tibia, patella, and/or distal femur. Eleven studies utilized the Knee Society Scores criteria to assess functional outcomes. All studies utilizing these criteria reported an improvement in functional and knee scores of patients following TKA. Further, studies reported an increased range of motion (ROM) and reduction of pain following surgery. The most commonly reported complications with TKA included infection,

stiffness, wound complications, intraoperative rupture of tendons, and osteolysis/polyethylene wear. The overwhelming majority of these complications occurred within the first two years following surgery. Six studies examined the survivorship of TKA with subsequent revision for any reason as an endpoint. Compared to patients with osteoarthritis, patients with PTA required more revisions, the majority for polyethylene wear.

CONCLUSION

Although associated with higher complication rates, TKA is an effective treatment for PTA, as it improves ROM, pain and functional outcomes.

Key words: Total knee arthroplasty; Post-traumatic arthritis; Tibial plateau fracture; Distal femur fracture; Patella fracture

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Core tip: There is a paucity in the literature regarding the effectiveness of total knee arthroplasty (TKA) for the treatment of post-traumatic arthritis (PTA). The goal of this systematic review is to summarize the functional outcomes, complications, and survivorship of TKA performed for the treatment of PTA. Majority of studies reported improvements in functional outcomes, increased range of motion, and decreased pain following TKA. There is a significant complication rate, including infection, stiffness, and wound complications. Revisions were performed most commonly for polyethylene wear. Although associated with higher complication rates, TKA is an effective treatment for PTA, as it improves range of motion, pain and functional outcomes.

Saleh H, Yu S, Vigdorchik J, Schwarzkopf R. Total knee arthroplasty for treatment of post-traumatic arthritis: Systematic review. *World J Orthop* 2016; 7(9): 584-591 Available from: URL: http://www.wjgnet.com/2218-5836/full/v7/i9/584.htm DOI: http://dx.doi.org/10.5312/wjo.v7.i9.584

INTRODUCTION

Post-traumatic arthritis (PTA) refers to structural damage following an injury to an articulating joint[1]. It commonly affects younger, more active individuals as they are more likely to participate in such activities that may cause injury (*i.e.*, sports, blunt trauma, motor vehicle accidents, *etc.*)[1]. Although any joint in the body may be involved, PTA is often more notable in weight-bearing joints[1]. It is estimated that 12% of all symptomatic osteoarthritis (OA) of the hip, knee, and ankle are due to PTA[2]. With a varied prevalence of 21%-44% reported in the literature, PTA of the knee occurs following intra- or extra-articular fractures of the proximal tibia, patella, and distal femur[3-5]. A combination of factors most likely contributes to the development of PTA following injury to the knee. First, mechanical imbalance may be due to ligamentous laxity, meniscal tears and malalignment[1]. Second, the release of pro-inflammatory cytokines into local tissue leads to imperfect remodeling of the cartilage. Lastly, non-unions and malunions following fractures may lead to PTA[4].

The treatment of PTA can be divided into non-operative and operative management. Activity modification, anti-inflammatory medications, ambulatory assist devices, and physical therapy are the mainstay of non-operative treatment[1]. After these are exhausted, surgical options range from arthroscopic debridement to arthrodesis[6]. Total knee arthroplasty (TKA) is an option for the treatment of end-stage PTA[7].

There is a paucity in the literature regarding TKA for the treatment of PTA. Compared to TKA for patients with primary OA, TKA performed for PTA is often more technically challenging due to previous surgeries and scarring, uses more hospital resources, and incurs a higher cost[8]. There are conflicting reports in the literature regarding the short and long term outcomes of these surgeries, as well as associated perioperative complications[8-10]. The goal of this systematic review is to summarize the functional outcomes, complications, and survivorship of TKA performed for the treatment of PTA.

MATERIALS AND METHODS

This systematic review was conducted according to the PRISMA guidelines. A comprehensive search of PubMed, Cochrane Library, and SCOPUS was performed for prospective and retrospective studies examining the use of TKA for the treatment of PTA. The initial search utilized the following key terms: Knee arthroplasty, TKA and traumatic arthritis. English-language studies that examined the short and/or long-term outcomes of TKA performed for traumatic arthritis were included. References from retrieved studies were further reviewed to identify additional articles of interest.

First, inclusion and exclusion criteria were applied to study titles and abstracts independently by two reviewers (Saleh H, Yu S) to identify potentially eligible studies; disagreements were settled and final selections made by a third reviewer (Schwarzkopf R). Studies discussing TKA and traumatic arthritis were included. Studies which focused on unicompartmental knee arthroplasty, osteotomy, and/or patients with primary OA were excluded. Those studies considered potentially eligible were retrieved in full for review. Again, two reviewers independently applied inclusion and exclusion criteria. Studies examining fractures of the proximal tibia, patella, and/or distal femur were included. All study methods, including case-control, cohort, randomized-controlled studies- prospective or retrospective- were included. Case reports, case series, and biomechanics studies were excluded (Figure 1). Included studies were systematically reviewed for methodology (*i.e.*, year of publication, sample size, study type, inclusion/exclusion criteria),

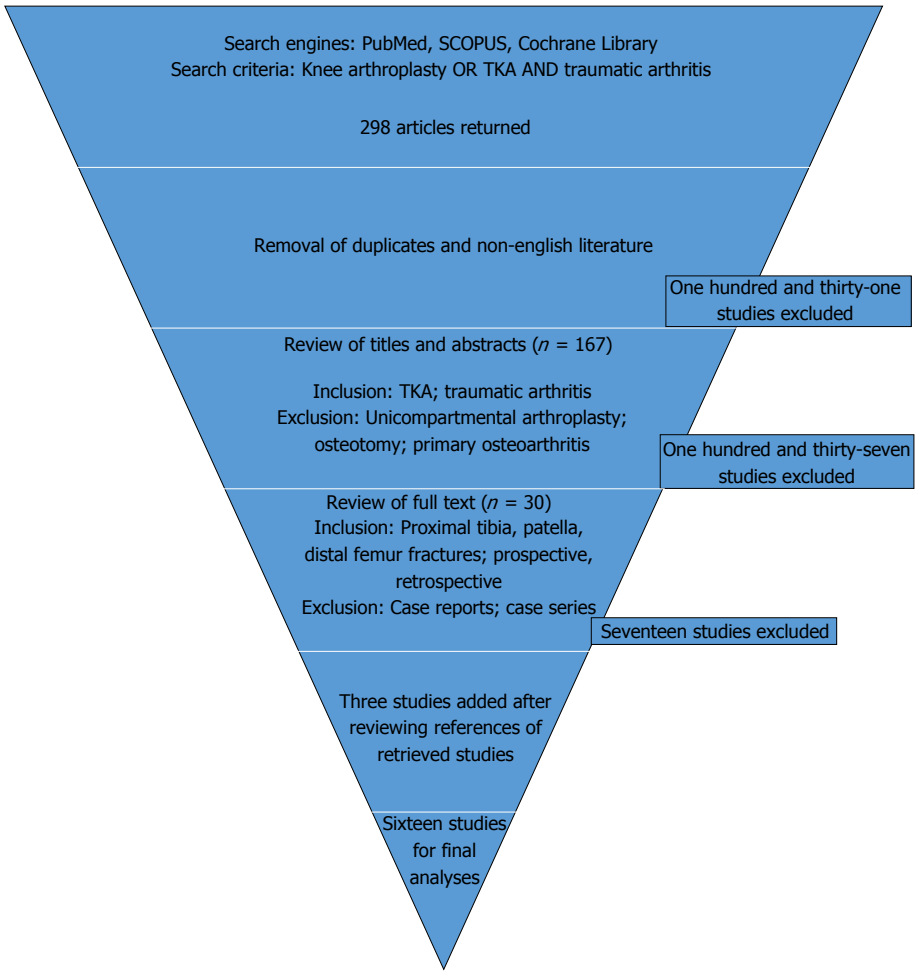

Figure 1 Flowchart summarizing the results of the literature search. TKA: Total knee arthroplasty.

demographics (*i.e.*, age, gender), and clinical outcomes (*i.e.*, follow-up period, preoperative diagnosis, implant selection criteria, pain, functional outcomes).

The main clinical outcomes studied regarding TKA following PTA included patient reported function, knee range of motion, and post-operative pain. Different studies utilized various criteria to assess these outcomes. Hospital for Special Surgery (HSS) Scores, International Knee Scores (IKS), Knee Osteoarthritis Outcomes Scores (KOOS), Oxford Knee Scores, and Knee Society Scores (KSS) were utilized by various studies to analyze the functional outcomes and pain following TKA. KSS was the most commonly utilized, however. The KSS is a 200-point scoring system which ascribes a maximum of 100 points each for function score (ability to walk, climb stairs, and need for assistive devices) and knee score (pain, range of motion, alignment, stability).

All studies examined complications following TKA for the treatment of PTA. The rate of complications was noted, as well as the specific complications observed. Six studies assessed the survivorship of TKA, with the endpoint defined as any subsequent surgery on the same knee. Studies followed patients for different averages of length of time, ranging from 3 to 15 years.

RESULTS

Demographics

Sixteen articles met the inclusion criteria. Ten studies were retrospective, four were prospective (two with the same study cohort), and two were prospective matched cohorts. All studies examined patients with PTA due to fractures of the proximal tibia, patella, and/or distal femur, including nonunions or malunions in three studies. Four studies compared patients with TKA to those with primary OA. The average length of follow-up ranged from 3 to 15 years (Table 1).

Clinical outcomes

Fifteen studies assessed the functional outcomes of TKA for PTA, using different scoring systems such as HSS, IKS, KOOS and KSS. All eleven studies utilizing the KSS criterion showed trends towards or significant improvement between pre- and post- operative function scores (Figure 2). Lizaur-Utrilla *et al*[11] reported no difference in the post-operative functional scores of patients with PTA *vs* primary OA. Lunebourg *et al*[8], utilizing the KOOS criteria, reported significantly lower post-operative scores for patients with PTA, compared to primary OA,

Table 1 Demographic information of the studies included in this systematic review

Ref.	Type of study	Total patients	Males (%)	Mean age	Fracture types	Mean follow-up time	Outcome criteria scoring
Abdel *et al*[14]	Prospective	62	36	63	Tibia	15	KSS
Bala *et al*[9]	Retrospective	PTA: 3509 Cont: 257, 611	PTA: 43 Cont: 35	N/A	Tibia/femur	N/A	CCI; Elixhauser
Benazzo *et al*[24]	Prospective	43	47	64	Tibia/femur/patella	6	KSS
Civinini *et al*[25]	Retrospective	25	36	57	Tibia	8	KSS
Deschamps *et al*[23]	Retrospective	78	42	63	Tibia/femur (includes malunions)	4	SOO
Lizaur-Utrilla *et al*[11]	Prospective matched cohort	PTA: 29 Cont: 58	35	PTA: 57.3 Cont: 59.2	Tibia	7	KSS, SF-12, WOMAC
Lonner *et al*[17]	Prospective	30	50	60	Tibia/femur	4	KSS
Lunebourg *et al*[8]	Retrospective	PTA: 33 Cont: 407	PTA: 55 Cont: 32	PTA: 69 Cont: 72	Tibia/femur	11	KSS, KOOS
Massin *et al*[13]	Retrospective	40	10	59	Tibia/femur	5	IKS
Papadopoulos *et al*[22]	Retrospective	47	21	65	Femur (includes malunions)	6	KSS
Parratte *et al*[19]	Retrospective	74	46	63	Tibia/femur/patella (includes malunion)	4	KSS
Saleh *et al*[6]	Retrospective	15	27	56	Tibia	6	HSS, SF-36
Scott *et al*[16]	Prospective matched cohort	PTA: 31 Cont: 93	26	66	Tibia	7	Oxford knee, SF-12
Shearer *et al*[10]	Retrospective	47	62	48	Tibia/femur	4	KSS
Weiss *et al*[12]	Prospective	62	36	63	Tibia	5	KSS
Wu *et al*[26]	Retrospective	15	80	58	Tibia/femur	3	KSS

PTA: Post traumatic arthritis; Cont: Control; OCS: Outcome criteria scoring; IKS: International Knee Scores; KOOS: Knee Osteoarthritis Outcomes Scores; HSS: Hospital for Special Surgery; KSS: Knee Society Scores.

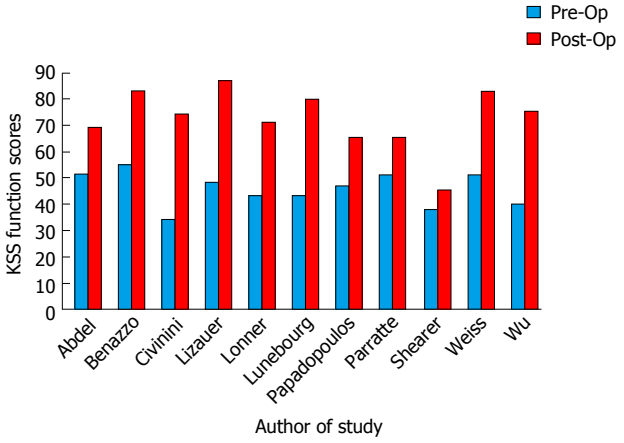

Figure 2 Comparison of pre- and post-operative Knee Society Scores function scores for patients who underwent total knee arthroplasty for treatment of post-traumatic arthritis. KSS: Knee Society Scores; Op: Operative.

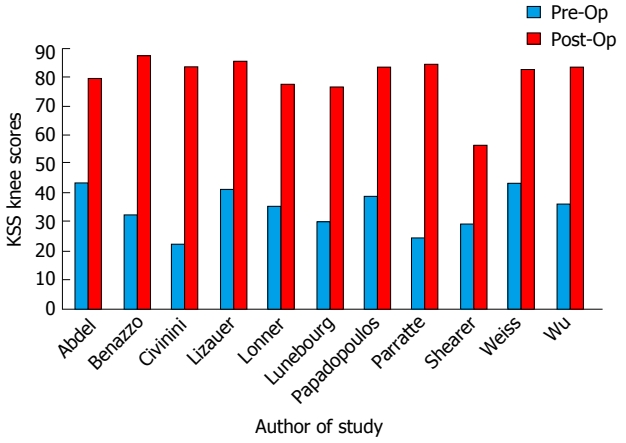

Figure 3 Comparison of pre- and post-operative Knee Society Scores knee scores for patients who underwent total knee arthroplasty for treatment of post-traumatic arthritis. KSS: Knee Society Scores; Op: Operative.

in all five categories - pain, symptoms, activities of daily living, sports activity, and quality of life.

With regards to knee and pain scores, all studies utilizing the KSS criteria showed trends towards or significant improvement in pre- and post-operative scores (Figure 3). Lizaur-Utrilla *et al*[11] reported no significant difference in post-operative scores between patients with PTA *vs* primary OA. They also found no significant difference in WOMAC pain scores between the two groups[11]. Further, Weiss *et al*[12] examined patient-reported pain. Whereas all patients reported at least mild pain prior to the PTA, 83.9% denied having any pain after the surgery.

Ten studies examined the effect of TKA on the range of motion (ROM). All studies found an improvement in the mean arc of motion (Figure 4). Arthroplasty provided a substantial gain in flexion[13]. Some studies further compared the ROM between patients with PTA and primary OA. Lunebourg *et al*[8] observed that while the degree of improvement in ROM was greater in patients who underwent TKA for PTA, the final results were still significantly lower than those with primary OA. However, Lizaur-Utrilla *et al*[11] reported no significant difference in the final ROM of patients who underwent TKA for PTA *vs*

Table 2 Summary of complications observed with total knee arthroplasty for patients with post-traumatic arthritis

Ref.	Total	S Infxn	D Infxn	STIFF	MUA	ROT	WC	O/P	INST	AL	REVR
Abdel *et al*[14]	34	3	5	10	[1]	[1]	5	8	3	6	18
Bala *et al*[9]	54	15	[1]	[1]	2	1	5	0	[1]	[1]	5
Benazzo *et al*[24]	21	[1]	2	5	[1]	[1]	[1]	[1]	[1]	2	7
Civinini *et al*[25]	32	4	4	8	[1]	4	4	[1]	[1]	4	[1]
Deschamps *et al*[23]	18	[1]	1	[1]	[1]	1	1	[1]	[1]	3	13
Lizaur-Utrilla *et al*[11]	14	3	[1]	[1]	3	3	3	[1]	[1]	3	3
Lonner *et al*[17]	57	[1]	10	[1]	[1]	3	6	[1]	[1]	[1]	[1]
Lunebourg *et al*[8]	21	[1]	6	6	[1]	[1]	[1]	[1]	[1]	3	9
Massin *et al*[13]	28	5	5	[1]	[1]	8	[1]	[1]	[1]	3	5
Papadopoulous *et al*[22]	19	[1]	6	[1]	[1]	2	4	[1]	2	[1]	13
Parratte *et al*[19]	26	3	3	8	[1]	4	[1]	[1]	1	[1]	[1]
Saleh *et al*[6]	67	[1]	15	[1]	20	[1]	[1]	7	7	[1]	[1]
Scott *et al*[16]	35	13	3	9	[1]	6	[1]	[1]	0	[1]	[1]
Shearer *et al*[10]	21	[1]	4	[1]	[1]	[1]	[1]	[1]	6	2	[1]
Weiss *et al*[12]	26	3	3	10	8	8	5	[1]	2	2	8
Wu *et al*[26]	47	13	[1]	[1]	27	13	[1]	[1]	7	[1]	[1]

All values are in percents. [1]Denotes the literature did not make mention of this complication, presumably because there were no such cases observed. S Infxn: Superficial infections; D Infxn: Deep infections; STIFF: Stiffness; MUA: Manipulation under anesthesia; ROT: Rupture of tendons; WC: Wound complications; O/P: Osteolysis/polywear; INST: Instability; AL: Aseptic loosening; REVR: Revision rate.

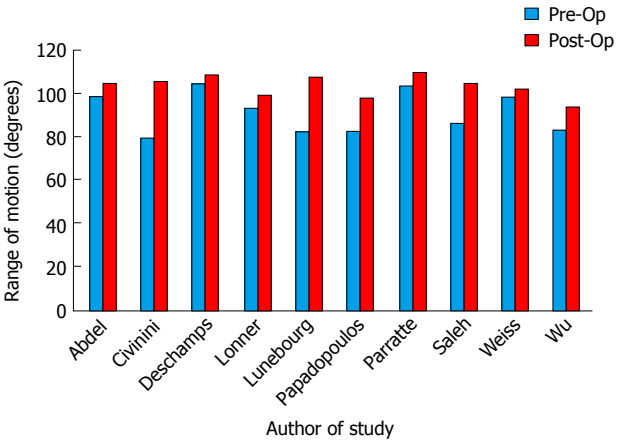

Figure 4 Comparison of average pre- and post-operative range of motions of the knee for patients who underwent total knee arthroplasty for treatment of post-traumatic arthritis. Op: Operative.

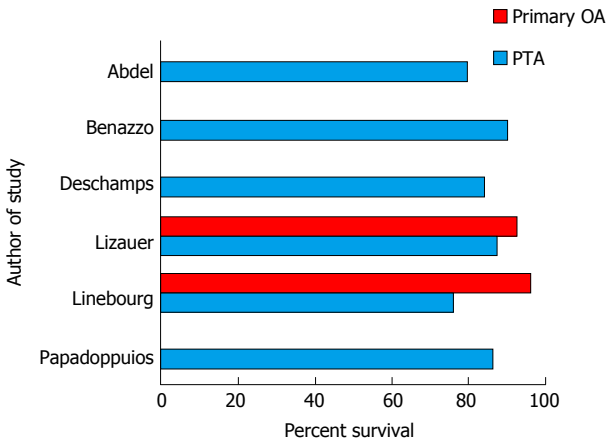

Figure 5 Comparison of survivorship at the longest time of follow-up of total knee arthroplasty performed for post-traumatic arthritis *vs* primary osteoarthritis. OA: Osteoarthritis; PTA: Post-traumatic arthritis.

primary OA.

