ISSN 2218-5836 (online)

World Journal of *Orthopedics*

World J Orthop 2017 January 18; 8(1): 1-86

Published by Baishideng Publishing Group Inc

WJO World Journal of Orthopedics

A peer-reviewed, online, open-access journal of orthopedics

Editorial Board

2015-2018

The *World Journal of Orthopedics* Editorial Board consists of 328 members, representing a team of worldwide experts in orthopedics. They are from 41 countries, including Australia (10), Austria (8), Bangladesh (1), Belgium (4), Brazil (10), Canada (4), Chile (1), China (29), Croatia (2), Cyprus (1), Denmark (2), Egypt (5), Finland (1), France (2), Germany (19), Greece (12), Hungary (1), India (17), Iran (4), Israel (6), Italy (21), Japan (14), Jordan (2), Malaysia (1), Netherlands (10), New Zealand (1), Poland (1), Saudi Arabia (2), Serbia (1), Singapore (4), Slovenia (2), South Korea (12), Spain (7), Sri Lanka (1), Sweden (8), Switzerland (4), Thailand (5), Turkey (11), United Arab Emirates (1), United Kingdom (16), and United States (65).

Denmark

Lars C Borris, *Arhus*
Morten Tange Kristensen, *Hvidovre*

Egypt

Barakat Sayed El-Alfy, *Mansoura*
Khaled M Emara, *Cairo*
Mohamed Mostafa Hosney El-Sayed, *Tanta*
Mohammad Masoud, *Assiut*
Elsayed Ibraheem Elsayed Massoud, *Sohag*

Finland

Hannu T Aro, *Turku*

France

Federico Canavese, *Clermont Ferrand*
Hechmi Toumi, *Orleans*

Germany

Ahmet Ali Altintas, *Koln*
Hagen Andruszkow, *Aachen*
Mike H Baums, *Wiesbaden*
Peter Bernstein, *Dresden*
Bilal Farouk El-Zayat, *Marburg*
Ahmad M Eweida, *Ludwigshafen*
Chrisitan B Frank, *Baden-Baden*
Michael Frink, *Marburg*
Andreas B Imhoff, *Munich*
Chlodwig Kirchhoff, *Munich*
Matthias Knobe, *Aachen*
Hans-Christoph Pape, *Aachen*
Markus Peter Regauer, *Munich*
Khaled Hamed Salem, *Paderborn*
Frank M Schiedel, *Muenster*
Volker Schoeffl, *Bamberg*
Hagen Schmal, *Freiburg*
Fritz Thorey, *Heidelberg*
Tobias Topp, *Berlin*

Greece

Antonios Angoules, *Athens*
Georgios I Drosos, *Alexandroupolis*
Konstantinos Fousekis, *Egio*
Michael Hantes, *Larissa*
Marios G Lykissas, *Athens*
George A Macheras, *Athens*
Konstantinos N Malizos, *Larissa*
Dimitrios Nikolopoulos, *Athens*
Vassilis Paschalis, *Trikala*
Dionysios J Papachristou, *Patras*
Georgios Constantinos Papachristou, *Athens*
Haris S Vasiliadis, *Ioannina*

Hungary

Andor Sebestyén, *Pécs*

India

Vikas Bachhal, *Chandigarh*
Roopesh Kumar VR, *Pondicherry*
Vikas Kulshrestha, *Delhi*
Ashokkumar Navratnamal Johari, *Mumbai*
Pramod V Lokhande, *Pune*
Vivek Mahajan, *New Delhi*
Karthik Selvaraj Murugappan, *Coimbatore*
Satya Ranjan Patra, *Bhubaneswar*
V Prakash, *Anand*
Joshua Samuel Rajkumar, MPT, *Bangalore*
Parag Sancheti, *Pune*
Gaurav Sharma, *Chandigarh*
Mohamed Shafi, *Gangavalli*
Ajay Pal Singh, *Punjab*
Sujit Kumar Tripathy, *Bhubaneswar*
Raju Vaishya, *New Delhi*
Divya Vohora, *New Delhi*

Iran

MT Karimi, *Isfahan*
Firooz Madadi, *Tehran*
Mohammad Ali Mohseni-Bandpei, *Tehran*
Amir Hossein Saveh, *Tehran*

Israel

Alexander Blankstein, *Ramat HaSharon*
Itay Fenichel, *Udim*
Youssef Maher Masharawi, *Tel Aviv*
Nahum Rosenberg, *Haifa*
Jona J Sela, *Jerusalem*
Yehuda Ullmann, *Haifa*