Complications

Nine studies examined complications from TKA. The total complication rate at the time of longest follow-up ranged from 14% to 67%. Lizaur-Utrilla *et al*[11] reported that the complication rate was significantly higher in patients with PTA *vs* primary OA. The most commonly reported complications included superficial infections, deep infections, stiffness, manipulation under anesthesia (MUA), rupture of tendons, wound complications, osteolysis/polyethylene wear, instability, and aseptic loosening (Table 2). Bala *et al*[9] further reported that compared to patients with primary OA, patients with PTA had significantly higher complication rates of cellulitis, closed fractures, and wound complications. However, there was no difference between the groups in the rates of bleeding, broken prostheses, mechanical complications, MUA, osteolysis/polyethylene wear, or rupture of tendons[9]. In addition, nine studies analyzed the rate of revisions. This ranged from 3% to 18%.

Survivorship

Six studies assessed the survivorship from any revision following TKA. Endpoints were defined as any surgery on the operated knee after the index TKA. Lizaur-Utrilla *et al*[11], after a mean follow-up of 7 years reported 90% survival, with no significant difference from those with primary OA. After a mean follow-up of 11 years, Lunebourg *et al*[8] reported a survivorship of 79%, significantly lower than patients with primary OA. Abdel *et al*[14], after a follow-up of 15 years, reported 82% survival (Figure 5).

DISCUSSION

There is a paucity in the literature regarding the out-

come of TKA performed for the treatment of PTA. This systematic review aimed to examine the current English literature to investigate the clinical outcomes, perioperative complications, and survivorship of TKA for PTA.

Several studies utilized different scoring systems to judge the functional outcomes of TKA in PTA patients. Most of the studies utilized the KSS criteria, which is composed of a functional and knee score. The functional score includes a patient assessment of walking distance, ability to climb stairs, and need for assistive devices; the knee score incorporates patient reported pain, ROM, alignment, and stability[10]. The overwhelming majority of these studies reported an improvement in the functional and knee scores of patients following TKA for PTA. Lizaur-Utrilla *et al*[11] further reported that there were no significant differences in knee or WOMAC pain scores of patients treated with TKA for PTA *vs* primary OA. Lunebourg *et al*[8], while reporting significant improvement in scores, noted lower post-operative scores for patients with PTA *vs* primary OA.

These results indicate that TKA is an effective treatment for patients with PTA. It results in functional improvement, as well as increased range of motion and reduction in pain. With regards to the lower post-operative scores noted above, despite significant improvement, it is reasonable to infer that this difference compared to patients undergoing TKA for primary OA may be due to differences in the pre-operative status of the patients[8]. Thus, the post-operative difference observed in patients with PTA *vs* primary OA, is not due to the intrinsic success of the procedure itself, but rather the poorer pre-operative status of patients with PTA[8].

Six studies examined the survivorship of TKA with revision for any reason as an end point. Lizaur-Utrilla *et al*[11] found no significant difference in survivorship between patients with PTA *vs* primary OA, whereas Lunebourg did observe a difference[8]. Perhaps this disparity is due to differences in the lengths of follow-up. With increased length of follow-up, there seems to be a significant difference, in that TKA performed for PTA required more revisions and thus had decreased survivorship, compared to TKA performed for primary OA. Abdel *et al*[14] reported that the majority of the TKA revisions were for polyethylene wear. Given that patients with PTA tend to present at a younger age than primary OA, it is reasonable to at least partially attribute the decreased survivorship of TKA in patients with PTA to increased use and wear due to the younger age of this patient group[12]. Again, the difference in survivorship of TKA may be due to the patient population, and not the intrinsic success of the surgery. For example, Stiehl *et al*[15] reported higher risk-adjusted rates of failure in females and younger patients. Further long-term studies are needed to better characterize the factors that affect the survivorship of TKA for PTA.

All sixteen studies reported complications with TKA, including infection, stiffness, wound complications, intraoperative rupture of tendons, and osteolysis/ polyethylene wear. Scott *et al*[16] observed no significant difference in the overall rate of complications between patients who underwent TKA for PTA and primary OA. However, the type of complication differed between the two groups; wound complications and stiffness were observed more frequently in patients with TKA[16]. Abdel *et al*[14], even with the longest follow-up time of 15 years, reported that 90% of their complications occurred within the first two years of surgery. This data suggests that perioperative complications are more of a concern than long-term complications of TKA[14]. Despite the high rate of complications, most did not affect functional outcomes nor require further surgeries[11].

Many factors likely contribute to this observed rate of complications. First, patients with PTA have an inherent health challenge, in that PTA causes severe joint deformity as it is often accompanied by arthrofibrosis and malunion/nonunion of the fracture[9]. Second, patients with PTA often have had previous operations, which may compromise the soft-tissue surrounding the knee and thus predispose these patients to infections and wound complications[12]. Prior fracture surgeries are associated with increased infection rates after TKA[17]. Piedade *et al*[18] reported that prior knee surgery predisposes to higher post-operative complication rates in primary TKA. Third, scarring of the tissue, including fibrosis, may complicate exposure during surgery and positioning of the implant during surgery[12,19]. Malpositioning has been shown to have a negative effect on the long-term survival of TKA[20]. Efforts to preserve skin and soft-tissue vascularity, restore limb alignment, and ensure proper positioning may help prevent these complications[21,22]. Osteotomies may be utilized to correct rotational deformities of the knee[23]. Regardless, majority of studies reported improvement with total knee arthroplasty, with only few observed complications[24-26].

There are several limitations to this systematic review. First, there was inconsistency among studies regarding the criteria utilized to assess functional outcomes of TKA. However, this only slightly limited inter-study comparison, as majority of studies did utilize the KSS scoring systems. Second, tibial, patellar, and/or femoral fractures were examined in studies, but the results were grouped in this review. Third, there was a wide range in the average length of follow-up among the studies, from 3 to 15 years. However, this revealed not only short-term but also long-term outcomes. Despite these limitations, this review compiled the available research regarding the efficacy of TKA for the treatment of PTA.

In conclusion, despite the paucity in the literature regarding total knee arthroplasty in the treatment of post-traumatic arthritis, several conclusions may be drawn. TKA is an effective treatment for PTA, as it improves functional outcomes, range of motion, and pain. The accelerated nature of PTA and thus poorer pre-operative status of patients may explain the observed differences in the results of TKA following PTA *vs* primary OA. There is a significant rate of complications associated with this surgery, majority of which occur in the perioperative

period. Scarring from the initial trauma and prior surgeries, as well as the inherent technical difficulty of the operation, likely contribute to this complication rate.

COMMENTS

Background

With a prevalence of 21%-44% reported in the literature, post-traumatic arthritis (PTA) of the knee occurs following intra- or extra-articular fractures of the proximal tibia, patella, and/or distal femur. After non-operative treatment is exhausted, total knee arthroplasty (TKA) is one of the surgical options. Compared to TKA performed for patients with primary osteoarthritis, TKA performed for PTA is often more technically challenging due to previous surgeries and scarring. There is a paucity in the literature regarding TKA for the treatment of PTA. The goal of this systematic review is to summarize the functional outcomes, complications, and survivorship of TKA performed for the treatment of PTA.

Research frontiers

Several factors contribute to PTA following injury to the knee. These include mechanical imbalance, release of pro-inflammatory cytokines, and nonunions and malunions following fractures. TKA following PTA is often challenging, utilizes more hospital resources, and incurs higher costs.

Innovations and breakthroughs

The number of total knee arthroplasties performed in the United States has been increasing over the years. Newer implants have had great success, improving outcomes while decreasing the need for revisions. However, majority of these studies focus on patients with primary OA, not PTA.

Applications

PTA is prevalent in symptomatic arthritis, mainly in weight-bearing joints such as hips, knees and ankles. These patients have usually had prior surgeries and subsequent scarring, making total knee arthroplasties in this population technically more challenging. Understanding the functional outcomes and complications associated with total knee arthroplasties performed following PTA will help the orthopaedic surgeon in providing appropriate quality of care to this challenging subset of patients.

Peer-review

The manuscript is well written and interesting.

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Biologic agents for anterior cruciate ligament healing: A systematic review

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Data sharing statement: All the source data used to perform the present systematic review are available from the corresponding author at berardo.dimatteo@gmail.com.

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Abstract

AIM

To systematically review the currently available literature concerning the application of biologic agents such as platelet-rich plasma (PRP) and stem cells to promote anterior cruciate ligament (ACL) healing.

METHODS

A systematic review of the literature was performed on the use of biologic agents (*i.e.*, PRP or stem cells) to favor ACL healing during reconstruction or repair. The following inclusion criteria for relevant articles were used: Clinical reports of any level of evidence, written in English language, on the use of PRP or stem cells during ACL reconstruction/repair. Exclusion criteria were articles written in other languages, reviews, or studies analyzing other applications of PRP/stem cells in knee surgery not related to promoting ACL healing.

RESULTS

The database search identified 394 records that were screened. A total of 23 studies were included in the final analysis: In one paper stem cells were applied for ACL healing, in one paper there was a concomitant application of PRP and stem cells, whereas in the remaining 21 papers PRP was used. Based on the ACL injury pattern, two papers investigated biologic agents in ACL partial tears whereas 21 papers in ACL reconstruction. Looking at the quality of the available literature, 17 out of 21 studies dealing with ACL reconstruction were randomized controlled trials. Both studies on ACL repair were case series.

CONCLUSION

There is a paucity of clinical trials investigating the role of stem cells in promoting ACL healing both in case of partial and complete tears. The role of PRP is still controversial and the only advantage emerging from the literature is related to a better graft maturation over time, without documenting beneficial effects in terms of clinical outcome, bone-graft integration and prevention of bony tunnel enlargement.

Key words: Platelet-rich plasma; Growth factors; Stem cells; Anterior cruciate ligament reconstruction; Anterior cruciate ligament repair; Anterior cruciate ligament healing; Sports medicine; Regenerative medicine

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Core tip: There has been a growing interest in the past years on regenerative approaches to stimulate healing of musculo-skeletal tissues. The present systematic review focuses on the clinical application of biologic agents [platelet-rich plasma (PRP) and stem cells] to favor anterior cruciate ligament healing during procedures of reconstruction or repair. We show that there is inconclusive evidence to support the use of biologic augmentations, also due to the paucity of trials currently available, especially concerning stem cells. Looking at PRP, positive findings in terms of promotion of graft maturation were documented, but no beneficial influence was observed in terms of clinical outcome, bone-graft integration and prevention of tunnel enlargement.

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INTRODUCTION

Anterior cruciate ligament (ACL) injuries are among the most common conditions treated in everyday orthopaedic practice, with an increasing incidence in the past years due to a concurrent increase of sports activities among the general population[1,2]. ACL lesions can be distinguished in complete tears, generally treated by reconstruction, and partial tears (*i.e.*, incomplete tears of one or both ACL bundles). Their management can be very challenging, ranging from non-operative treatment to surgery (augmentation or traditional reconstruction), depending on the patients' symptoms and functional needs[3]. Epidemiological studies reveal an average incidence of 30 ACL injuries per 100000 people annually. Every year 175000 patients undergo ACL reconstruction in the United States[4]. These numbers highlight the social and economical impact of ACL injuries, and therefore justify the large interest in optimizing the treatment strategies for this particular injury. Several reconstructive techniques have been proposed in the past decades, mainly differing in terms of graft selection and graft fixation. The overall results are quite satisfactory, even at long-term evaluation, without a difference in terms of outcome among different surgical techniques[5,6]. Nevertheless, a documented failure rate of up to 14% for ACL reconstruction[7], stimulates scientific efforts to find solutions that could promote better graft maturation and healing to minimize the risk of failure and to allow a faster recovery for patients. Beyond maximizing the results of ACL reconstruction, there is an increasing demand for minimally invasive options to enhance intrinsic ACL healing in case of partial ruptures. These injuries represent a substantial amount of ACL injuries, whose treatment algorithm is still controversial. The possibility of promoting ACL healing without reconstruction is regarded as an attractive perspective, due to the inherent lower surgical morbidity and the faster return to physical activities.

The recent progress in the field of regenerative medicine has led to the application of biologic agents (platelet-derived growth factors and stem cells), which could provide a positive stimulus to tissue healing. Platelet-rich plasma (PRP) is currently the most exploited biological augmentation used in orthopaedic practice, both for the treatment of degenerative disease (like osteoarthritis and tendinopathies), and sports-related injuries[8,9]. It is an autologous blood derived product which is obtained by centrifugation or filtration of peripheral blood in order to concentrate platelets, which are a reservoir of several growth factors and bioactive molecules involved in tissue homeostasis and anabolism[10,11]. Several *in vitro* and animal studies demonstrated that intra-ligamentary administration of PRP determines an increase in cellular density and neovascularization of the ACL. This results in a better organization of collagen fibers for superior tensile resistance and biomechanical properties[12-14]. In light of these promising pre-clinical data, and also due to the easy preparation modalities, platelet-rich products are used more and more by clinicians from all over the world. In more recent times, mesenchymal stem cells from different sources have been proposed to augment ACL reconstruction or repair. In this case, flourishing pre-clinical literature suggests that stem cell administration could stimulate tissue maturation, improve histological appearance, and favor bone-to-tendon integration[15,16]. Therefore, the implementation of experimental techniques in the clinical practice seems reasonable. A relevant number of clinical reports have been published investigating the actions of these fashionable biological strategies so far. The aim of the present paper is to systematically review the available literature concerning the application of PRP or stem cells to stimulate ACL healing, and to trace the state of the art in the use of biologic agents in this particular field of sports medicine. Moreover, this paper reveals if these novel strategies could really play a beneficial role in promoting graft maturation and healing and provide a better clinical outcome in the treatment of

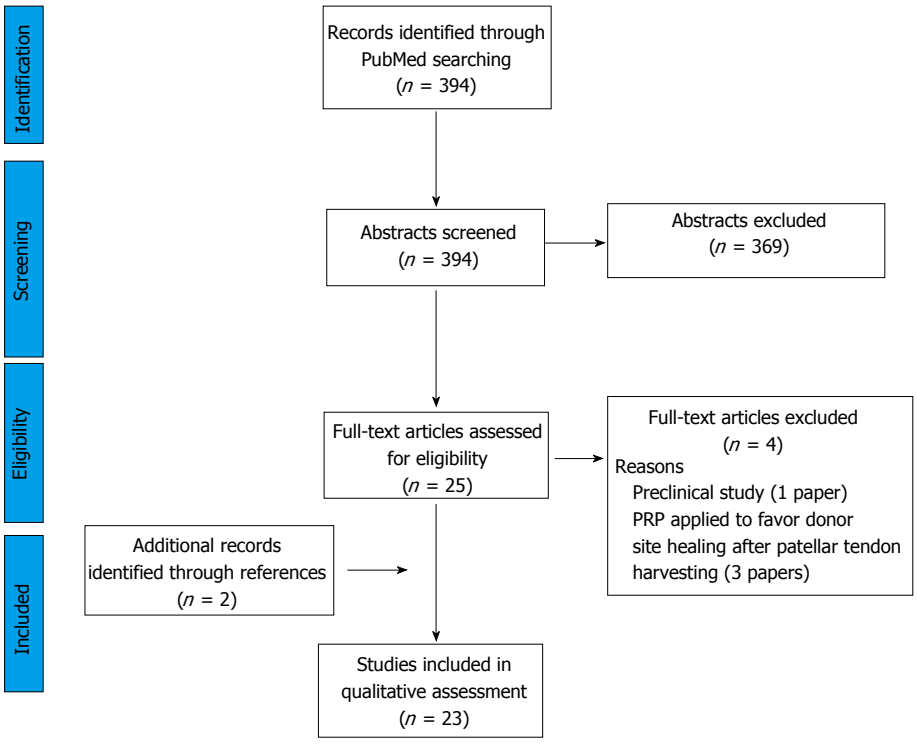

Figure 1 PRISMA flowchart resuming the papers' selection process. PRP: Platelet-rich plasma.

complete and partial ACL lesions.

MATERIALS AND METHODS

A systematic review of the literature was performed on the use of biologic agents (*i.e.*, PRP or stem cells) to promote ACL healing during surgical reconstruction or repair. The search was conducted on the PubMed database on March 31, 2016 using the following formula: [(PRP or platelet concentrate or platelet gel or platelet rich plasma or ACP or autologous conditioned plasma or PRGF or PRF or platelet lysate or platelet derived growth factors or plasma growth factors or platelet rich fibrin) or (stem cell or mesenchymal or mesenchymal stem cell or bone marrow concentrate or bone marrow aspirate or adipose derived or peripheral blood)] and (ACL or anterior cruciate ligament).

Screening process and analysis were conducted separately by two independent observers (Di Matteo B and Andriolo L). First, the articles were screened by title and abstract. The following inclusion criteria for relevant articles were used during the initial screening of titles and abstracts: Clinical reports of any level of evidence, written in English language, published in the past 20 years (1996-2016), on the use of PRP or stem cells during ACL reconstruction/repair. Exclusion criteria were articles written in other languages, reviews, or studies analyzing other applications of PRP/stem cells in knee surgery not related to promoting ACL healing. In the second step, the full texts of the selected articles were screened, with further exclusions according to the previously described criteria. Moreover, the articles not reporting clinical, magnetic resonance imaging (MRI), or histologic results were excluded. Reference lists from the selected papers were also screened. A flowchart of the systematic review is provided in Figure 1. Relevant data were then extracted and collected in a unique database, with the consensus of the two observers, to be analyzed for the purposes of the present manuscript.

RESULTS

Qualitative synthesis of trials included in the review

The database search identified 394 records, and the abstracts were screened and selected according to the inclusion/exclusion criteria. As shown in Figure 1, a total of 27 full-text articles were assessed for eligibility. Four articles did not fulfill the inclusion criteria and were further excluded, leading to a total of 23 studies included in the final analysis (Figure 1). Only one paper dealt with the application of stem cells for ACL healing[17], one paper investigated the concurrent action of PRP and stem cells[18], whereas the remaining 21 papers focused on PRP application solely (one in partial rupture and 20 in ACL reconstruction)[19-39]. Based on the ACL injury pattern, two papers investigated biologic agents in ACL partial tears[18,19] whereas 21 papers in ACL reconstruction[17,20-39].

Looking at the quality of the available literature, 17 out of 21 studies dealing with ACL reconstruction were randomized controlled trials (RCTs) (Table 1), whereas only case series are available for ACL repair.

Concerning delivery methods of biologic agents, several different strategies were tested by authors, sometimes in combination (Table 1): Simple intra-articular injection, intra-ligamentary injection, local

application onto the surface of the tendon graft, local injection within the bony tunnels, multiple intra-tendinous depots, or even selective administration through a spongy membrane soaked in PRP and sutured around the graft.

The different application methods will be discussed separately according to the specific ACL treatment analyzed in the clinical trials, *i.e.*, repair (2 studies) or reconstruction (21 studies). A detailed description of the trial features is presented in Table 1.

Biologic agents in ACL repair

Two papers investigated the contribution of biologic agents applied to promote healing of ACL in case of partial rupture. The first one, a retrospective case series, was published by Seijas *et al*[19] in 2014. They analyzed a small cohort of 19 football players who were treated by arthroscopic intra-ligamentary injection of 4 mL of leukocyte-poor PRP, followed by a 6 mL intra-articular injection at the end of surgery. The results were pretty satisfactory and 16 out of 19 patients were able to return to previous sports activity level with stable knees (evaluated by KT-1000), and in particular patients with Tegner Score 10 achieved the fastest return to sports. In the prospective trial published by Centeno *et al*[18], ten patients in total were treated by fluoroscopic guided intra-ligamentary injection of PRP + platelet lysate + bone marrow derived stem cells (harvested from the iliac crest and concentrated in the operating room). Overall results were satisfactory, with seven out of ten patients presenting signs of ACL healing at MRI evaluation performed at average 3 mo from the procedure. This evidence suggested a potential clinical usefulness of this approach to be confirmed by a larger trial.

Biologic agents in ACL reconstruction

Twenty-one papers[17,20-39] investigated the role of biologic agents during ACL reconstruction; only one paper dealt[17] with the use of bone marrow concentrate, whereas 19 focused on PRP. With regards to the graft used for reconstruction, in 14 trials authors employed hamstrings, in three patellar tendon, in two trials ACLs were either reconstructed with hamstrings or patellar tendon, and just one paper documented the use of allograft. The papers published analyzed the following main outcomes after biologic agents administration (Table 1): (1) clinical results evaluated by functional scores, objective measurements and time to return to sports; (2) bony tunnel enlargement over time [evaluated by computed tomography (CT)]; (3) ACL graft-bone interface integration (evaluated by MRI); and (4) ACL graft maturation/remodeling (evaluated by MRI).

Looking at clinical outcomes and functional scores, eight papers[20-27] analyzed this specific aspect, seven of which were RCTs. Overall results were controversial: The RCTs authored by Del Torto *et al*[21], Darabos *et al*[22] and Vogrin *et al*[23] showed significant advantage of PRP administration over the control group. In particular, Del Torto *et al*[21] documented superior clinical outcome (IKDC subjective score) for the PRP group at any follow-up evaluation up to 24 mo; similar results were reported by Darabos *et al*[22], who documented less swelling and better performance in functional tests at 6 mo, and also a significant difference in WOMAC Stiffness subscale at 12 mo. Interestingly, also a reduced synovial fluid concentration of IL-1b was found in the PRP group after 10 d from the procedure. Vogrin *et al*[23] reported a significant difference in favor of PRP when comparing KT-2000 values at 3 and 6 mo after surgery. It was suggested that growth factors played a substantial role in enhancing knee stability. Conversely, four RCTs[24-27] were not able to document any clinical benefit from PRP administration. In particular the trial authored by Valentí Azcárate *et al*[24] included 150 patients divided into three treatment groups and evaluated up to 24 mo. Two different PRP formulations (PRGF and lab made PRP) were tested without demonstrating any clinical benefit over control groups, either in terms of objective or subjective measurements, with the exception of swelling, which was observed to be less 24 h after surgery in the PRGF group compared to PRP and control groups.

The issue of prevention of bony tunnels enlargement was addressed in six trials, all of which were RCTs[22,25,28-31]. Only in two of them[22,28] it was demonstrated that PRP, injected locally into the tunnels[28] or intra-articularly[22], could prevent their enlargement over time. Conversely, four papers revealed no significant difference with regard to this specific outcome between treatment groups. Additionally, one paper[31] revealed that the only positive effect in preventing tunnel widening was achieved by implanting a bone plug into the tunnel.

Concerning the graft-bone tunnel integration, eight papers (six RCTs)[17,21,24,31-35] investigated this specific issue. In only two RCTs the use of PRP provided beneficial effects in terms of better corticalization of the tunnel walls[32] or higher vascularization at the graft-bone interface[33], whereas in the remaining trials[17,21,24,31,34,35] no inter-group difference was observed over time. Among the papers reporting negative results for PRP in this specific parameter, there is also only one study[17] documenting the role of bone marrow concentrate, which was not able to provide beneficial effects.

Diverging results were reported when analyzing the graft maturation over time after ACL reconstruction. Eight papers in total (five RCTs)[27,31,33,34,36-39] assessed this specific parameter, and six of them (four RCTs) documented a positive influence of PRP administration[27,31,36-39], whereas just two papers (one RCT) failed to reveal any inter-group difference[33,34]. In the vast majority of cases graft maturation was evaluated by imaging assessment, revealing a helpful role of PRP in stimulating a faster and better MRI or CT appearance of the graft. Signal of the graft was more similar to the posterior cruciate ligament, which points out an overall positive modulation of the ligamentization process. One paper[39] reported also histologic evaluation of the grafts, which were biopsied during second look arthroscopies performed after a mean of 15 mo from primary ACL reconstruction. In the PRP group, the graft presented a significantly better

Table 1 Synopsis of all clinical trials dealing with the application of biologic agents to promote anterior cruciate ligament healing

Ref.	Study design	Methods	Results
Clinical results			
+ Del Torto *et al*[21]	Prospective comparative study (PRFM *vs* control) 28 patients (14 *vs* 14)	ACL reconstruction with hamstring tendon graft fixed in the femoral tunnel through the RIGIDFIX system (DePuy) and in the tibial tunnel through the Bio-INTRAFIX system (DePuy) PRFM was prepared using Cascade Medical Enterprises 2 tube kit (Cascade Medical Enterprises, Wayne, NJ). PRFM clot was sutured in the proximal graft loop and it reaches the proximal tunnel once the graft is pulled in place. Distally, the PRFM clot was inserted between the four strands of the G-ST graft before the interference screw system was applied	PRFM-augmented patients showed a statistically significant higher clinical improvement at 24 mo follow-up (P = 0.032) Objective clinical evaluation both through IKDC score and with Rolimeter arthromether did not show any difference between the two groups
Magnussen *et al*[20]	Retrospective comparative study (PRP *vs* control) 58 patients (29 *vs* 29)	ACL reconstruction with allograft tibial tendon, fixed with absorbable cross pin in femoral tunnel and absorbable interference screw in tibial tunnel After graft positioning, intra-articular portion was coated with PRP prepared with GPS Ⅱ Platelet Concentrate Separation Kit (Biomet)	Decreased effusions at 10 ± 4 d was noted in the PRP group, but this difference disappeared by 8 ± 4 wk No differences in patient-reported outcomes were noted in the 58 patients with two-year outcome data
Darabos *et al*[22]	Randomized trial (ACS *vs* control) 62 patients (31 *vs* 31)	ACL reconstruction with hamstring (30) or patellar tendon (32), fixed with BioTransFix (Arthrex) or RigidFix (Mytek) at femoral side, and with an interference screw at the tibial side ACS was produced drawing venous blood into syringes containing pre-treated glass beads, and after a period of incubation serum is extracted through centrifugation. ACS was administered with an injection regime of 4 injections on day 0 (day of surgery), day 1, day 6, and day 10	Clinical outcomes were consistently better in patients treated with ACS at all data points and for all outcome parameters, with statistically significant differences in the WOMAC stiffness subscale after 1 yr Decrease in IL-1b synovial fluid concentration was more pronounced in ACS group, with statistically significant lower values in the ACS group at day 10
Vogrin *et al*[23]	Randomized trial (PRP *vs* control) 45 patients (22 *vs* 23)	ACL reconstruction with double-looped semitendinosus and gracilis tendon graft fixed with two bioabsorbable cross pins in the femoral tunnel and one bioabsorbable interference screw in the tibial tunnel PRP was produced with Magellan system (Medtronic) and applied into the femoral and tibial tunnels as well as onto the graft itself	PRP group demonstrated significantly better anteroposterior knee stability than control group: Calculated improvements in knee stability at 6 mo were 1.3 ± 1.8 mm in the control group and 3.1 ± 2.5 mm in the platelet gel group (P = 0.011)
- Valentí Azcárate *et al*[24]	Randomized trial (PRP *vs* PRGF *vs* control) 150 patients (50 *vs* 50 *vs* 50)	ACL reconstruction using a patellar tendon allograft transtibial technique fixed with a RigidFix technique (DePuy Mitek,) with two biodegradable cross pins at the femoral bone and a tibial biodegradable (Byocril) interference screw PRP was produced with a double-spin procedure using a standard centrifuge and applied covering the ligament and suturing it over itself with gel in its interior, and introducing the gel obtained after activating the poor platelet concentration after implantation of the graft inside the tibial tunnel PRP was produced following Anitua's technique (PRGF-Endoret Technology) and applied injecting it into the graft before implantation, with the biocompatible fibrin applied into the tibial tunnel at the end of surgery	No significant differences in functional results at the final follow-up of 24 m No statistically significant differences between the three groups in CRP 1 and VAS 24 h after surgery No significant differences in the range of knee motion, muscle torque, KT-1000 or IKDC score The PRGF group showed a statistically significant improvement in swelling scores 24 h after surgery compared with the PRP and control groups
Vadalà *et al*[25]	Randomized trial (PRP *vs* control) 40 patients (20 *vs* 20)	ACL reconstruction with hamstrings (Out-In technique), fixed with Swing-Bridge device on femoral side and Evolgate screw on tibial side PRP was produced with Fast Biotech kit (MyCells PPT-Platelet Preparation Tube) and applied as follows: 5 mL between peripheral part of the graft and the femoral tunnel wall; 5 mL in semisolid pattern above the graft; 5 mL of liquid and semisolid PRP on the tibial side	Physical examination as well as the evaluation scales used showed no differences between the two groups at 14.7 mo of follow-up
Nin *et al*[26]	Randomized trial (PRP *vs* control) 100 patients (50 *vs* 50)	ACL reconstruction with patellar tendon allograft, fixed with two biodegra-dable cross pins in femur and a tibial biodegradable interference screw Ligament was covered with PRP (produced with standard centrifuge) and sutured over itself with PRP in its interior. The rest of the gel was introduced after implantation of the graft inside the tibial tunnel	The results did not show any statistically significant differences between the groups for inflammatory parameters, magnetic resonance imaging appearance of the graft, and clinical evaluation scores after 18 mo

	Ventura *et al*[27]	Randomized trial (PRP *vs* control) 20 patients (10 *vs* 10)	ACL reconstruction with quadruple hamstring tendon graft, with a femoral transcondylic fixation (BioTransFix) and tibial interference screw (BioRCI, Smith and Nephew) PRP was obtained according to the GPS Biomet-Merck technique (Biomet) and applied in femoral and tibial tunnels	There were no significant differences concerning clinical score and examination between the two groups 6 mo after ACL surgery
Tunnel enlargement			
+	Starantzis *et al*[28]	Randomized trial (PRP *vs* control) 51 patients (25 *vs* 26)	ACL reconstruction with hamstring tendons (Semitendinosus and Gracilis) as a quadrupled graft, using distal fixation in the femur (Crosspin Linvatec or Endobutton Linvatec) and tibial fixation with a biodegradable interference screw (Linvatec) plus bone bridge suture anchoring Half of the PRP (produced using the Biomet GPS Ⅲ kit) was added between the strands of the graft and left to form a clot before the graft fixation. Then, the remaining 3 mL was injected into the femoral tunnel using an introducer	The morphology of the dilated tunnels was conical in both groups There was a statistical significant difference in the mid distance of the tunnels between the two groups 1 yr after surgery No significant difference of the Lysholm scores between the two groups during the observation period was detected
	Darabos *et al*[22]	Randomized trial (ACS *vs* control) 62 patients (31 *vs* 31)	ACL reconstruction with hamstring (30) or patellar tendon (32), fixed with BioTransFix (Arthrex) or RigidFix (Mytek) at femoral side, and with an interference screw at the tibial side ACS was produced drawing venous blood into syringes containing pre-treated glass beads, and after a period of incubation serum was extracted through centrifugation. ACS was administered with an injection regime of four injections on day 0 (day of surgery), day 1, day 6, and day 10	Bone tunnel enlargement measured with CT scans was significantly less (6 mo: 8%, 12 mo: 13%) in ACS group than in control group (6 mo: 31%, 12 mo: 38%)
-	Vadalà *et al*[25]	Randomized trial (PRP *vs* control) 40 patients (20 *vs* 20)	ACL reconstruction with hamstrings (Out-In technique), fixed with Swing-Bridge device on femoral side and Evolgate screw on tibial side PRP was produced with Fast Biotech kit (MyCells PPT-Platelet Preparation Tube) and applied as follows: 5 mL between peripheral part of the graft and the femoral tunnel wall; 5 mL in semisolid pattern above the graft; 5 mL of liquid and semisolid PRP on the tibial side	The use of PRP did not seem to be effective in preventing tunnel enlargement at 14.7 mo of follow-up
	Mirzatolooei *et al*[29]	Randomized trial (PRP *vs* control) 46 patients (23 *vs* 23)	ACL reconstruction with single-bundle quadrupled autograft of hamstrings, fixed with a cross-pin in femoral tunnel and a bio-absorbable interference screw in tibial tunnel Graft was immersed in the PRP solution (produced with Double syringe system, Arthrex) for five minutes before implantation; 2 mL of PRP was injected into the femoral tunnel and 1.5 mL into the tibial tunnel at the end of the surgery	Despite slightly less tunnel widening in the PRP group, there were no significant differences at any of the sites of measurement between immediately after surgery and three months post-operatively
	Silva *et al*[30]	Randomized trial (4 groups) 40 patients (10 control *vs* 10 PRP in FT *vs* 10 PRP in FT and intra-articular at 2- and 4 wk *vs* 10 PRP activated with thrombin in FT)	Double-bundle arthroscopic ACL reconstruction with autologous hamstring tendons, fixed with two Endobuttons for the AMT and PLT in the femur and two bioabsorbable interference screws in the tibia PRP (produced with GPS Ⅲ Kit, Biomet) was placed between the strands of the graft in each femoral tunnel	At 3 mo postoperatively, all tunnels had enlarged compared to the diameter of the drill and most tunnels enlarged more in the midsection than at the aperture in a fusiform manner The use of growth factors during and after surgery did not show any influence in the tunnel enlargement (P = 0.563)
	Orrego *et al*[31]	Randomized trial (4 groups) 108 patients (27 control *vs* 26 PC *vs* 28 BP *vs* 27 PC + BP)	ACL reconstructions with quadruple semitendinosus-gracilis graft, fixed with a biodegradable transfixing pin proximally and a biodegradable inter-ference screw distally; BP was placed by interference fit at the femoral tunnel Five milliliter PRP (produced with Biomet GPS Ⅱ kit, Biomet) was added between the graft strands before passing it into the tunnel. After fixation, 1 mL of PRP was injected into the femoral tunnel between the graft strands	The use of PC did not show any significant effect in the tunnel widening evolution at 6 mo follow-up The use of a BP effectively prevented tunnel widening The BP and PC combination did not show a synergic effect as compared to PC or BP individually
ACL graft-bone interface/integration			
+	Rupreht *et al*[32]	Randomized trial (PRP *vs* control) 41 patients (21 *vs* 20)	ACL reconstruction with double-looped semitendinosus and gracilis tendon autograft, fixed with two bioabsorbable cross pins in femoral tunnel and one bioabsorbable interference screw in tibial tunnel. PRP was applied after autograft positioning, into the femoral and tibial tunnels (1 mL in each of them), and onto the graft itself (3 mL)	A gradual increase in the percentage of the tunnel wall consisting of tunnel wall cortical bone (TCB) during the follow-up was observed. At 6 mo the mean percentage of TCB was significantly higher (P = 0.003) in the PRP group than in the control group

	Vogrin *et al*[33]	Randomized trial (PRP *vs* control) 41 patients (21 *vs* 20)	ACL reconstruction with double-looped semitendinosus and gracilis tendon graft fixed with two bioabsorbable cross pins in the femoral tunnel and one bioabsorbable interference screw in the tibial tunnel PRP was produced with Magellan system (Medtronic) and applied into the femoral and tibial tunnels as well as onto the graft itself	After 4-6 wk, there was a significantly higher level of vascularization in the osteoligamentous interface in PRP group (0.33 ± 0.09 *vs* 0.16 ± 0.09, $P < 0.001$) In the intra-articular part of the graft, there was no evidence of revascularization in either group
-	Del Torto *et al*[21]	Prospective comparative study (PRFM *vs* control) 28 patients (14 *vs* 14)	ACL reconstruction with hamstring tendon graft fixed in the femoral tunnel through the RIGIDFIX system (DePuy) and in the tibial tunnel through the Bio-INTRAFIX system (DePuy) PRFM was prepared using Cascade Medical Enterprises 2 tube kit (Cascade Medical Enterprises). PRFM clot was sutured in the proximal graft loop and it reaches the proximal tunnel once the graft is pulled in place. Distally, the PRFM clot was inserted between the four strands of the G-ST graft before the interference screw system was applied	MRI evaluation considering graft–tunnel interface and graft signal intensity provided similar results between the two examined groups, without any statistically significant difference. In the majority of the cases, a good signal quality of the graft and a scarce film of synovial fluid at the graft–tunnel interface were observed
	Silva *et al*[17]	Randomized trial (BMC *vs* control) 43 patients (20 *vs* 23)	ACL reconstruction with double-looped semitendinosus and gracilis tendon autograft fixed with a Toggleloc Ziploop (Biomet) in femoral tunnel and a bioabsorbable interference screw (Biomet) in tibial tunnel Bone marrow was harvested from the iliac crest and concentrated to obtain 3 mL BMC. 1.5 mL of BMC concentrate was injected inside the femoral end of the graft itself before graft positioning, and the remaining 1.5 mL BMC injected within the tunnel around the graft, from the bottom down to the entrance of the tunnel	Adult non-cultivated BMC did not seem to accelerate graft-to-bone healing in ACL reconstruction: No difference in the signal-to-noise ratio of the inter-zone on MRI between the experimental and the control group 3 mo after surgery
	Valentí Azcárate *et al*[24]	Randomized trial (PRP *vs* PRGF *vs* control) 150 patients (50 *vs* 50 *vs* 50)	ACL reconstruction using a patellar tendon allograft transtibial technique fixed with a RigidFix technique (DePuy Mitek) with two biodegradable cross pins at the femoral bone and a tibial biodegradable (Byocril) interference screw PRP was produced with a double-spin procedure using a standard centrifuge and applied covering the ligament and suturing it over itself with gel in its interior, and introducing the gel obtained after activating the poor platelet concentration after implantation of the graft inside the tibial tunnel PRP was produced following Anitua's technique (PRGF-Endoret Technology) and applied injecting it into the graft before implantation, with the biocompatible fibrin applied into the tibial tunnel at the end of surgery	No statistically significant differences were noted between groups in intensity, thickness, or uniformity of graft at 6 mo MRI
	Figueroa *et al*[34]	Comparative study (PRP *vs* control) 50 patients (30 *vs* 20)	ACL reconstruction with hamstring tendons fixed with a cross-pin in femoral tunnel and a bio-absorbable interference screw in tibial tunnel PRP was produced with Magellan Magellan system (Medtronic) and applied under arthroscopy in both the tibial (3 mL) and femoral (3 mL) tunnels with a long needle syringe, and directly applied in the intra-articular graft portion (4 mL)	No statistically significant benefit in the PRP group in terms of integration assessment at 6 mo follow-up
	Silva *et al*[35]	Randomized trial (4 groups) 40 patients (10 control *vs* 10 PRP in FT *vs* 10 PRP in FT and intra-articular at 2- and 4 wk *vs* 10 PRP activated with thrombin in FT)	Double-bundle arthroscopic ACL reconstruction with autologous hamstring tendons, fixed with two Endobuttons for the AMT and PLT in the femur and two bioabsorbable interference screws in the tibia PRP (produced with Mini GPS Ⅲ Kit, Biomet) was placed between the strands of the graft in each femoral tunnel	The graft integration was not complete at 3 mo after surgery in the PL and AM femoral tunnel, and the use of PRP isolated or with thrombin seemed not to accelerate tendon integration
	Orrego *et al*[31]	Randomized trial (4 groups) 108 patients (27 control *vs* 26 PC *vs* 28 BP *vs* 27 PC + BP)	ACL reconstructions with quadruple semitendinosus-gracilis graft, fixed with a biodegradable transfixing pin proximally and a biodegradable interference screw distally; BP placed by interference fit at the femoral tunnel 5 mL PRP (produced with GPS Ⅱ kit, Biomet) was added between the graft strands before passing it into the tunnel. After fixation, 1 mL of PRP was injected into the femoral tunnel between the graft strands	The use of PC did not show any significant effect in the osteoligamentous interface at 6 mo follow-up
ACL graft remodeling				