Italy

Alessandro Aprato, *Torino*
Andrea Angelini, *Bologna*
Luigi Valentino Berra, *Milano*
Matteo Cadossi, *Bologna*
Lawrence Camarda, *Palermo*
Giuseppe Maurizio Campo, *Messina*
Andrea Camera, *Pietra Ligure*
Stefano Carbone, *Rome*
Patrizia D'Amelio, *Torino*
Cesare Faldini, *Bologna*
Olimpio Galasso, *Catanzaro*
Umile Giuseppe Longo, *Roma*
Alberto Grassi, *Bologna*
Nicolò Martinelli, *Milan*
Raffaele Mugnai, *Modena*
Giuseppe Musumeci, *Catania*
Roberto Postacchini, *Rome*
Barbara Rossi, *Rome*
Roberto Rossi, *Torino*
Stefano Marco Paolo Rossi, *Pavia*
Luigi Tarallo, *Modena*

Japan

Ukei Anazawa, *Ichikawa*
Yoichi Aota, *Yokohama*
Masahiro Hasegawa, *Tsu City*
Takafumi Hiranaka, *Takatsuki*
Eichi Itadera, *Narita*
Hiroshi Kawaguchi, *Tokyo*
Shigeru Kobayashi, *Eiheiji*
Makoto Makishima, *Itabashi-ku*
Kanji Mori, *Otsu*
Tsuyoshi Ohishi, *Hamamatsu*
Kazuya Oshima, *Osaka*
Hirotaka Sano, *Sendai*
Jun Takahashi, *Matsumoto*
Kotaro Yamakado, *Fukui*

Jordan

Alia A Alghwiri, *Amman*
Bashar Abuzayed, *Irbid*

Malaysia

Arezoo Eshraghi, *Kuala Lumpur*

Netherlands

Michel Pieter Jozef van den Bekerom, *Amsterdam*
Peter RG Brink, *Maastricht*
Yvon Marielle den Hartog, *Rotterdam*
Izaak Frederik Kodde, *Amsterdam*
Jesse WP Kuiper, *Alkmaar*
Tom M van Raaij, *Groningen*
Hugo Christiaan van der Veen, *Groningen*
Alexander TM van de Water, *Enschede*
Walter van der Weegen, *Geldrop*
Eline W Zwitser, *Leiderdorp*

New Zealand

Gary J Hooper, *Christchurch*

Poland

Agnieszka Tomaszewska, *Gdańsk*

Saudi Arabia

Ahmed Bakhsh, *Al-Khobar*
Mohamed Zamzam, *Riyadh*

Serbia

Miroslav Ziva Milankov, *Novi Sad*

Singapore

Yee Han Dave Lee, *Singapore*
Anselm Mak, *Singapore*
Sean Ng, *Singapore*
Ken Lee Puah, *Singapore*

Slovenia

Gregor Recnik, *Maribor*
Matjaz Sajovic, *Celje*

South Korea

Yong Ahn, *Seoul*
Seung-Hoon Baek, *Daegu*
Chang-Ho Hwang, *Ulsan*
Jin Ho Hwang, *Seoul*
Jung-Taek Hwang, *Chuncheon*
Tae-Young Kim, *Anyang*
Sung-Uk Kuh, *Seoul*
Haejung Lee, *Busan*
Young-Kyun Lee, *Seongnam*
Soon Hyuck Lee, *Seoul*
Sang-Ki Lee, *Daejeon*
Hee-Soo Seo, *Seoul*

Spain

Miguel Angel Ruiz Iban, *Madrid*
Rafael Arriaza, *La Coruna*
Enrique Guerado, *Malaga*
Albert Isidro, *Barcelona*
Sergio Hernandez-Sanchez, *Sant Joan D'alacant*
Nuria Vilaboa, *Madrid*
Rafael Villalba, *Córdoba*

Sri Lanka

Janaka Lenora, *Galle*

Sweden

Allan Abbott, *Linkoping*
Paul W Ackermann, *Enebyberg*
Johan von Heideken, *Stockholm*
Karin Larsson, *Gothenburg*
Anna Nordstrom, *Umea*
Yan Li, *Stockholm*
Jonas Ranstam, *Lund*
Ola Rolfson, *Gothenburg*

Switzerland

Marco Barbero, *Manno*
Dimitrios-Stergios Evangelopoulos, *Bern*
Ladislav Mica, *Zurich*
Michael Tobias Hirschmann, *Bruderholz*