+	Seijas *et al*[36]	Randomized trial (PRP *vs* control) 98 patients (49 *vs* 49)	ACL reconstruction with autologous patellar tendon grafts with 9 mm bone plugs and fixed with hydroxyapatite screws in femur and tibia 8 mL of PRP was produced with PRGF technique (BTI Systems Vitoria, Spain) and percutaneously injected into the suprapatellar joint after portal suture	More patients in the PRP group than controls attained higher stages of remodeling at month 4 (P = 0.003), month 6 (P = 0.0001), and month 12 (but NS P = 0.354)
	Rupreht *et al*[37]	Randomized trial (PRP *vs* control) 41 patients (21 *vs* 20)	ACL reconstruction with double-looped semitendinosus and gracilis tendon autograft, fixed with two bioabsorbable cross pins in femoral tunnel and one bioabsorbable interference screw in tibial tunnel PRP was applied after autograft positioning, into the femoral and tibial tunnels (1 mL in each of them), and onto the graft itself (3 mL)	MRI measurements indicated a reduced extent of edema during the first postoperative month as well as an increased vascular density and microvessel permeability in the proximal tibial tunnel at 1 and 2.5 postoperative months as the effect of the application of PRP
	Radice *et al*[38]	Comparative study (PRP *vs* control) 50 patients (25 *vs* 25)	ACL reconstructions with BPTB autograft (15 *vs* 10) or Harmstring (10 *vs* 15). Fixation in BPTB autograft with metallic interference screws, in hamstring autograft with metallic or bioabsorbable cross-pin in the femur and a bioabsorbable screw with a metallic staple in the proximal tibia PRP (produced with GPS Ⅲ Kit, Biomet) was administered with the help of a sutured and compressed Gelfoam; 5 mL PRP was added homogeneously so as to completely cover the graft	ACL reconstruction with the use of PRPG achieved complete homogeneous grafts assessed by MRI, in 179 d compared with 369 d for ACL reconstruction without PRPG. This represented a time shortening of 48% with respect to ACL reconstruction without PRPG
	Sánchez *et al*[39]	Comparative study (PRP *vs* control) 37 patients (22 *vs* 15)	ACL reconstruction with hamstring tendons, fixed with transcondylar screw proximally and PRGF-treated bone plug and two metal staples distally 6 mL PRP was produced with BTI System Ⅱ (BTI Biotechnology Institute) and injected within the tendon graft fascicles with several punctures performed along the graft length, graft soaked in PRP until implantation and the remaining aliquots applied at the portals during suturing	PRGF resulted in more mature tissue than controls at histology (P = 0.024) Histologically evident newly formed connective tissue enveloping the graft was present in 77.3% of PRGF-treated grafts and 40% of controls Overall, arthroscopic evaluations were not statistically different between PRGF and control groups (P = 0.051)
	Orrego *et al*[31]	Randomized trial (4 groups) 108 patients (27 control *vs* 26 PC *vs* 28 BP *vs* 27 PC + BP)	ACL reconstructions with quadruple semitendinosus-gracilis graft, fixed with a biodegradable transfixing pin proximally and a biodegradable inter-ference screw distally; BP placed by interference fit at the femoral tunnel 5 mL PRP (produced with Biomet GPS Ⅱ kit, Biomet) was added between the graft strands before passing it into the tunnel. After fixation, 1 mL of PRP was injected into the femoral tunnel between the graft strands	The use of PC had an enhancing effect on the graft maturation process evaluated only by MRI signal intensity at 6 mo follow-up
	Ventura *et al*[27]	Randomized trial (PRP *vs* control) 20 patients (10 *vs* 10)	ACL reconstruction with quadruple hamstring tendon graft, with a femoral transcondylic fixation (BioTransFix, Arthrex) and tibial interference screw (BioRCI, Smith and Nephew) PRP was obtained according to the GPS Biomet-Merck technique (Biomet) and applied in femoral and tibial tunnels	CT highlighted a significant difference (P < 0.01) between ACL density of the two groups and showed that ACL density was similar to that of the posterior cruciate ligament in GF-treated group at 6 mo follow-up
-	Figueroa *et al*[34]	Comparative study (PRP *vs* control) 50 patients (30 *vs* 20)	ACL reconstruction with hamstrings fixed with a femoral cross-pin and a tibial bio-absorbable interference screw PRP was produced with Magellan Magellan system (Medtronic, Minneapolis, MN) and applied under arthroscopy in both the tibial (3 mL) and femoral (3 mL) tunnels with a long needle syringe, and directly applied in the intra-articular graft portion (4 mL)	No statistically significant benefit in the PRP group in terms of graft maturation (ligamentization) at 6 mo of follow-up
	Vogrin *et al*[33]	Randomized trial (PRP *vs* control) 41 patients (21 *vs* 20)	ACL reconstruction with double-looped semitendinosus and gracilis tendon graft fixed with two bioabsorbable cross pins in the femoral tunnel and one bioabsorbable interference screw in the tibial tunnel PRP was produced with Magellan system (Medtronic, Minneapolis, MN) and applied into the femoral and tibial tunnels as well as onto the graft itself	After 4-6 wk, significantly higher level of vascularization in the osteoligamentous interface in PRP group (0.33 ± 0.09 *vs* 0.16 ± 0.09, P < 0.001). No evidence of revascularization in the intra-articular part in either group
ACL repair				
+	Centeno *et al*[18]	Prospective study (BMC, PRP, PL) 10 patients	Pre-injection of hypertonic dextrose solution into the ACL using fluoroscopic guidance 2-5 d prior to BMC injection in order to prompt a brief inflammatory response in the ACL Intra-ligamentous injection of autologous BMC (harvested from iliac crest and isolated through	Patients included had ACL laxity on exam, and MRI evidence of grade 1, 2, or 3 ACL tears < 1 cm retraction 7/10 patients showed improvement in objective measures of ACL integrity in their post-procedure MRIs

		centrifugation), PRP and PL (prepared from venous blood *via* centrifugation and recentrifugation after freezing) using fluoroscopic guidance. Remaining BMCs were injected into the joint	The mean VAS change was a decrease of 1.7 (P = 0.25), the mean LEFS change was an increase of 23.3 (P = 0.03), and mean reported improvement was 86.7%
Seijas *et al*[19]	Retrospective study (PRGF-Endoret) 19 patients	PRGF-Endoret was produced using the technique described by Anitua and applied with a spine needle in both the proximal origin of the bundle and in the middle portion thereof in an amount of about 4 cc At the end of the surgery another injection of PRGF-Endoret was administered (6 cc) in the articular space.	16/19 professional soccer players with partial ACL tears returned to the same level Normal KT-1000 values in all operated cases Time to return to play: 16.2 ± 1.4 wk for Tegner 9 pts, 12.3 ± 1.1 for Tegner 10

PRP: Platelet rich plasma; ACL: Anterior cruciate ligament; PRFM: Platelet rich fibrin matrix; ACS: Autologous conditioned serum; PC: Platelet concentrate; BP: Bone plug; FT: Femoral tunnel; PLT: Posterolateral tunnel; AMT: Anteromedial tunnel; BPTB: Bone-patellar; PRGF: Plasma preparation rich in growth factors; BMC: Bone marrow concentrate; PL: Platelet lysate; VAS: Pain visual analog scale; NS: Non-significant; LEFS: Lower extremity functional scale.

enveloping by mature connective tissue, with signs of improved graft maturation, depending on the time passed from surgery.

DISCUSSION

The main findings of the present systematic review are that: (1) there is a paucity of clinical trials investigating the role of stem cells in promoting ACL healing, both in the treatment of partial and complete ACL tears. Therefore, no conclusive statement can be issued regarding the efficacy of this treatment approach; (2) despite the high number of RCTs, the role of PRP in ACL healing is still controversial, and it is not possible to fully endorse this biologic strategy to this particular indication; and (3) the use of biologic agents in partial ACL rupture is very limited, with just two clinical trials published, and therefore, the possibility of treating this kind of injuries by regenerative approaches remains an open question.

Biologic approaches to enhance healing of musculoskeletal injuries are for sure a fashionable topic in the field of regenerative medicine. The overall brilliant results documented by *in vitro* and *in vivo* trials have stimulated their use in clinical practice, with different indications and targets, ranging from degenerative conditions (such as osteoarthritis and tendinopathies) to muscle and ligament injuries[8,9]. The first product that has encountered a large clinical application (together with a large commercial success) is PRP, whose use has been documented in papers published more than a decade ago. Despite being no more a "novel" treatment option, there is still uncertainty about its real effectiveness and, up to the present moment, there is no clear recommendation for its use in any of the clinical conditions. Therefore, we underline the fact once again, that the positive findings from pre-clinical studies cannot be reproduced in the *in vivo* model, whose complexity cannot be fully mirrored in laboratory experiments[40].

Looking at PRP potential in ACL healing, the literature is not conclusive with regards to the benefit of PRP application in providing a faster recovery and better functional outcome after ACL reconstruction. However, the evidence is currently limited to short term evaluations (up to 24 mo), whereas no trial has yet pointed out if the administration of platelet-derived growth factors could be effective at longer follow-up, providing more stable results or lower rate of recurrent injury. Interestingly, most of the studies documented a superior graft maturation over time after PRP administration. These findings were achieved by imaging evaluation, and in one case also by histology[39]. A better ligamentization of the graft may be related to superior and longer lasting mechanical properties that could impact clinical outcome at middle-to-long term evaluation. In light of that, further studies correlating imaging, histology and functional scores are expected to better clarify the role of PRP. Considering that patients after ACL reconstruction have high expectations in terms of durability of results, the possibility of reducing re-injury rate and providing a more stable clinical outcome seems very attractive and could justify the use of biologic agents. With regards to aspects such as bone-graft integration and prevention of bony tunnel enlargement, results are controversial and, overall, the majority of trials fail to support the use of PRP for this indication. By the way, research is moving forward in the attempt to optimize PRP technology to obtain the best possible results[41]. The main limiting factor that scientists and clinicians have to overcome is the great inter-product variability and the absence of a well defined therapeutic protocol[42]. When so many variables come into play, there is an intrinsic difficulty in finding the right way to move on. First of all, there are plenty of different PRP products that could be used. All of them differ in many fundamental aspects, such as preparation procedures, cellular content, platelet concentration rate, physical properties and eventual use of activators to enhance growth factors' release. Authors have been using either lab made products or commercial kits from several companies, all characterized by different preparation protocols that rendered different PRP formulations[11,43,44]. In particular, the aspect of cellularity is currently the most debated one and there are controversial findings regarding the role of the different components of PRP, especially leukocytes whose presence has been deemed as detrimental based on laboratory findings that have not been confirmed in the clinical setting, leaving many questions open to investigation[45,46].

Another fundamental issue regards the application modalities of PRP during ACL reconstruction or repair. Several different approaches have been proposed, ranging from simple intra-articular injections to intra-ligamentary deposition, graft coating, topical use into

the bony tunnels, or at the bone-graft interface. Even more complex strategies, such as suturing PRP clots or PRP-soaked sponges directly onto the graft have been suggested. In any case, based on the available data, it is impossible to endorse an ideal product or an ideal therapeutic modality to stimulate ACL healing.

Looking at the application of mesenchymal stem cells, they have been introduced into clinical practice more recently than PRP, and they have been tested mainly in the field of cartilage regeneration/osteoarthritis[47]. With regards to ACL healing, the current evidence is strongly affected by the paucity of literature available that prevents any indications for the use of such biological augmentation. As pointed out previously, only two papers in total (one RCT and one case series) investigated the potential efficacy of bone marrow concentrate in this particular field of sports medicine[17,18]. One of these studies applied the stem cell concentrate to treat partial ACL tears together with PRP, which prevents any clear understanding of the real contribution of each biological product. The lack of data is a severe flaw, also considering that stem cell therapy is characterized by the same great variability described in the case of PRP products. Many factors should be taken into account. First of all, the source of stem cells should be considered, since it is possible to obtain them from different anatomical sites (bone marrow, adipose tissue, synovial tissue, peripheral blood and so on), and this peculiar aspect could play a major role in determining clinical outcome. Furthermore, stem cells could be used as a concentrate, or could be expanded *in vitro* and then applied during surgery[48]. By the way, the application of cellular therapy in orthopaedics is under strict surveillance and clinicians have to face regulatory burdens that are currently limiting the number of ongoing clinical trials[49]. For this reason, there is such a great dichotomy between the flourishing pre-clinical literature and the very limited data coming from clinical studies. This explains the fact that mainly bone marrow concentrate has been tested for ACL healing at the moment, since it is the easiest and safest way to collect and administer stem cells in a surgical setting. In light of these remarks, both in the field of PRP and stem cell augmentation for ACL healing, there is a need of further basic science studies to better understand the mechanisms of action of these powerful biological agents. Moreover, there is also a need of more high-level comparative trials that could clarify if some specific "products" or applicative modalities are truly better than others.

A further consideration should be issued on the ACL injury patterns that have been treated with biologic agents. The large majority of papers (21) were focused on their application during ACL reconstructive surgery, whereas only two trials, both case series, have investigated their potential in partial ACL tears (Table 1). The possibility of enhancing ACL healing in case of partial rupture is very attractive, because it can contribute to functional recovery and avoid the higher surgical stress of traditional reconstruction. However, even in this case, the current lack of data prevents a reliable assessment of the efficacy of biologic agents, when applied for this specific purpose. The technique described in the literature to deliver PRP or stem cells into the injured ACL (intra-ligamentary injection under fluoroscopic or arthroscopic check) is feasible[18,19] and results seem to be encouraging. Again further high quality trials, with higher number of patients and longer follow-up, are needed to confirm these preliminary findings. Furthermore, considering that partial ACL tears may have variable features, it would also be clinically relevant to introduce and validate a classification system, with the aim of understanding whether the biological approach could be more effective in specific lesion patterns.

In conclusion, based on the available clinical evidence, there is a lack of data about the efficacy of stem cells in ACL healing, whereas the data concerning the role of PRP are not conclusive to understand if it could provide a faster recovery and better functional outcome during ACL repair/reconstruction. Despite some positive findings in terms of graft maturation and clinical outcome, further long-term studies are needed to identify whether the administration of PRP could truly play a beneficial role during ACL reconstruction. Lastly, in contrast to the large number of trials dealing with ACL reconstruction, the treatment of partial ACL tears with biologic agents has been poorly investigated, and therefore there is need of more high quality data to understand the efficacy of biologic agents in this particular application.

COMMENTS

Background

Complete and partial anterior cruciate ligament (ACL) tears are among the most common injuries treated by orthopaedic surgeons every day. Currently, there are several surgical approaches that have been proposed to reconstruct/repair torn ACL and, despite overall satisfactory clinical outcome at medium-long term, there is still a failure rate up to 14% as documented by some studies. The current trend of research is aimed at finding solutions that could provide better and longer lasting results by stimulating ligament regeneration through the use of powerful biologic agents, such as platelet-rich plasma (PRP) and stem cells. The main goal is to achieve a tissue quality which is more similar to the one of the native ligament. The aim of the present paper is to systematically review the state of art regarding the application of biologic agents to promote ACL healing.

Research frontiers

Tissue engineering and regenerative approaches are currently widely applied in orthopaedics to stimulate healing of several tissues, from bone to cartilage and ligaments. In particular, PRP and stem cells are the most exploited strategies tested in clinical practice. Their application in the field of ACL healing (both for reconstruction and repair) represents the current cutting-edge technology to stimulate ligament regeneration in the attempt to improve clinical outcomes.

Innovations and breakthroughs

A total of 23 studies were included in the final analysis. In one paper stem cells were applied for ACL healing, in one paper there was a concomitant application of PRP and stem cells, whereas in the remaining 21 papers PRP was used. The main findings of the present systematic review are that: (1) there is a paucity of clinical trials investigating the role of stem cells in promoting ACL healing, both in the treatment of partial and complete ACL tears. Therefore, no conclusive indication can be issued regarding the efficacy of this treatment approach; (2) despite the high number of randomized controlled trials, the role of PRP in ACL healing is still controversial, and it is not possible to fully endorse this biologic

strategy to this particular indication; and (3) the use of biologic agents in partial ACL rupture is very limited, with only two clinical trials published, and therefore, the possibility of treating this kind of injuries by regenerative approaches remains an open question.

Applications

The application of PRP and stem cells in the field of ACL repair/reconstruction is technically feasible and safe. Several different approaches have been proposed, ranging from simple intra-articular injections to intra-ligamentary deposition, graft coating, topic use into the bony tunnels, or at the bone-graft interface. Even more complex strategies, such as suturing PRP-clots or PRP-soaked sponges directly onto the graft have been suggested. However, at present moment, it is impossible to endorse an ideal biologic product or an ideal therapeutic modality to stimulate ACL healing. There is a need of further basic studies to better understand the mechanisms of action of these powerful biological agents and also more high-level comparative trials are required to clarify if some specific "products" or applicative modalities are truly better than others.

Terminology

PRP is an autologous blood derivative which contains a higher concentration of platelets with respect to whole blood. The platelets act as a resorvoir of a milieau of growth factors that could play a fundamental role in stimulating tissue healing and regeneration. Stem cells in orthopaedics are usually mesenchymal stem cells obtained from bone marrow. They can be concentrated or expanded in lab for being used as a biologic augmentation during surgical procedures or as an injective approach for treating a wide range of musculo-skeletal disorders.

Peer-review

This is a very interesting review article on biologic agents for ACL injury healing. It is well-written and has a correct methodology and structure.

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Arterial complications, venous thromboembolism and deep venous thrombosis prophylaxis after anterior cruciate ligament reconstruction: A systematic review

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Abstract

AIM

To summarize the current knowledge on vascular complications and deep venous thrombosis (DVT) prophylaxis after anterior cruciate ligament (ACL) reconstruction.

METHODS

A systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement. MEDLINE, EMBASE, Cochrane, Web of Science, CINAHL, PubMed publisher, and Google scholar medical literature databases were searched up to November 10, 2015. Any arthroscopic surgical method of primary or revision intra-articular ACL reconstruction of all graft types in humans was included. A risk of bias assessment was determined.

RESULTS

Fourty-seven studies were included in the review. Pseudaneurysms were the most frequently reported arterial complication after ACL reconstruction, irrespective of graft type or method of graft fixation with an incidence of 0.3%. The time to diagnosis of arterial complications after ACL reconstruction varied from days to mostly weeks but even years. After ACL reconstruction without thromboprophylaxis, the incidence of DVT was 9.7%, of which 2.1% was symptomatic. The incidence of pulmonary embolism was 0.1%. Tourniquet time

> 2 h was related to venous thromboembolism. Thromboprophylaxis is indicated in patients with risk factors for venous thromboembolism.

CONCLUSION

After ACL reconstruction, the incidence of arterial complications, symptomatic DVT and pulmonary embolism was 0.3%, 2.1% and 0.1% respectively. Arterial complications may occur with all types of arthroscopic ACL reconstruction, methods of graft fixation as well as any type of graft. Patients considered to be at moderate or high risk of venous thromboembolism should routinely receive thromboprophylaxis after ACL reconstruction.

Key words: Anterior cruciate ligament reconstruction; Arterial complication; Pseudoaneurysm; Venous thromboembolism; Pulmonary embolism; Thromboprophylaxis

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Core tip: Vascular complications after anterior cruciate ligament (ACL) reconstruction of the knee may present serious morbidity and even mortality. Although rare, it is necessary to understand the main risks and symptoms of these devastating lesions. This systematic review presents the current knowledge on arterial injuries, venous thromboembolism and thromboprophylaxis after ACL reconstruction.

Janssen RPA, Reijman M, Janssen DM, van Mourik JBA. Arterial complications, venous thromboembolism and deep venous thrombosis prophylaxis after anterior cruciate ligament reconstruction: A systematic review. *World J Orthop* 2016; 7(9): 604-617 Available from: URL: http://www.wjgnet.com/2218-5836/full/v7/i9/604.htm DOI: http://dx.doi.org/10.5312/wjo.v7.i9.604

INTRODUCTION

Vascular complications after anterior cruciate ligament (ACL) reconstructions cause serious morbidity and potential mortality[1]. They can be categorized in arterial and venous thromboembolic complications. The incidence of arterial complications after ACL reconstruction is unknown[1]. Case reports have been published using various techniques of ACL reconstruction[1].

Venous thromboembolism (VTE) after ACL reconstruction may present clinically as symptomatic or asymptomatic deep venous thrombosis (DVT), pulmonary embolism (PE) and postthrombotic syndrome[1-3]. The incidence of VTE after ACL reconstruction varies from 0.2%-14%[1,2,4-11]. The variable incidence of VTE after ACL reconstruction depends on the diagnostic methods of DVT (clinical parameters, venography, ultrasound or magnetic resonance venography), the heterogeneity of patient demographics (age, risk factors, surgical time, concomitant surgery, tourniquet time and postoperative mobilisation) and DVT prophylaxis[1,12]. Deep venous thrombosis may cause pulmonary embolism which may be fatal in its immediate course or may result in pulmonary hypertension in the long term[1,13]. The postthrombotic syndrome may cause serious morbidity and affects 23% of limbs 2 years after DVT, 35%-69% and 49%-100% at 3 and at 5-10 years respectively[1,4,14]. ACL reconstruction ranks number 6 of most performed orthopedic operations[15]. However uniform evidence-based clinical practice guidelines for DVT prophylaxis after ACL reconstruction are lacking[1,2,16].

A thorough understanding of the incidence, risk factors and potential methods for prevention of vascular complications after ACL reconstruction is critical to optimize patient safety[17]. This systematic review presents the current knowledge of arterial complications, VTE and thromboprophylaxis after arthroscopic ACL reconstruction. The review will highlight the incidence, types and risk factors of arterial complications and VTE after ACL reconstruction as well as the current recommendations for DVT prophylaxis.

MATERIALS AND METHODS

The reporting in this systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[18].

Eligibility criteria

Inclusion criteria were all study designs evaluating arterial complications and VTE after ACL reconstruction. Any arthroscopic surgical method of primary or revision intra-articular ACL reconstruction of all graft types was included. Only human *in vivo* studies were eligible for inclusion in the systematic review. The full inclusion and exclusion criteria are presented in Table 1.

Electronic search

MEDLINE, EMBASE, Cochrane, Web of Science, CINAHL, PubMed publisher, and Google scholar medical literature databases were searched up to November 10, 2015. Search terms included synonyms for anterior cruciate ligament reconstruction, and synonyms for vascular complications. Additionally, the reference lists of all eligible studies were manually screened.

Study selection

All eligible articles were screened by title and abstract by 2 teams of reviewers. One author screened all abstracts and 2 co-authors scored both half of the abstracts independently of the first author. After this first inclusion, the full-text articles were assessed. Disagreements on inclusions were resolved by discussion and, if necessary, a final decision was made by a fourth reviewer. Furthermore, all references of both excluded and included articles were analyzed for eligible articles. The consequences of the search strategy (screening

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Studies (randomized, non-randomized, case series, prospective or retrospective design, case reports) evaluating vascular and thromboembolic complications after ACL reconstruction
All types of ACL reconstruction surgery related arterial and venous complications
All types of ACL reconstruction surgery related thromboembolic complications
Any arthroscopic surgical method of primary or revision intra-articular ACL reconstruction
All graft types for ACL reconstruction
Multiligament reconstructions including ACL
Combined ACL reconstruction and meniscal surgery
Human *in vivo* studies with reported outcome
English language
Full text available
Exclusion criteria
Animal studies
Cadaveric studies
Nonsurgical related vascular or thromboembolic complications

ACL: Anterior cruciate ligament.

of title and abstract) are that only those studies will be eligible for inclusion if arterial complications, VTE or DVT prophylaxis after ACL reconstruction are reported in the abstracts. Studies that did not report these findings in their abstract were consequently not included in the current review.

Data collection process
Two reviewers extracted the study characteristics, type of vascular complications, and if available the incidence of vascular complications in the study population.

Data items
The data included study type, patient demographics, type and incidence of vascular or thromboembolic complication (arterial, pulmonary embolism, symptomatic or asymptomatic DVT), surgical technique, graft type, graft fixation method, thromboprophylaxis, tourniquet time and pressure and comorbidity for vascular and thromboembolic complications.

Synthesis of results
Incidence of DVT (separated for all and symptomatic) and PE was pooled of the studies reporting data of isolated ACL reconstruction without thromboprophylaxis. Additionally, the incidence numbers of those studies with low risk of bias on the items patient selection and classification were pooled.

Assessment of risk of bias
Risk of bias was assessed in the studies used for the determination of the incidence of vascular and/or venous complications following an ACL reconstruction procedure. Risk of bias was not assessed for case reports. Two reviewers independently assessed the risk of bias of the studies. In case of disagreement, the two reviewers tried to achieve consensus. If consensus was not achieved, a third reviewer was asked for final judgment. Those items of the checklist of the Dutch Cochrane Centre of risk of bias of studies reporting the incidence of adverse events, suitable for the current study objectives, were used for the risk of bias assessment[19]. All items could be rated "positive" (+), "negative" (-) or "not clear" (?).

Studies were classified as low risk of selection bias when they scored "positive" on the item: "The authors reported inclusion of 'all' or 'consecutive' patients". Studies were classified as low risk of information bias when they scored "positive" on the items: "Follow-up period was minimally 1 year" and "if all included patients were evaluated for complications".

Research questions
The following research questions were formulated.

Arterial complications: (1) What is the incidence of arterial complications after ACL reconstruction? (2) What types of arterial complications occur after ACL reconstruction? (3) Is there a correlation between arterial complications and fixation methods for ACL reconstruction? (4) What is the time to diagnosis of arterial complications after ACL reconstruction?

Venous complications: (1) What is the incidence of VTE after ACL reconstruction without thromboprophylaxis? (2) Is tourniquet time related to VTE after ACL reconstruction? (3) Is thromboprophylaxis indicated after ACL reconstruction?

RESULTS
Study selection
The PRISMA flow chart of the systematic review is presented in Figure 1. A total of 47 studies were included: 2 randomized controlled trials (RCT)[20,21], 8 prospective cohort studies[5,6,10,11,22-25], 9 retrospective cohort studies[2,4,7,8,26-30] and 28 case reports[13,31-57].

Risk of bias assessment
The results of the risk of bias assessment for the included studies are presented in Table 2. Case reports were not eligible for risk of bias assessment.

Details of arterial complications and thromboprophylaxis
The results of the arterial complications are specified in Table 3. The details of VTE and thromboprophylaxis are detailed in Table 4. Table 5 presents the incidence of DVT and PE after pooling the data for isolated ACL reconstructions without thromboprophylaxis.

Results of individual studies and answers to research questions
Arterial complications: (1) What is the incidence of arterial complications after ACL reconstruction?

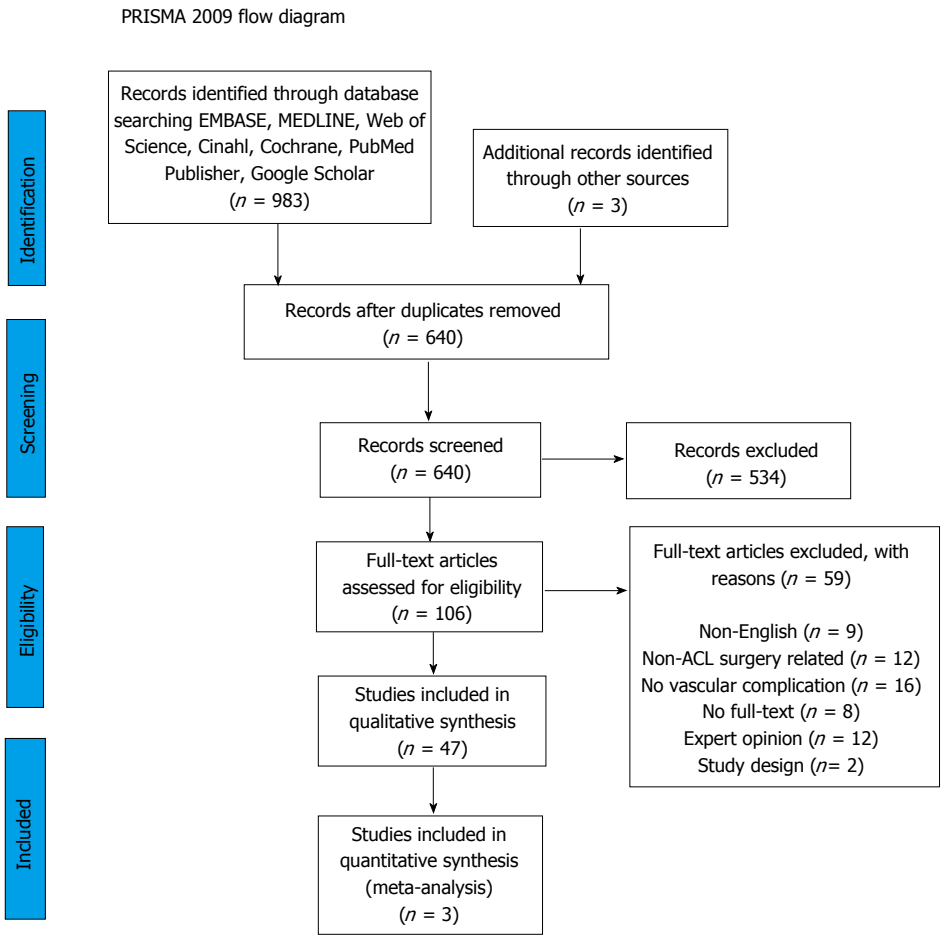

Figure 1 Prisma flow chart. ACL: Anterior cruciate ligament.

Table 2 Risk of bias of studies reporting venous complications

Ref.	Study design	Patient selection[1]	Follow-up[2]	Classification[3]
Adala *et al*[6]	PC	+	-	+
Born *et al*[26]	RS	+	-	-
Cullison *et al*[10]	PC	?	-	+
Dong *et al*[8]	RS	?	-	+
Ettema *et al*[27]	RS	-	?	-
Gaskill *et al*[2]	RS	+	-	-
Hetsroni *et al*[30]	RS	?	?	-
Hirota *et al*[22]	PC	-	-	+
Hirota *et al*[25]	PC	-	-	+
Jameson *et al*[28]	RS	?	-	-
Jaureguito *et al*[7]	RS	+	-	+
Lind *et al*[23]	PC	+	?	-
Maletis *et al*[11]	PC	?	?	-
Marlovits *et al*[20]	RCT	-	-	+
Mohtadi *et al*[21]	RCT	+	+	-
Struijk-Mulder *et al*[5]	PC	+	-	+
Sun *et al*[29]	RS	+	-	+
Williams *et al*[24]	PC	-	-	+
Ye *et al*[4]	RS	?	-	+

[1]Inclusion of consecutive patients; [2]Was follow-up period adequate (minimum 1 year) for exposure of adverse event? [3]Was the used classification shown to be valid and reliable? +: Yes; -: No; ?: Not clear; RCT: Randomized controlled trial; PC: Prospective cohort study; RS: Retrospective study.

Twenty-two studies reported arterial complications after ACL reconstruction. These papers described a total of 23 case reports. Arterial complications after ACL reconstruction are rare. The incidence of arterial lesions after ACL reconstruction is only described in 1 study. Janssen *et al*[45] have analysed their consecutive series retrospectively and found an incidence of 0.3% for arterial pseudoaneurysm in a series of 299 arthroscopic ACL reconstructions.

The incidence of arterial complications after ACL reconstruction is very low. The incidence of 0.3% presented in a retrospective series may be overestimated considering the fact that only case reports have been published in the literature. Long-term studies are necessary for analysis of the incidence of arterial complications after ACL reconstruction.

(2) What types of arterial complications occur after ACL reconstruction? Table 3 presents the details of the 23 published arterial complications after ACL reconstruction. The described complications were arterial-occlusions, avulsions, penetrating injuries, arteriovenous fistulae or pseudoaneurysms. Pseudoaneurysm was the most frequently reported arterial complication (13 cases). Various arteries around the knee were injured: Popliteal artery, posterior tibial

Table 3 Results arterial injuries (case reports)

Ref.	ACLR	Graft type	Fixation femur	Fixation tibia	Vascular injury	Diagnosis after ACLR	Treatment	Cause vascular complication
Spalding *et al*[31]	Primary	Gore-Tex	?	?	Compression popliteal artery	8 yr	Cyst removal	Compression by cyst containing ruptured Gore-tex graft
Aldridge *et al*[32]	Primary	BPTB	Interference screw	Interference screw	Avulsion middle gen. artery	4 wk	Direct repair avulsion	Lesion artery by shaver
Evans *et al*[[33]	Primary	BPTB	Interference screw	Interference screw	Pseudoaneurysm med. inf. gen. artery	5 wk	Ligation pseudoaneurysm	Elevation periosteum medial tibia (tunnel preparation)
Friederich *et al*[34]	Primary	BPTB	Staples	Staples	Lesion sup. lat. gen. artery	5 mo	Removal staples	Hardware femur
Kanko *et al*[35]	Primary	BPTB	Interference screw	Bicortical screw	Pseudoaneurysm popliteal artery	2 yr	Ligation pseudoaneurysm	Drill bit for bicortical tibia fixation?
Keçeci *et al*[36]	Primary	BPTB	Interference screw	Interference screw	Popliteal arteriovenous fistula	18 mo	Venous re-anastomosis	Break-out posterior femoral cortex
Lamo-Espinosa *et al*[37]	Primary	BPTB	Interference screw	Interference screw	Lesion lat. inf. gen. artery	1 d	Embolization	Simultaneous lateral meniscectomy
Mello *et al*[38]	Primary	BPTB	Interference screw	Interfererce screw	Pseudoaneurysm med. inf. gen. artery	6 wk	Embolization	Direct lesion artery by shaver
Pereira *et al*[39]	Primary	BPTB	Interference screw	Interference screw	Pseudoaneurysm sup. lat. gen. artery	11 d	Ligation pseudoaneurysm	Hardware femur
Roth *et al*[40]	Primary	BTPB + augmentation	Staple	?	Occlusion popliteal artery	6 wk	Venous bypass	Entrapment between graft and femur
Tam Kelvin *et al*[41]	Primary	BPTB	Endobutton	Interference screw	Pseudoaneurysm popliteal artery	8 d	Repair by venous graft	Direct trauma by guide pin femoral canal
Lee *et al*[42]	Rerevision	?	Rigidfix cross pin	?	2 lesions sup. to level of med. and lat. gen. artery	6 wk	Venous re-anastomosis	Drill tip for Rigidfix cross pin
Ambrosia *et al*[57]	Primary	Hamstring	TightRope	Interference screw	Pseudoaneurysm popliteal artery	7 wk	Venous bypass	Hamstring harvest/previous catheterization-angioplasty?
Buda *et al*[43]	Primary	Hamstring ACL + allograft PCL	Staples	Staples	Pseudoaneurysm post. tibial artery	1 wk	Embolization	Surgical approach PCL or hamstring harvest?
Galanakis *et al*[44]	Primary	Hamstring + extra-artic. rec.	Staples	Pes anserinus	Pseudoaneurysm popliteal artery	Day of surgery	Venous re-anastomosis	Lesion artery by shaver and popliteal entrapment syndrome
Janssen *et al*[45]	Primary	Hamstring	Bone Mulch Screw	WasherLoc	Pseudoaneurysm popliteal artery	12 d	Venous repair	Drill tip for bicortical tibial fixation
Janssen *et al*[47]	Primary	Hamstring	Bone Mulch Screw	WasherLoc	Subtotal occlusion popliteal artery	19 d	Embolectomy	Preexistent intimal lesion after knee dislocation
Janssen *et al*[47]	Primary	Hamstring	Bone Mulch Screw	WasherLoc	Pseudoaneurysm and occlusion popliteal artery	9 d	Venous re-anastomosis	Drill tip for bicortical tibial fixation
Milankov *et al*[48]	Primary	Hamstring	Interference screw	Interference screw	Pseudoaneurysm med. inf. gen. artery	1 d	Ligation pseudoaneurysm	Hamstring harvest?
Panigrahi *et al*[56]	Primary	Hamstring ACL + PCL	?	?	Occlusion popliteal artery	Day of surgery	Embolectomy	Preexistent thrombotic occlusion after knee dislocation
Tsubosaka *et al*[54]	Primary	Hamstring	Cortical buttons	Screw post	Pseudoaneurysm med. inf. gen. artery	2 d	Embolization	Anteromedial portal
Pereira *et al*[39]	Revision	Hamstring	Transverse screw	Interference screw	Pseudoaneurysm sup. lat. gen. artery	2 d	Ligation pseudoaneurysm	Hardware femur
Carr *et al*[49]	Primary	Achilles tendon allograft	Interference screw	Suture+ washer bone plug	Traumatic arteriovenous fistula	7 wk	Ligation fistula	Injury at medial superior portal site

ACL: Anterior cruciate ligament; ACLR: ACL reconstruction; BPTB: Bone-patellar tendon-bone; PCL: Posterior cruciate ligament.

Table 4 Data venous thromboembolism and thromboprophylaxis

Ref.	Study design	Number ACLR	Mean age (yr)	Male (M) Female (F)	Graft type	Mean duration surgery (min)	Mean tourniquet time (min)	BMI (kg/m^2)	Thrombop-rophylaxis	Hospital stay (d)
Marlovits *et al*[20]	RCT	140 (87 *vs* 88 placebo)	29.9 ± 7.4 *vs* 30.2 ± 6.9	M 63% F 60%	BTPB	Mean > 120	?	Comparable between groups	Yes (enoxaparin 3-8 d + 20 d enoxaparin *vs* enoxaparin 3-8 d + placebo)	3-8
Mohtadi *et al*[21]	RCT	330	28.5 (14-50)	M 183 F 147	BPTB, hamstring	?	?	?	?	?
Adala *et al*[6]	PC	112	31.6	M 61 F 51	Hamstring	64.9 ± 7.8	?	?	None	2
Cullison *et al*[10]	PC	67	26.5 (19-39)	All men	BPTB	?	83 (0-115)	?	None	?
Hirota *et al*[25]	PC	30	24.1 ± 8.3	M 14 F 16	?	?	?	?	None	?
Hirota *et al*[22]	PC	40 (20 ACLR *vs* 20 TKA)	26.7 ± 13.4 *vs* 71.3 ± 6.8	M:F ACLR 10:10 *vs* TKA 6:14	?		87.1 ± 24.4 *vs* 87.2 ± 18.4	?	None	?
Lind *et al*[23]	PC	5818	?	M approximately 57%	BPTB and hamstring	Prim. ACLR 69.4 ± 21.1; rev. ACLR 90.0 ± 32.3	?	?	18.5% (prim. ACLR 15.7%; rev. ACLR 20.8%)	?
Maletis *et al*[11]	PC	Prim. ACLR 15101	Prim. ACLR 29.5 ± 11.5	M 9604 F 5497	Autograft 57.6%, allografts 42.4%	?	?	⩾ 30 = 23.3%	?	?
		Rev. ACLR 1091	Rev. ACLR 29.8 ± 10.7	M 693 F 398	Autograft 20.9%, allografts 78.8%	?	?	⩾ 30 = 20.8%	?	?
Struijk-Mulder *et al*[5]	PC	100	30.0 ± 10.0	M 77 F 23	Autograft HS 84, BPTB 14 allograft 2	68.0 ± 22.0	76.0 ± 23.0	25.0 ± 4.0	None	1 to 2
Williams *et al*[24]	PC	23	31 (19-42)	M 17 F 6	BPTB	?	103 (89-136)	?	None	2-3
Born *et al*[26]	RC	136 ACLR + multiligament rec.	VTE group 42 (24-43); Non-VTE group 31 (SD 11)	DVT group M: F 3:0; Non-VTE group 103:28	?	VTE group 152.0; Non-VTE group 233 ± 76	VTE group 78.0; Non-VTE group 102 ± 54	VTE group 35 (28-42); Non-VTE group 30 (SD 7)	Yes (before 2007, 3 wk aspirin. After 2007, LMWH 3 wk)	?
Dong *et al*[8]	RC	152 ACLR	34.9	M 91 F 61	Hamstring/ allograft	?	3 groups < 90, 90-120, > 120	22.6	None	?
Ettema *et al*[27]	RC	?	?	?	?	?	?	?	50% prescribed LMWH or coumarin during hospital stay; 5% for 1-2 wk; 2% for 3-4 wk and 35% for 6 wk	
Gaskill *et al*[2]	RC	15767 ACLR + HTO/PCL non specified	28.9 (SD 7.6)	M 13794	?	?	?	27.8	?	? ?
Hetsroni *et al*[30]	RC	58863 ACLR, total 418323 arthroscopies	PE group 50.3 (15-79) *vs* non-PE group 45.5 (0-100)	F 2764 PE group F 57.3% *vs* non-PE group	?	?	?	(SD 4.0) ?	?	?
Jameson *et al*[28]	RC	13941	29.3 (8-83)	F 46.8% M 79.5%	?	?	?	?	?	1-4

Jaureguito *et al*[7]	RC	131 group 1 (knee arthroscopy)	?	F 20.5% M 73	-	?	?	?	Aspirin (325 mg) daily for 3 wk postsurgery if age > 45 yr	?
		108 group 2 (ACLR, osteotomy)		F 58 M 60	?	?	?	?	Idem	?
Sun *et al*[29]	RC	231	23.6	F 48 M 69.3%	?	88.4	67.5	24.5	None	?
Ye *et al*[4]	RC	171	30.1 ± 10.0	F 30.7% M 123 F 48	Hamstring	86.9 ± 26.4	69.9 ± 15.9	24.4 ± 3.2	None	4
Ackerman *et al*[55]	CR	1	45	F 1	BPTB	?	0	?	Aspirin 325 mg daily	Outpatient
Chien *et al*[50]	CR	1	34	M 1	?	110	?	30	none	?
Janssen *et al*[13]	CR	1	19	F 1	Hamstring	96	110	27.5	LMWH during hospital stay	3
Kang *et al*[51]	CR	1 (+MCL rec.)	48	F 1	Hamstring	?	90	?	None	?
Liu *et al*[52]	CR	1	34	M 1	Hamstring	110	119	30.1	None	5
Theron *et al*[53]	CR	1	30	F 1	?	?	?	?	?	Occurred day after surgery

ACLR: ACL reconstruction; BPTB: Bone-patellar tendon-bone; TKA: Total knee arthroplasty; LMWH: Low molecular weight heparin; HTO: High tibial osteotomy; VTE: Venous thromboembolism; PCL: Posterior cruciate ligament; prim: Primary; MCL: Medial collateral ligament; rev: Revision; RCT: Randomized controlled trial; PC: Prospective cohort study; RS: Retrospective study; CR: Case report; SD: Standard deviation; DVT: Deep venous thrombosis; rec.: Reconstruction.

artery, medial and lateral inferior genicular arteries and lateral superior genicular artery. Clinical presentations were repeated hemarthrosis, pain and a pulsatile mass after ACL reconstruction.