Thailand

Sugalya Amatachaya, *Maung*
Theerachai Apivatthakakul, *Chiang Mai*
Wiroon Laupattarakasem, *Mueang*
Boonsin Tangtrakulwanich, *Hat Yai*
Tulyapruek Tawonsawatruk, *Bangkok*

Turkey

Tuncay Colak, *Kocaeli*
Abdullah Demirtas, *Istanbul*
Mehmet Erdil, *Istanbul*
Kemal Gokkus, *Antalya*
Alper Kaya, *Istanbul*
Serdar Kahraman, *Istanbul*
Ramazan Kahveci, *Ankara*
Yavuz Kocabey, *Kocaeli*
sKemal Nas, *Sakarya*
Salih Ozgocmen, *Kayseri*
Namik Sahin, *Bursa*

United Arab Emirates

Ashraf Fathi Hefny, *Al Ain*

United Kingdom

Nawfal Al-Hadithy, *London*
Sarah Cartmell, *Manchester*
Nick Caplan, *Newcastle upon Tyne*
Andrew Douglas Carrothers, *Cambridge*
Efstathios Drampalos, *Wigan*
Prithee Jettoo, *Middlesbrough*
Saravana Vail Karuppiah, *Nottingham*
Hammad Malik, *Manchester*
Riazuddin Mohammed, *Wigan*
Gohar Naqvi, *Cambridge*
Christopher William Oliver, *Edinburgh*
Philip Socrates Pastides, *London*
Greg A Robertson, *Edinburgh*
Adnan Saithna, *Liverpool*
Praveen Sarda, *Gillingham*
Deepak Gubbi Shivarathre, *Liverpool*

United States

Daniel Louis Aaron, *Pawtucket*
Ashish Anand, *Jackson*
Huston Davis Adkisson, *St Louis*
Keith Baldwin, *Philadelphia*
Adam Brufsky, *Pittsburgh*
Ali Bydon, *Baltimore*
Nicole J Chimera, *Amherst*
Ock K Chun, *Storrs*
Suresh Chinthakunta, *Collegeville*
Alan H Daniels, *Providence*
Nabanita S Datta, *Detroit*
Deanna C Dye, *Bozeman*
Scott Forsyth Dye, *San Francisco*
Clark Dickin, *Muncie*
Hossein Elgafy, *Toledo*
Brandon J Erickson, *Chicago*
Nathan Joseph Fanter, *Hines*
Ashraf S Gorgey, *Richmond*
Timothy August Hartshorn, *Manhattan Beach*
John E Herzenberg, *Baltimore*
Jake Paul Heiney, *Toledo*
Matthew C Hoch, *Norfolk*
Johanna Marie Hoch, *Norfolk*
Mozammil Hussain, *Chesterfield*
Pier Francesco Indelli, *Albuquerque*
Michael Joseph, *Storrs*
Srinath Kamineni, *Lexington*
Eldin E Karaikovic, *Evanston*
Jeffrey Bruce Knox, *Honolulu*
Fatih Kucukdurmaz, *Philadelphia*
Kevin Laudner, *Normal*
KH Lee, *Rockville*
Bingyun Li, *Morgantown*
Xinning Li, *Boston*
Zong-Ming Li, *Cleveland*
Randall Loder, *Indianapolis*
Mark Kevan Lyons, *Phoenix*
Eleftherios A Makris, *Davis*
Aditya Vikram Maheshwari, *Brooklyn*
Paul David Metzger, *North Chicago*
Subburaman Mohan, *Loma Linda*
Arash Momeni, *Palo Alto*
Freeman Miller, *Wilmington*
Rahul Kumar Nath, *Houston*
Ripul R Panchal, *Sacramento*
Vinod Panchbhavi, *Galveston*
Nikolaos K Paschos, *Davis*
Ming Pei, *Morgantown*
Shannon MBravo Petersen, *Des Moines*
Matthew Robert Schmitz, *Fort Sam Houston*
Bruce M Rothschild, *Indiana*
Ran Schwarzkopf, *Orange*
Jason Scott Scibek, *Pittsburgh*
Shahin E Sheibani-Rad, *Los Angeles*
Manish K Sethi, *Nashville*
Vani Sabesan, *Dearborn*
Kern Singh, *Chicago*
William D Smith, *Las Vegas*
Ettore Vulcano, *Baltimore*
Ying-Chih Wang, *Milwaukee*
Joshua T Weinhandl, *Norfolk*
Charalampos Zalavras, *Los Angeles*
Chunfeng Zhao, *Rochester*
Nigel Zheng, *Charlotte*