The types of arterial complications after ACL reconstruction may be categorized in arterial- occlusions, avulsions, penetrating injuries, arteriovenous fistulae or pseudoaneurysms. Pseudoaneurysm is the most common arterial complication (13/23 cases).

(3) Is there a correlation between arterial complications and fixation methods for ACL reconstruction? Twenty-three case reports on arterial complications have been published using various techniques of ACL reconstruction, detailed in Table 3. There was no correlation between arterial complications and ACL reconstruction technique, methods of graft fixation or graft type. Eighteen studies reported that the vascular injury was caused by instruments during the ACL reconstruction (shaver, a drill bit for graft fixation, portal incision, previous catheterization and graft harvest). Pseudoaneurysm was the most frequently reported arterial complication after ACL reconstruction, irrespective of graft type or method of graft fixation. Four studies related their vascular complications to concurrent lateral meniscectomy, PCL reconstruction and preexistent intimal popliteal artery injury due to a previous knee dislocation.

No correlation was found between arterial complications and ACL reconstruction technique, methods of graft fixation or graft type.

(4) What is the time to diagnosis of arterial complications after ACL reconstruction? Six studies reported a time to diagnosis of 0-2 d after ACL reconstruction (Table 3). All other studies showed a certain delay in diagnosis (1-7 wk postsurgery up to 8 years). Contrast-, CT- or MRI- angiographies are the diagnostic tools of choice[46]. Remarkably, most case reports described palpable dorsalis pedis and posterior tibial arterial pulses at time of clinical presentation with swelling and pain around the popliteal area. These findings have misled surgeons to underestimate vascular complications after ACL reconstruction. Prolonged follow-up and a high level of suspicion, with clinical symptoms of painful pulsating mass and sensory deficits in lower leg and foot, is mandatory in detecting these potentially devastating lesions. An immediate surgical exploration is imperative in limiting neurological damage[45]. Other than the Gore-Tex rupture ligament case[31], all patients maintained adequate ACL stability after vascular surgery. The neurological deficits however may be permanent.

The time to diagnosis of arterial complications after ACL reconstruction varies from days to mostly weeks but even years.

Venous complications: (1) What is the incidence of venous thrombo-embolism after ACL reconstruction without thromboprophylaxis? The incidence of VTE after ACL reconstruction without thromboprophylaxis varied from 1.5%-17.9%[1,58]. The variable incidence of VTE after ACL reconstruction depended on the diagnostic methods of DVT (clinical parameters, venography, ultrasound or magnetic resonance venography) and

Table 5 Incidence venous thromboembolism, risk factors and thromboprophylaxis recommendations

Ref.	Study design	Incidence DVT (symptomatic if specified)	Incidence PE (symptomatic if specified)	Detection method VTE	Risk factors DVT	Thromboprophylaxis recommendations
Marlovits *et al*[20]	RCT	2 = 2.8% with extended prophylaxis; 28 = 41.2% without extended prophylaxis	0%	MRI venography	Comparable between groups	Age > 30, prolonged immobilisation and complex procedures
Mohtadi *et al*[21]	RCT	1 (0.3%) symptomatic	1 (0.3%) symptomatic	Clinical, additional exam in suspected cases	None	-
Adala *et al*[6]	PC	2 = 1.78% (1 pt symptomatic)	0%	Ultrasound preop and day 2-3	None	None if absent high risk factors DVT or age < 45 yr
Cullison *et al*[10]	PC	1 = 1.5%	0%	Ultrasound preop, day 3 and 4 wk	None	None in male patients < 40 yr and absence of risk factors
Hirota *et al*[25]	PC	0%	Peak emboli 50s after tourniquet release	Transoesophageal echocardiography	?	-
Hirota *et al*[22]	PC	0%	0%	Transoesophageal echocardiography	?	-
Lind *et al*[23]	PC	?	?	?	?	-
Maletis *et al*[11]	PC	26 = 0.2% in primary ACLR	15 = < 0.1% in primary ACLR	Various methods	?	?
		2 = 0.2% in revision ACLR	0% in revision ACLR	Idem	?	?
Struijk-Mulder *et al*[5]	PC	9 = 9.0% (symptomatic 4 = 4.0%)	1 = 1%	Bilateral ultrasound	Age, contraceptive use	Further research for DVT prophylaxis, especially when risk factors are present
Williams *et al*[24]	PC	0%	0%	Bilateral ultrasound preop and 7-14 d postop	In 3 patients, non-specified	Future studies needed
Born *et al*[26]	RC	3 = 2.0% sympromatic	?	Clinical, ultrasound in suspected cases	Multiligamentous injury, age, history DVT	In multiligament reconstruction. cf guidlines ACCP "major orthopaedic surgery"
Dong *et al*[8]	RC	17 = 8.5% (44.1% nonsymptomatic of all DVT cases = 12.1% of all patients)	?	Color doppler ultrasound < 24 h after admission and 3 and 7 d postsurgery	Multiligament reconstruction, tourniquet time > 2 h, age	In case of PCL reconstruction and tourniquet time > 2 h
Ettema *et al*[27]	RC	?	?	?	?	None
Gaskill *et al*[2]	RC	55 symptomatic	35	Clinical, additional exam in suspected cases	Age ⩾ 35, smoking, cocomitant HTO/ PCL surgery	Further research for VTE prophylaxis
Hetsroni *et al*[30]	RC	?	117 = 0.0003% all symptomatic	Clinical, additional exam in suspected cases	Female gender, age, surgical time, previous cancer	Further research for thromboprophylaxis in high risk patients
Jameson *et al*[28]	RC	42 = 0.3% all symptomatic	25 = 0.8% all symptomatic	Clinical, additional exam in suspected cases	Age > 40	No advise due to lack of evidence
Jaureguito *et al*[7]	RC	Retrospectively clinically 0.24% Prospectively 7 (2.9%, 5 asymptomatic = 2.1%)	0%	Duplex ultrasonography pre-operatively and 5 and 10 d postsurgery	None	-
Sun *et al*[29]	RC	total 36 = 15.6% (4 prox DVT = 2.4%. Distal DVT 32 = 13.9%)	0%	Venography day 3 postsurgery	Age, multiligament surgery	None
Ye *et al*[4]	RC	24 = 14.0% (4 pts prox. DVT)	0%	Chest X-ray and venography day 3 post ACLR	Female gender, age > 35 yr	In female patients and age > 35 yr
Ackerman *et al*[55]	CR	1 = 100%	0%	Clinical, ultrasound, CT and venography	May-Thurner Syndrome	In case of high risk patient
Chien *et al*[50]	CR	?	1 = 100%	Clinical, CT scan	BMI, ACL surgery	Further investigation for thromboprophylaxis after knee arthroscopy needed

Janssen *et al*[47]	CR	1 = 100%	1 = 100%	Clinical, transoesophageal echocardiography	Misdiagnosis DVT, Protein S deficiency? ACL surgery, contraceptive use	Further investigation for thromboprophylaxis after knee arthroscopy needed
Kang *et al*[51]	CR	1 = 100%	0%	Clinical, ultrasound	Primary thrombocytopenia, Factor VIII, Proteine C and S	None
Liu *et al*[52]	CR	1 = 100%	1 = 100%	Clinical, cardiac sonography	BMI	Patients with increased risk and prolonged tourniquet time
Theron *et al*[53]	CR	?	1 = 100%	Clinical, CT	Contraceptive use	None

ACLR: ACL reconstruction; BPTB: Bone-patellar tendon-bone; TKA: Total knee arthroplasty; LMWH: Low molecular weight heparin; HTO: High tibial osteotomy; VTE: Venous thromboembolism; PCL: Posterior cruciate ligament; prim: Primary; RCT: Randomized controlled trial; PC: Prospective cohort study; RS: Retrospective study; CR: Case report; CT-scan: Computerized tomography-scan; BMI: Body mass index; DVT: Deep venous thrombosis; ACL: Anterior cruciate ligament; rec.: Reconstruction; pts: Patients; prox.: Proximal.

Table 6 Incidence of venous thromboembolism

Ref.	ACLR (*n*)	Incidence DVT (*n*)	Incidence sympt DVT (*n*)	Incidence PE (*n*)	Thromboprophylaxis	Risk of bias
Adala *et al*[6]	112	2	1	0	No	Low
Cullison *et al*[10]	67	1		0	No	-
Dong *et al*[8]	152	11		NA	No	-
Jamesonet *al*[28]	13941	42	42	25	NA	-
Maletis *et al*[11]	15101	26		15	NA	-
Marlovits *et al*[20]	140 (72 *vs* 68)	2 *vs* 28		0	Yes	-
Mohtadi *et al*[21]	330	1	1	1	NA	-
Struijk-Mulder *et al*[5]	100	9	4	1	No	Low
Sun *et al*[29]	231	36		0	No	Low
Williams *et al*[24]	23	0	0	0	No	-
Ye *et al*[4]	171	24		0	No	-

Pooled incidence: All DVT: 79/14093 = 9.7%; symptomatic DVT: 5/235 = 2.1%; all DVT of low risk bias studies: 47/443 = 10.6%; PE = 1/704 = 0.1%. ACLR: Anterior cruciate ligament reconstruction; DVT: Deep venous thrombosis; sympt: Symptomatic; PE: Pulmonary embolism; NA: Not applicable.

the heterogeneity of patient demographics (age, risk factors, surgical time, concomitant surgery, tourniquet time and postoperative mobilisation). Eleven studies reported data of isolated ACL reconstruction without thrombophylaxis (Table 5). The pooled total incidence of DVT was 9.7%, of which 2.1% was symptomatic. The pooled incidence of DVT in only low-risk bias studies was 10.6%. The pooled incidence of PE was 0.1% (Table 6).

After ACL reconstruction without thromboprophylaxis, the incidence of DVT is 9.7%, of which 2.1% is symptomatic. The incidence of PE is 0.1%.

(2) Is tourniquet time related to VTE after ACL reconstruction? Eight studies that were evaluated by risk of bias analysis documented tourniquet time in ACL reconstruction. This varied from 67.5 min to > 2 h. Deep venous thrombosis was more frequent with tourniquet time > 2 h. Extended tourniquet time was associated with combined ACL reconstruction and concomitant surgery. The incidence of DVT among patients with tourniquet lasting > 2 h increased from 12.1% to 17.4%[1,58]. In these cases, thromboprophylaxis was recommended with > 2 h tourniquet time.

Tourniquet time > 2 h is related to VTE after ACL reconstruction.

(3) Is thromboprophylaxis indicated after ACL reconstruction? Eight studies made recommendations for thromboprophylaxis after knee ligament surgery. No thromboprophylaxis was deemed necessary in case of isolated ACL reconstruction in patients without risk factors. Risk factors for VTE were those reported in the ACCP guidelines[59], female gender, > 30 years of age, complex or concomitant surgical procedures, prolonged immobilization and tourniquet time > 2 h. Further research on thromboprophylaxis is recommended by most authors.

Thromboprophylaxis is indicated in patients considered to be at moderate or high risk of VTE[20].

DISCUSSION

The most important finding of the present study is that after ACL reconstruction, the incidence of arterial complications, symptomatic DVT and PE was 0.3%, 2.1% and 0.1% respectively. The incidence of 0.3% of arterial complications may be overestimated considering the fact that only case reports have been published in the literature. However, the pooled incidence of DVT after ACL reconstruction without thromboprophylaxis was 9.7%, of which 2.1% of patients was symptomatic.

Pseudaneurysms were the most frequently re-

ported arterial complication after ACL reconstruction, irrespective of graft type or method of graft fixation. Pseudoaneurysms differ from true aneuryms in that they do not contain all the layers of an artery. They resemble organized hematomas that have internal arterial flow[1]. A direct arterial trauma by a drill bit, shaver, hardware or fixation device for ACL reconstruction may cause a pseudoaneurysm. This condition usually presents with repeated hemarthrosis and a pulsatile mass within days to weeks after ACL reconstruction. Their growth may lead to neuropraxia and DVT due to compression of nerves and nearby veins, respectively[1]. Patients with poor collateral development may have severe ischemia and poor prognosis, even leading to amputation[1,35,38].

Krupp *et al*[60] analysed the safety of femoral cross-pin in ACL reconstruction. They concluded that insertion angle, not tunnel drilling method, influenced saphenous nerve and femoral artery/vein injury at risk[60]. Post *et al*[61] studied the relative position of the neurovascular structures at risk when drilling bicortical screws for tibial fixation in ACL reconstruction[45]. Arthroscopic tibial tunnels were made in cadaver human knees using lateral X-rays for accurate positioning. A 4.5 mm bicortical drill hole was placed perpendicular to the tibial surface 1 cm distal to the tibial tunnel. The distances from the posterior tibial drill exit point to the nearby neurovascular structures were measured with a caliper. The closest structure to the exit point was the bifurcation of the popliteal artery/vein (11.4 ± 0.6 mm). The next closest was the anterior tibial vein (11.7 ± 1.6 mm). The closest any individual hole came to a neurovascular structure was 3.5 mm from the anterior tibial vein. They concluded that bicortical screw and spiked washer fixation of soft tissue ACL grafts appears to be relatively safe[45,61]. Curran *et al*[58] performed an *in vitro* study comparing 2 techniques for ACL tibial fixation with a bicortical screw. They concluded that aiming the screw towards the fibula reduced the risk of vascular injury compared to screws drilled perpendicular to the cortex. Other possible recommendations to prevent neurovascular damage are the use of a drill bit stop for bicortical screws or a single cortex fixation on the tibia without compromising stability of fixation[1]. The incidence of arterial complications in the present review (0.3%)[45] was updated in a consecutive series of 1961 ACL reconstructions with hamstring autografts and bicortical tibia fixation by the same authors[1]. The incidence was reduced from 0.3% to 0.15% after the safety measures were applied as suggested by Janssen *et al*[1] and Curran *et al*[58].

A high level of suspicion, with clinical symptoms of painful pulsating mass and sensory deficits in lower leg and foot, is mandatory in detecting these potentially devastating lesions. The differential diagnosis should include compartment syndrome and DVT[47]. Doppler examination and intact dorsal pedal and posterior tibial pulses are unreliable in diagnosing arterial lesions after ACL reconstruction[47]. Contrast-, CT- or MRI-angiographies are the diagnostic tools of choice[45,46]. Surgical exploration and vascular repair (or ligation/embolization of the feeding vessel) remain standard management[45,46]. An immediate surgical exploration is imperative in limiting neurological damage[1,45,46].

A meta-analysis of DVT after knee arthroscopy without thromboprophylaxis found an overall DVT rate of 9.9% (3.1%-17.9%) when routine screening using ultrasound or contrast venography was used[13]. Proximal DVT rate was 2.1% (0%-4.9%)[13,62]. Proximal DVT may progress to PE, however the clinical significance of distal DVT remains questionable[62-64]. Sun *et al*[29] found that the total incidence of VTE, diagnosed with venography on the third day after arthroscopic knee surgery, was 14.9%, of which only 3.7% were symptomatic. Delis *et al*[14] found 50% of the DVT patients to be completely asymptomatic. They also examined the history of DVT if treated (aspirin in calf DVT, heparin-warfarin in proximal DVT)[13]. Following early diagnosis, total clot lysis was documented in 50% and partial clot lysis in the remaining 50%, within 118 d median follow-up. Segmental venous reflux developed in at least 75% of the legs sustaining thrombosis. A previous thrombosis or the presence of two or more risk factors for thromboembolism significantly increased the incidence of DVT. No symptoms or signs of PE were documented[13,14].

The current review showed that after ACL reconstruction without thromboprophylaxis, the incidence of DVT was 9.7%, of which 2.1% was symptomatic. The incidence of PE was 0.1%. These findings are similar to the conclusions by Erickson *et al*[3]. They described an 8.4% rate of DVT after ACL reconstructions in patients without postoperative thromboprophylaxis (73% was asymptomatic), while the rate of symptomatic PE was 0.2%[3]. Maletis *et al*[11] described symptomatic DVT in 0.2% of 16192 primary and revision ACL surgeries. However, the authors did not specify the use of thromboprophylaxis[11]. Cullison *et al*[10] and Adala *et al*[6] found comparable rates of DVT of 1.5% and 1.8% respectively using prospective pre- and postoperative ultrasonography in patients without VTE risk factors. The authors recommended that thromboprophylaxis is not necessary in the absence of risk factors in patients younger than 45 years of age with early postoperative mobilization[6]. In a study of 282 Chinese patients, the incidence of DVT was 12.1% after ACL reconstruction. Tourniquet time > 2 h and concomitant PCL reconstructions were risk factors for DVT[8]. Ye *et al*[4] found that the incidence of DVT was 14%, diagnosed by unilateral venography on the third day after ACL reconstruction. Proximal DVT occurred in 16.7% of DVT patients. None of the DVT patients developed PE. The authors recommended thromboprophylaxis in female patients and patients older than 35 years[4]. The described variable incidence of VTE after ACL reconstruction depends on the diagnostic methods of DVT (clinical parameters, venography, ultrasound or magnetic resonance venography) and the heterogeneity

of patient demographics (age, risk factors, surgical time, concomitant surgery, tourniquet time and postoperative immobilization).

The use of a tourniquet improves operative visualisation during arthroscopic ACL reconstruction[65,66]. Various authors reported that tourniquet time in excess of 90 min increased the rates of VTE[8,17,30,67]. Smith *et al*[65] published a meta-analysis of tourniquet assisted arthroscopic knee surgery. There was no difference in complication rate if tourniquet time exceeded 60 min. Hirota *et al*[22,25] quantified pulmonary emboli after tourniquet release in patients during ACL reconstruction (extramedullary) *vs* total knee arthroplasty (intramedullary procedure)[13]. They chose these two groups for having more than 60 min tourniquet time and detected pulmonary emboli in all patients after release of the tourniquet using transesophageal echocardiography with a peak at 30-40 s postrelease[13]. The amount of emboli was defined as percentage of total emboli formed in relation to the right atrial area. This percentage returned to baseline levels 2 min after tourniquet release in the ACL group. They found a significant linear correlation between the amount of emboli and duration of tourniquet inflation in the ACL group. In comparison, the total knee arthroplasty group had a significant larger amount of emboli (4-5 fold) with no return to baseline levels during the assessment period. No patient in either group showed signs of PE[13,22,25]. In a recent systematic review, Papalia *et al*[66]. concluded that a tourniquet can be used safely, provided that the inflation pressure is not excessive and tourniquet time is less than 2 h.

Asymptomatic pulmonary emboli occur in all patients with ACL reconstructions after tourniquet release[1,13]. Furthermore, PE may occur as a result of proximal DVT[13,24,50,52]. Hetsroni *et al*[30] analysed 418323 arthroscopic knee procedures and found an incidence of 0.03% for symptomatic PE. Risk factors were female sex, age, history of cancer and prolonged operating time (> 90 min). In spite of improved prevention and treatment of PE, the mortality is still estimated to be 20%-30%[68]. It is the third most common cardiovascular cause of death, with 2/3 of the death occurring within the first few hours as a result of severe hemodynamic and respiratory disturbances[53,68,69]. Janssen *et al*[1,13] found an incidence of fatal PE of 0.05% in a consecutive series of 1961 arthroscopic ACL reconstructions[1]. Risk factors were preexistent coagulopathy, oral contraceptive medication and delay in DVT diagnosis.

Thromboprophylaxis after ACL reconstruction remains controversial[1,9,16,27,50,52,59,70,71]. Geerts *et al*[59] reviewed the evidence-based literature for thromboprophylaxis in knee arthroscopy and only recommend prophylaxis with Low Molecular Weight Heparin in patients with risk factors for VTE (Grade 2B level of evidence). Risk factors in their study were history of DVT, age $\geqslant$ 40 years, surgical time > 60 min. and a complicated/prolonged procedure[59]. Additional risk factors for VTE after ACL reconstruction in other studies on VTE were smoking, oral contraceptive use or hormone replacement, BMI > 30 kg/m^2, chronic venous insufficiency, cancer and thrombophilic conditions[1,12,14,30,52,59,64,72]. In a randomized controlled trial, Marlovits *et al*[20] concluded that extended duration of thromboprophylaxis with enoxaparin by an additional 20 d significantly reduced venographically detected DVT after ACL reconstruction without an increase in major bleeding compared to enoxaparin limited to in-hospital thromboprophylaxis for 3-8 d. The authors found a 41.2% incidence of DVT for discharged patients who had a placebo as postdischarge thromboprophylaxis in contrast to 2.8% in the thromboprophylaxis group. Risk factors for DVT were age over 30 years, prolonged immobilization and surgical time[20]. It should be noted that their mean surgical time as a teaching hospital (> 2 h) as well as their hospital stay of 3-8 d do not reflect most current ACL surgery practices with early discharge and mobilization. A Cochrane systematic review on interventions for preventing VTE in adults undergoing knee arthroscopy reported that no strong evidence was found to conclude that thromboprophylaxis is effective to prevent VTE in people with unknown risk factors for thrombosis[20,68,70]. This is confirmed by other recent studies on DVT prophylaxis after ACL reconstruction and knee arthroscopic procedures[2,17,64]. It is now common practice in a surgical setting to use a risk-assessment model, such as the one developed by Capriani *et al*[20]. Patients considered to be at moderate or high risk of VTE should routinely receive thromboprophylaxis[1]. However, recommendations for the best type and duration of prophylaxis after ACL reconstruction still need to be defined[5]. In spite of the scientific effort to date, no recommendations for routine thromboprophylaxis in ACL reconstruction can be provided in the absence of risk factors for VTE[1,13]. Further investigation is required to analyse actual incidence and severity of venous thromboembolism as well as the efficacy-to-bleeding tradeoff for routine thromboprophylaxis after ACL reconstruction in patients without risk factors for VTE[1,13].

This systematic review has several limitations. In the search for the available knowledge on vascular complications, studies of various level of evidence were included. Another weakness of this review is the inclusion of studies with small population size. Both the quality and limited amount of studies for specific research questions may limit the level of evidence for this review. Although strict and adapted for various study types, the risk of bias assessment of the Cochrane Library and the classifications of "low", "questionable" and "high" risk of bias for the studies may limit the strength of evidence. One might argue that a "low" risk of bias RCT study is of higher level of evidence than a "low" risk of bias prospective cohort study. Another weakness of this study is that only articles in English were included. Additional relevant articles published in languages other than English could contribute to the level of evidence presented in this review.

The clinical relevance of this review is that patients

undergoing ACL reconstruction may be informed that vascular complications can occur with any type of reconstruction and that thromboprophylaxis should be prescribed in patients with risk factors for VTE.

After ACL reconstruction, the incidence of arterial complications, symptomatic DVT and PE was 0.3%, 2.1% and 0.1% respectively. Arterial complications may occur with all types of arthroscopic ACL reconstruction, methods of graft fixation as well as any type of graft. Patients considered to be at moderate or high risk of VTE should routinely receive thromboprophylaxis after ACL reconstruction.

COMMENTS

Background

A thorough understanding of the incidence, risk factors and potential methods for prevention of vascular complications after anterior cruciate ligament (ACL) reconstruction is critical to optimize patient safety. This systematic review presents the current knowledge of arterial complications, venous thromboembolism (VTE) and thromboprophylaxis after arthroscopic ACL reconstruction. The review highlights the incidence, types and risk factors of arterial complications and VTE after ACL reconstruction as well as the current recommendations for deep venous thrombosis prophylaxis.

Research frontiers

This systematic review is related to research on thromboprophylaxis after ACL reconstruction.

Innovations and breakthroughs

This review presents a systematic overview of the incidence and type of arterial complications after ACL reconstruction. Such an overview has not been presented previously. Furthermore, an overview of the incidence, risk factors and indications for thromboprophylaxis after ACL reconstruction are presented. There is a need for this current knowledge due to the controversy in this field of research. Suggestions for further research are presented in the study.

Applications

Clinical implications are presented for adequate diagnosis and treatment of vascular complications after ACL reconstruction. Risk factors and indications for thromboprophylaxis are discussed.

Terminology

All terminology is explained in the manuscript.

Peer-review

This is an interesting systematic review that aims to evaluate the arterial and venous complications, by analyzing the relevant studies.

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CASE REPORT

Compartment syndrome following total knee replacement: A case report and literature review

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Author contributions: Shaath M and Sukeik M designed the report; Sukeik M, Mortada S and Masterson S collected the patient's clinical data; Shaath M, Sukeik M, Mortada S and Masterson S analyzed the data; Shaath M and Sukeik M wrote the paper.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at Queens Hospital.

Informed consent statement: Unfortunately in December 2014, the patient died from causes unrelated to the contents of this case report. Written consent was therefore not obtained despite the patient verbally agreeing to publish it in the immediate postoperative phase. However, in light of the importance of the article message, we have included no identifiable patient information and feel this report should still be published.

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Abstract

Compartment syndrome is a rare complication of total knee replacement (TKR) surgery that needs prompt diagnosis and treatment as it may be associated with high morbidity and mortality. We have found very few reports in the literature describing compartment syndrome after TKRs and therefore, present a relevant case which occurred in the immediate postoperative phase and was treated with fasciotomy and subsequent operations to close the soft tissue defects.

Key words: Compartment syndrome; Complications; Knee replacement; Treatment

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Core tip: A case report and literature review of compartment syndrome following total knee replacement surgery is presented. Predisposing factors supported by literature are detailed and compared to findings from this case report emphasizing on early intervention to prevent subsequent complications.

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INTRODUCTION

Compartment syndrome is a serious condition that occurs due to elevation of interstitial pressure in closed fascial compartments resulting in microvascular compromise, myoneuronal function impairment and soft tissue necrosis. Fractures, crush injuries, vascular injuries, prolonged tourniquet application, anticoagulation and deep-vein thrombosis have all been associated with compartment syndrome[1], with fractures and soft tissue injuries accounting for approximately 80% of all cases. Pain out of proportion and pain on passive stretching of the affected compartment have been described as the most reliable clinical indicators of compartment syndrome. These symptoms alongside palor, pulselessness, paraesthesia and paralysis are characteristic for compartment syndrome. Paraesthesia and paralysis arise as a result of significant compartmental ischaemia, after which a full recovery becomes unlikely[1].

The increase in intracompartmental pressures can be measured using the Wick catheter technique[2] or a handheld manometer. A manometer device attached to a needle is inserted into each compartment to provide a pressure reading. A normal compartmental pressure reflects the capillary pressure of 0 to 8 mmHg. When measured, an intracompartmental pressure of 30 mmHg and delta (differential) pressure of 30 mmHg or less are used as an indication for fasciotomy[3].

Despite the relative scarcity in the incidence of compartment syndrome following total knee replacement (TKR), it remains an important complication which may potentially be limb as well as life threatening.

We hereby, present a case of a compartment syndrome which occurred following TKR surgery and discuss the potential factors which may have contributed to its development.

CASE REPORT

In May 2013, a 72-year-old white British lady with background of chronic obstructive pulmonary disease (COPD), hypertension, prior pulmonary embolism, oesophagitis and cataracts was admitted with a diagnosis of primary osteoarthritis for an elective right TKR. Her medications included spiriva18 mcg, uniphyllin 200 mg, ramipril 1.25 mg, folic acid 5 mg, amlodipine 10 mg, ipratropium 500 mcg, omeprazole 20 mg and salbutamol inhaler and she had no medication allergy. The patient occasionally also used home oxygen therapy for COPD exacerbations. Past surgical history included epistaxis needing cautery, duodenal ulcer surgery and gastroscopy. Family history was insignificant. She was a housewife and lived alone, a previously heavy smoker but stopped one year prior to her presentation and drank alcohol occasionally. Her clinical examination confirmed tenderness over the medial and lateral knee compartments as well as the retropatellar region with a range of movement from 0-120 degrees of flexion. There were no signs of neurological deficit or vascular compromise in the lower limbs. Radiographs taken pre-operatively showed tricompartmental osteoarthritis. Her ASA grading was 3[4]. The surgical procedure was performed as per the surgeon's routine practice under a spinal/epidural anaesthetic. Patient had three doses of perioperative cefuroxime as per hospital antibiotic prophylaxis guidelines. After elevation of the limb, a pneumatic tourniquet around the upper part of the thigh was inflated to a pressure of 300 mmHg. A midline skin incision and medial parapatellar approach were utilised to expose the knee joint. Standard surgical techniques for intraoperative haemostasis were used. A cemented Columbus® TKR was implanted. After all components were cemented into place, a thorough washout with normal saline was performed and the wound was closed in layers. No surgical drain was used. The tourniquet was released after the application of dressings. Tourniquet time was 90 min. Forty mgs of clexane (enoxaparin) was given on the day of surgery with the plan to continue for 4 wk. The patient returned to the recovery unit where an anteroposterior and lateral X-rays of her right knee were performed as per departmental protocol (Figure 1). After an uneventful recovery, she was transferred to the ward to undergo rehabilitation. The following day she started complaining of pain in the right lower leg which by midday became excruciating and was exacerbated by any passive movement of the toes. The patient experienced tension across the entirety of the calf as well as paraesthesia. The distal pulses in the leg were palpable but weak. A clinical diagnosis of compartment syndrome of the leg was made based on these clinical findings and a Stryker Intra-Compartmental Pressure Monitor measured pressures of 26, 32 and 42 mmHg in the anterior, lateral and posterior compartments respectively (Figure 2).

Therefore she was taken immediately to the operating theatre and a decompression of all 4 compartments was performed using lateral and medial longitudinal incisions. Post fasciotomies the blood supply to the muscles which were deemed viable at the time of surgery was restored and pain was markedly relieved. The patient had to go back to theatre three times subsequently in order to completely close the wounds. The lateral incision was closed 3 d postoperatively while the medial incision was closed 3 wk later after a period of vacuum pump application.

The patient was followed up as an inpatient until complete closure of all wounds. On further examination, she was mobilizing fully weightbearing with no restrictions and achieved a range of movement from 0-95 degrees of flexion. At 12 mo follow-up appointment, the patient maintained her good functional outcome with no neurovascular deficit in the right lower limb and hence got discharged. However, in December 2014, she died from respiratory failure secondary to lung cancer. Reviewing her case notes did not show any deterioration

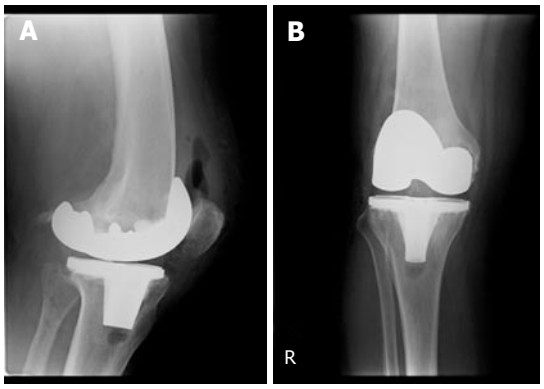

Figure 1 Immediate postoperative X-rays of the total knee replacement in recovery (A and B).

Figure 2 The Stryker Intra-Compartmental Pressure Monitor is a hand held monitor for measurement of compartmental pressure.

of her knee prior to her death.

Literature review

Owing to the rarity of this complication, a comprehensive literature review aiming to identify contributing factors was conducted. The exploded MeSH terms "total knee replacement" and "Compartment syndrome" were used to search MEDLINE and EMBASE databases for relevant articles in English. Two authors independently reviewed the titles and abstracts and when in doubt the full articles were retrieved and reviewed to reach consensus. Following this irrelevant studies were excluded. We included only cases where a unilateral primary TKR was performed to provide direct comparisons with the current case report. This yielded 12 studies which were relevant to our case report[3,5-15]. A PRISMA chart with the study selection process is outlined in Figure 3.

Result of literature review

The literature review showed that compartment syndrome varies with regards to its onset and implications after TKR surgery. The time period from TKR to fasciotomy ranged from 14 to 192 h (Table 1). Such variation may be attributed to the masking effect of spinal/epidural anaesthesia. Eight out of 25 patients who underwent fasciotomies had no complications. However, 15 patients developed complications 8 of whom had permanent

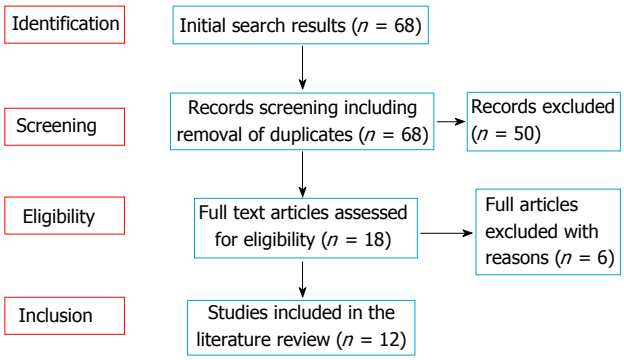

Figure 3 PRISMA chart of the study selection process.

foot drop; one patient underwent an above and another patient below knee amputation. It is therefore important to intervene in a timely fashion and have a low threshold of performing a fasciotomy to prevent such serious complications. On the other hand, a recent review of 6 cases of compartment syndrome post TKR surgery showed overall high complication rates associated with treatment in this group of patients[3]. In particular, 2 patients developed periprosthetic infections one of whom ended up with an above knee amputation and 2 developed foot drops. As a result, authors suggested that surgeons need to maintain a relatively higher threshold for performing a fasciotomy following TKR in comparison to trauma patients who develop a compartment syndrome. However, it is worth mentioning that in this case series, all patients not only had a spinal anaesthetic but most of them also underwent vascular procedures prior to the fasciotomies. This may have adversely affected the result of the fasciotomies which were delayed in favour of such vascular interventions. In our case, had it not been for our low threshold for surgery and high index of suspicion, our patient may have developed complications. Therefore we disagree with the suggestion of delayed intervention in compartment syndrome developing after TKR surgery and support early treatment to avoid any complications.

DISCUSSION

Compartment syndrome following TKR is an exceptionally rare complication, with only a small number of cases documented in the literature[3,5-15]. The commonest explanation is that a TKR involves the joint space without affecting the adjacent compartments[6,7,15]. However there have been sporadic cases of compartment syndrome following TKR affecting the gluteal, thigh and leg compartments. The recommended treatment is urgent fasciotomy with subsequent debridement and wound closure.

Numerous factors contributing to the development of compartment syndrome and the delay in diagnosing it have been suggested in the literature as follows.

Tourniquet pressure

Tourniquet pressure has been highlighted as a potential cause of raised intracompartmental pressure due to

Table 1 Studies reporting compartment syndrome after total knee replacement

	Age	Tourniquet pressure (mmHg)	Anticoagulation	Anaesthetic	Time to treatment (h)	Location	Fasciotomy	Complications
Boonstra *et al*[5]	62	350	Yes	GA and Femoral block	24	Thigh	Yes	None
Haggis *et al*[6]	69	350	No	Epidural	14	Leg	Yes	Foot drop and equinus
	53	N/A	No	Epidural	38	Thigh	Yes	Foot drop and equinus
	65	300	No	Spinal	24	Leg	Yes	None
	48	350	No	Epidural	192	Leg	Yes	Foot drop and numb sole
	39	350	Yes	Epidural	20	Leg	Yes	Foot drop and equinus/ infected TKR
	49	350	No	Epidural	51	Leg	Yes	Foot drop
	61	350	Yes	Epidural	38	Leg	Yes	Below knee amputation
Hailer *et al*[7]	43	275	Yes	Epidural	50	Leg	Yes	Pes equinus. Complete plegia of all muscle groups distal to the knee. Anesthesia of the sole of the foot
Kort *et al*[8]	44	300	N/R	Spinal + Epidural	22	Leg	Yes	Neurologic impairment and pain
Kumar *et al*[9]	46	N/R	No	Spinal + Epidural	48	Gluteal	Yes	None
	72	N/R	Yes	Epidural	47	Gluteal	Yes	Trendelenburg gait
Lareau *et al*[10]	73	N/R	N/R	GA and Femoral block	Approximately 36	Thigh	Yes	None
Nadeem *et al*[11]	71	N/R	Yes	N/R	N/R	Thigh	Yes	None
Osteen *et al*[12]	52	N/R	N/R	Epidural	Approximately 48	Gluteal	Yes	None
Pacheco *et al*[13]	47	N/R	N/R	Epidural	44	Gluteal	Yes	Gluteal discomfort
	71	N/R	N/R	Epidural	Approximately 48	Gluteal	Yes	Motor and sensory impairment distal to the knee
Smith *et al*[14]	66	N/R	Yes	Epidural	N/R	Thigh	No	None
Tang *et al*[15]	62	300	N/R	Epidural	Approximately 48	Leg	Yes	Calf numbness
Vegari *et al*[3]	81	350	No	Spinal	20	Leg	Yes	Non-healing wounds
	74	325	No	Spinal + Epidural	24	Leg	Yes	Skin/muscle necrosis
	61	250	Yes	Spinal + Epidural	70	Leg	Yes	Foot drop
	56	300	Yes	Spinal + Epidural	17	Leg	Yes	None
	70	250	Yes	Spinal	18	Leg	Yes	Above knee amputation
	62	250	Yes	Spinal	26	Leg	Yes	Foot drop
Our case	72	300	Yes	Spinal + Epidural	31	Leg	Yes	None

N/R: Not recorded; N/A: Not applicable; GA: General anaesthesia; TKR: Total knee replacement.

reperfusion following tourniquet release[8]. Haggis *et al*[6] suggested a correlation between higher tourniquet pressure and long term complications with the patient having the lowest tourniquet pressure suffering no long term complications. However when holistically considering all the cases described; a correlation between tourniquet pressure and severity of long term complications could not be established (Table 1).

Anaesthesia

Epidural anaesthesia has been discussed in several case reports. Two studies[7,15] described how a delay in the diagnosis of compartment syndrome due to the epidural masking pain, led to long term functional deficits. Two further studies[9,13] found that symptoms of gluteal compartment syndrome in four patients following TKR only appeared after withdrawal of the epidural. Hence, Hailer *et al*[7] suggested that epidural anaesthesia should be avoided after any lower limb orthopaedic surgery in order to allow for early detection of compartment syndrome.

Thromboprophylaxis

Despite papers suggesting that thromboprophylaxis may predispose to compartment syndrome due to associated excessive bleeding, only half of the cases presented in the literature received anticoagulant medication[3,5-15].

Vascular injury

Vegari *et al*[3] stated that vascular injury is the commonest cause of compartment syndrome following TKR. However, cases described in this review failed to determine any direct causal relationship.

Rehabilitation following surgery

Lareau *et al*[10] suggested overuse of the continuous passive movement machine as a cause of compartment syndrome. Continuous flexion and extension of the knee joint for a prolonged period may decrease the volume of the compartments thereby increasing intra-compartmental pressure. Another case of compartment syndrome of the thigh following TKR reported that compartmental pressures (measured using a continuous intracompartmental

pressure monitor) would only increase on flexion of the knee joint[14]. Knee flexion exacerbated the pain whilst increasing the compartmental pressures which confirms that pain is a very reliable indicator of the severity of compartment syndrome.

In the case presented hereby, we believe that a combination of using a tourniquet and maybe thromboprophylaxis were contributive factors for developing compartment syndrome. However, the use of regional anaesthetic certainly added to the delay in presenting the symptoms as well.

This case report and review of the literature emphasizes the importance of having a high index of suspicion and low threshold of intervention for compartment syndrome occurring after TKRs.

COMMENTS

Case characteristics

A 72-year-old presented with excruciating right lower leg pain one day following an elective total knee replacement.

Clinical diagnosis

Pain on passive movement of the toes, tension across the entirety of the calf as well as paraesthesia. The distal pulses in the leg were palpable but weak.

Differential diagnosis

Compartment syndrome *vs* simple postoperative swelling after total knee replacement (TKR) surgery.

Laboratory diagnosis

Not relevant in this case report. However, the Stryker Intra-Compartmental Pressure Monitor was used to measure intracompartmental pressures of the anterior, lateral and posterior compartments.

Treatment

Fasciotomy with decompression of all four leg compartments, followed by wound closure.

Related reports

Compartment syndrome following TKR is an exceptionally rare complication, with only a small number of cases documented in the literature. Factors potentially contributing to the development of compartment syndrome and the delay in its diagnosis include vascular injury, thromboprophylaxis, the use of a tourniquet and regional anaesthesia delaying the diagnosis.

Term explanation

Compartment syndrome is a serious condition that occurs due to elevation of interstitial pressure in closed fascial compartments resulting in microvascular compromise, myoneuronal function impairment and soft tissue necrosis.

Experiences and lessons

Compartment syndrome following TKR is rare. However, a high index of suspicion and low threshold of intervention is necessary in order to avoid disastrous consequences.

Peer-review

The authors presented a case with compartment syndrome following TKR, which was a rare complication successfully treated by urgent fasciotomy. The manuscript is well written.

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CASE REPORT

Lateral subtalar dislocation: Case report and review of the literature

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Author contributions: All authors contributed to the acquisition of data, drafting and revision of this manuscript.

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Informed consent statement: The patient involved in this study gave her verbal informed consent authorizing use and disclosure of her protected health information.

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Abstract

A case of complicated lateral subtalar dislocation is presented and the literature concerning this injury is reviewed. Subtalar joint dislocations are rare and often the result of a high-energy trauma. Complications include avascular necrosis of the talus, infection, posttraumatic osteoarthritis requiring arthrodesis and chronic subtalar instability. Negative prognostic factors include lateral and complicated dislocations, total talar extrusions, and associated fractures. A literature search was performed to identify studies describing outcome after lateral subtalar joint dislocation. Eight studies including fifty patients could be included, thirty out of 50 patients suffered a complicated injury. Mean follow-up was fifty-five months. Ankle function was reported as good in all patients with closed lateral subtalar dislocation. Thirteen out of thirty patients with complicated lateral subtalar joint dislocation developed a complication. Avascular necrosis was present in nine patients with complicated injury. Four patients with complicated lateral subtalar dislocation suffered deep infection requiring treatment with antibiotics. In case of uncomplicated lateral subtalar joint dislocation, excellent functional outcome after closed reduction and immobilization can be expected. In case of complicated lateral subtalar joint dislocation immediate reduction, wound debridement and if necessary (external) stabilisation are critical. Up to fifty percent of patients suffering complicated injury are at risk of developing complications such as avascular talar necrosis and infection.

Key words: Trauma; Dislocation; Subtalar joint; Foot injury; Hindfoot surgery; External fixators

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Core tip: Subtalar dislocations are a rare and severe injury which is often result of high-energy trauma. Sub-

talar dislocations represent 1%-2% of all dislocations. The foot is displaced laterally in about 25% of cases. Excellent outcome can be expected in patients with uncomplicated lateral subtalar dislocation if immediate closed reduction is achieved. In case of complicated subtalar joint dislocations requiring open reduction, wound debridement, appropriate joint reduction and additional stabilisation with an external fixation are critical. A complication rate up to 50% can be expected in these patients.

Veltman ES, Steller EJA, Wittich P, Keizer J. Lateral subtalar dislocation: Case report and review of the literature. *World J Orthop* 2016; 7(9): 623-627 Available from: URL: http://www.wjgnet.com/2218-5836/full/v7/i9/623.htm DOI: http://dx.doi.org/10.5312/wjo.v7.i9.623

INTRODUCTION

Subtalar joint dislocation is defined as a simultaneous dislocation of the subtalar (talocalcaneal) and talonavicular joint[1]. Subtalar dislocations are rare and often the result of high-energy trauma[1,2]. Rarity of this injury can be attributed to the presence of strong ligaments connecting the talus and the calcaneus, the strong biomechanical properties of the ankle and the tight joint capsule[2]. The trauma causing this type of injury is frequently a fall from considerable height or a motor vehicle accident[4]. In American literature, a large number of patients feature trauma after jumps during a basketball game, which has led to the term "basketball foot"[3,4].

Subtalar joint dislocations are frequently accompanied by fractures of the adjacent tarsal and metatarsal bones. Severe soft tissue injury can also be present[1]. The currently used classification of subtalar dislocations was introduced by Broca in 1853 and adjusted by Malgaigne *et al*[5] in 1856. Dislocations of the talus are classified based on the direction in which the foot is dislocated[1,6]. In about 72% of patient the talus is dislocated medially, lateral dislocation is present in 26% of patients and posterior or anterior dislocation in the remainder of patients[1]. Lateral subtalar joint dislocations are produced by forced eversion with the foot in dorsiflexion[1]. Inability to reduce lateral subtalar dislocations can be caused by interposition of the posterior tibialis tendon in case of rupture of the flexor retinaculum[7,8]. Pure ligamentous dislocations have an excellent prognosis after proper reduction[9]. Diagnosing additional injury is essential, as fractures of the lateral talar process and the sustentaculum tali may lead to the rapid development of posttraumatic osteoarthritis of the subtalar joint[10]. Talar avascular necrosis is reported in up to 50% of patients after complicated lateral subtalar dislocation[11].

Isolated lateral subtalar joint dislocation has only scarcely been described in literature. We report the case of a patient suffering complicated lateral subtalar joint dislocation and we give a comprehensive review of the available literature on lateral subtalar joint dislocations.

CASE REPORT

In May 2015, a 31-year-old male was presented to the emergency room with pain of the foot after eversion trauma while jumping on a trampoline. Initial trauma screening revealed a hemodynamically stable patient with a complicated (Gustilo type 3) subtalar joint dislocation of the right leg (Figure 1). During trauma screening no other injuries were detected. The patient was transported to the OR within 4 h of presentation. The dislocated talus was immediately reduced using a surgical spoon and a femoral head impactor. We performed meticulous wound debridement, after which the wound was closed transcutaneously over a subcutaneous low vacuum drain. A joint bridging external fixator was constructed with additional kirschner-wires for reduction and temporary stabilisation (Figure 2). A postoperative computed tomography (CT) scan showed several small fracture fragments of the talar bone with congruent ankle and subtalar joints. There were no fractures of the adjacent tarsal and metatarsal bones.

The medial wound healed uneventfully. Eight weeks postoperatively the external fixator and kirschner wires were removed during a visit at the outpatient clinic. At this time the patient engaged in physical therapy and commenced bearing full weight on the affected leg. One year after injury the patient is walking without pain, only using a cane for long distances. Range of motion of the ankle is not restricted (Figure 3). Conventional radiographs show early signs of talar avascular necrosis (Figure 4), without associated clinical symptoms.

Review of the literature

Methods: The search was limited to humans aged over eighteen years with a subtalar dislocation. PubMed/MEDLINE, EMBASE, and the Cochrane Library were searched from up to April 1st 2016. Exclusion criteria were minor age and subtalar dislocation in medial, anterior or posterior direction. Case reports were excluded to limit report bias. The lists of references of retrieved publications were manually checked for additional studies potentially meeting the inclusion criteria and not found by the electronic search. Studies reporting various types of subtalar dislocation were identified and only included if the results of patients with lateral subtalar dislocation could be extracted separately.

We collected all information regarding the level of evidence, baseline patient characteristics, baseline clinical findings and mean period of follow-up. Data regarding type and timing of surgery, postoperative regimen, complications, functional outcome, radiological outcome and patient satisfaction were extracted.

Results: The literature search displayed 367 studies, of which eight studies including fifty patients could be included[6,11-17]. General characteristics can be found in Table 1. All reported numbers are sample-size weighted.

Table 1 General characteristics

Ref.	Year	No.of patients	Follow-up (mo)	Age	Male	Female	Left	Right	Complicated injury	Avascular necrosis	Infection
Camarda *et al*[12]	2015	3	69	50	x	x	x	x	0	0	0
Edmunds *et al*[13]	1991	4	36	43	4	0	3	1	4	3	1
Garofalo *et al*[14]	2004	5	122	32	4	1	3	2	4	0	0
Goldner *et al*[11]	1995	10	36	26	8	2	x	x	10	5	2
Jungbluth *et al*[6]	2010	6	58	42	4	2	x	x	2	0	0
Karampinas *et al*[15]	2009	9	21	32	7	2	4	5	9	1	1
Merchan *et al*[16]	1992	10	66	36	7	3	2	8	1	0	0
Ruhlmann *et al*[17]	2016	3	84	39	3	0	2	1	0	0	0
Total/mean		50	55	34	37	10	14	17	30	9	4

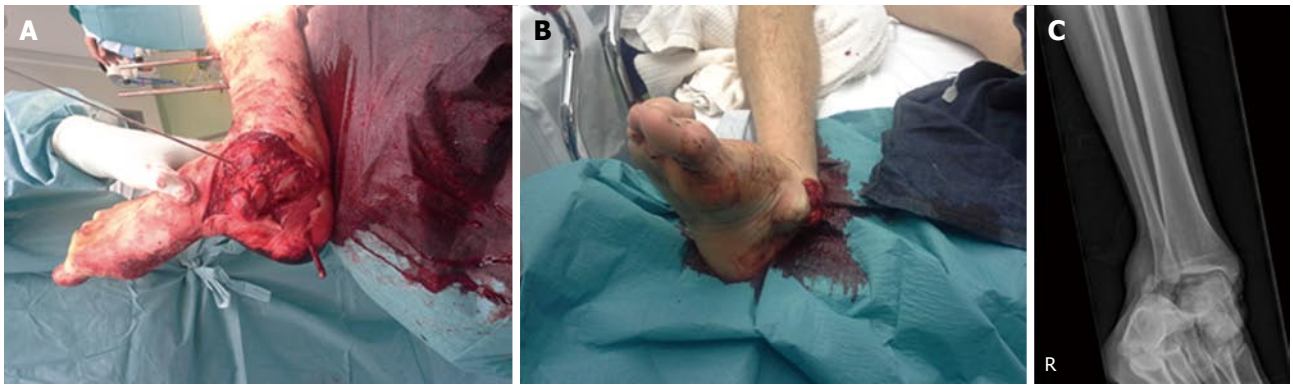

Figure 1 Initial trauma screening revealed a hemodynamically stable patient with acomplicated (Gustilo type 3) subtalar joint dislocation of the right leg. A and B: Gustilo grade 3 complicated lateral dislocation of the right foot; C: Radiograph showing lateral dislocation of the subtalar joint.

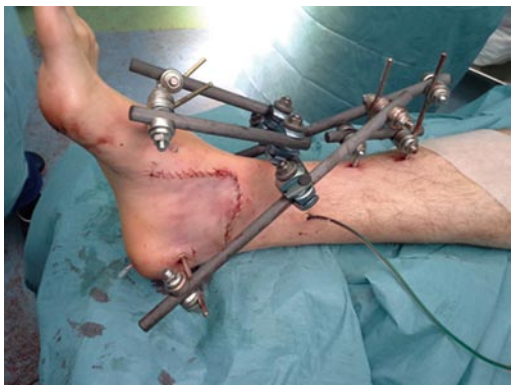

Figure 2 The wound is closed primarily after meticulous debridement and an external fixator is applied.

Eighty-seven percent of patients were male. Mean age was thirty-four years. Subtalar dislocations were evenly distributed over de left and right extremity. Thirty out of 50 patients suffered a complicated injury. Unfortunately Gustilo grading of complicated injury was not reported in all studies and therefore not available for analysis in this study. Associated fractures of the tarsal or metatarsal bones were present in seventeen patients, posterior tibial tendon rupture was present in six patients.

Closed lateral subtalar dislocations were treated with reduction and below the knee casting. Closed reduction was successful in all of these cases. All complicated lateral subtalar dislocations were treated with wound debridement. Additional fixation with k-wires was performed in three patients. An external fixator was placed in eleven patients, the other nineteen patients were treated with a below the knee cast. The patients were non-weight bearing for a mean period of seven weeks (range 4-12), after which the cast was removed and patients were allowed to bear weight. Mean follow-up was fifty-five months. Four studies[6,12,15,17] provide patient reported outcome with the use of the American Orthopaedic Foot and Ankle Society score (AOFAS)[18], which has not been validated for this purpose. Mean AOFAS score at follow-up was 82. Ankle function was reported as good in all patients with closed lateral subtalar dislocation. Severe pain was reported in nine patients with avascular necrosis and in two additional patients with severe osteoarthritis.

Radiologic assessment revealed subtalar osteoarthritis (Altman *et al*[19] type 2 or 3) in eight out of fifty patients. Avascular necrosis was present in nine additional patients. Patients with avascular necrosis were eventually treated with arthrodesis of the ankle in most cases. Four patients with complicated lateral subtalar dislocation suffered deep infection requiring treatment with antibiotics.

DISCUSSION

Lateral subtalar joint dislocation is a rare and severe injury. The number of patients reported with this type of injury is therefore small. The high-energy trauma which is needed to cause lateral dislocation is reflected in the percentage of patients with severe soft tissue damage.

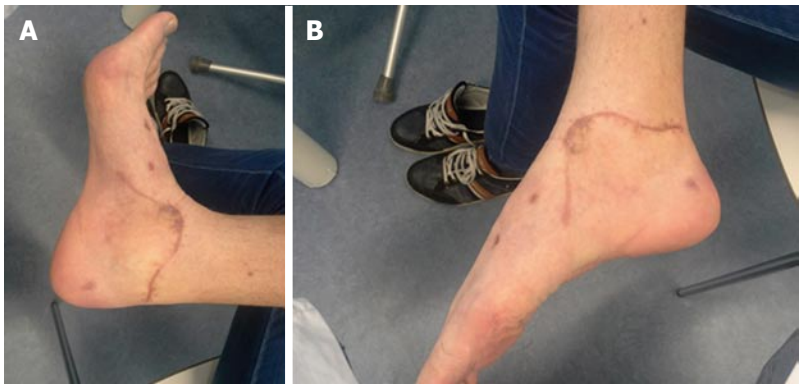

Figure 3 Excellent ankle function is restored at final follow-up (A and B).

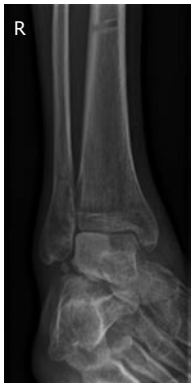

Figure 4 Radiograph of the ankle at follow-up, showing early signs of avascular talar necrosis.

Immediate reduction, extensive wound debridement and when necessary additional stabilisation are key features of treatment and should be performed as short after presentation as possible.

Complications are not evenly distributed among patients with closed and complicated injury. The literature review reports avascular necrosis or deep infection in 13 out of 30 patients with complicated lateral subtalar dislocation, compared to no avascular necrosis or deep infection in twenty patients with closed subtalar dislocation. Complicated injury is the main predictor of poor outcome. Avascular necrosis or deep infection can be expected in about 50% of cases.

In all cases, in addition to plain ankle and foot radiographs, a CT-scan should be performed after reduction to document additional bony injury to the subtalar area and adjacent bones. Additional injury is often underestimated in a plain radiograph of the hindfoot, but can have serious consequences such as osteoarthritis or chronic instability if undetected.

The duration of immobilization remains controversial. In uncomplicated injury an early weight-bearing protocol seems possible, after a lower leg cast for a period of 3-4 wk. In case of complicated injury or instability the use of an external fixator might be necessary, prohibiting patients from walking for a period of 6-12 wk depending on the extent of additional fractures of the tarsal and metatarsal bones.

This study gives a comprehensive review of the literature concerning lateral subtalar joint dislocation, treatment and expected outcome. Unfortunately, our literature search shows a lack of quality evidence. High level evidence on treatment and prognosis of subtalar joint dislocations is absent due to the rarity of this injury. The weaknesses of the original studies are reflected in our results. Patient specific characteristics such as smoking, obesity and diabetes, which affect the risk of developing avascular necrosis or infection, were not reported in the original studies and therefore not analysed. Daily practice would benefit from a large scale prospective study on optimal treatment, however with the extremely low number of patients suffering this injury this can be qualified as wishful thinking.

Excellent outcome can be expected in patients with uncomplicated lateral subtalar dislocation if immediate closed reduction is achieved. In case of complicated subtalar joint dislocations requiring open reduction, wound debridement, appropriate joint reduction and additional stabilisation with an external fixation are critical. A complication rate up to 50% can be expected in these patients. The review helps physicians treating a patient with a lateral subtalar dislocation to discuss treatment and prognosis of this severe injury of the foot.

COMMENTS

Case characteristics

Hindfoot pain and Gustilo grade 3 complicated injury of the hindfoot after jumping the trampoline.

Clinical diagnosis

Gustilo grade 3 complicated, isolated lateral subtalar joint dislocation.

Differential diagnosis

Ankle luxation fracture, talar fracture, talar extrusion, talar fracture, calcaneal fracture.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Plain radiographs (before reduction) of the foot showed a lateral subtalar

dislocation. A post-reduction computed tomography-scan demonstrated multiple small fracture fragments of the talar bone, without fractures of the adjacent bones.

Treatment
Immediate reduction, wound debridement and external fixation.

Related reports
See reference list for more articles on the same subject.

Experiences and lessons
Immediate reduction and meticulous wound debridement are key features in treating subtalar dislocations. In case of instability external fixation can be applied.

Peer-review
A simple rare article with simple to understand and something to learn.

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