World Journal of Orthopedics

Contents

Monthly Volume 8 Number 1 January 18, 2017

FRONTIER

MINIREVIEWS

ORIGINAL ARTICLE

Case Control Study

Retrospective Study

Clinical Trials Study

Observational Study

CASE REPORT

World Journal of Orthopedics
Volume 8 Number 1 January 18, 2017

Contents

NAME OF JOURNAL
World Journal of Orthopedics

ISSN
ISSN 2218-5836 (online)

LAUNCH DATE
November 18, 2010

FREQUENCY
Monthly

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Orthopedics
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
January 18, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.1

World J Orthop 2017 January 18; 8(1): 1-11
ISSN 2218-5836 (online)

FRONTIER

Glucosamine and chondroitin for the treatment of osteoarthritis

Haris S Vasiliadis, Konstantinos Tsikopoulos

Haris S Vasiliadis, Orthopaedie Sonnenhof, 3006 Bern, Switzerland

Konstantinos Tsikopoulos, 1st Orthopaedic Department, 424 Army General Training Hospital, 56429 Thessaloniki, Greece

Author contributions: Both authors contributed to this paper.

Conflict-of-interest statement: The authors declare no conflict of interest.

Manuscript source: Invited manuscript

Correspondence to: Haris S Vasiliadis, MD, PhD, Orthopaedie Sonnenhof, Buchserstrasse 30, 3006 Bern, Switzerland. vasiliadismd@gmail.com
Telephone: +41-79-8883610

Received: July 22, 2016
Peer-review started: July 26, 2016
First decision: September 6, 2016
Revised: September 19, 2016
Accepted: October 17, 2016
Article in press: October 18, 2016
Published online: January 18, 2017

Abstract

The prevalence of primary or idiopathic osteoarthritis (OA) of knee and hip joints has substantially increased in general population during the last decades. Analgesics and non-steroidal anti-inflammatory drugs are currently extensively used as non-surgical treatment options. However, they act as symptomatic treatments, not offering a cure of OA and they are accused for an increased risk of adverse events. Glucosamine (GL) and chondroitin (CH) are nutritional supplements that have recently gained widespread use as treatment options for OA. They potentially or theoretically act as chondroprotectors or/and as "disease-modifying OA drugs" offering not only symptomatic relief but also alteration of the natural history of OA. However, although many studies have showed a significant treatment effect, accompanied with remarkable safety, there is still controversy regarding their relative effectiveness compared with placebo or other treatments. The scope of this review is to present and critically evaluate the current evidence-based information regarding the administration of GL and CH for the treatment of knee or hip OA. Our focus is to investigate the clinical efficacy and safety after the use of these supplements. An effect of GL and CH on both clinical and radiological findings has been shown. However, only a few high-quality level I trials exist in the literature, especially on the assessment of radiological progression of OA. The effect sizes are generally small and probably not clinically relevant. Even the validity of these results is limited by the high risk of bias introduced in the studies. Both GL and CH seem to be safe with no serious adverse events reported. There is currently no convincing information for the efficacy of GL and CH on OA.

Key words: Glucosamine; Chondroitin; Osteoarthritis; Knee; Cartilage

Core tip: In this review we present and critically evaluate the current information regarding the administration of glucosamine (GL) and chondroitin (CH) for the treatment of knee or hip osteoarthritis. A clinical and radiological effect of GL and CH has been shown. However, only a few high quality trials exist. The effect

sizes are small and probably not clinically relevant. The validity of these results is limited by high risk of bias introduced in the studies. Both GL and CH seem to be safe with no serious adverse events but there is currently no convincing information for their efficacy as treatment options in osteoarthritis.

Vasiliadis HS, Tsikopoulos K. Glucosamine and chondroitin for the treatment of osteoarthritis. *World J Orthop* 2017; 8(1): 1-11 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/1.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.1

INTRODUCTION

The prevalence of primary or idiopathic osteoarthritis (OA) of knee and hip joints has substantially increased in general population during the last decades. The aging of the population and the increment of life expectance are contributing factors; however, there is also a high incidence of OA in younger ages[1,2]. Approximately 5% of the population aged between 35 and 54 years has radiographic signs of knee osteoarthritis, which reaches 30% for ages between 45 and 65[3]. Except from post-traumatic OA, a reason for younger patients may be the wide participation in high competitive sports and the increment of recreational athletes even in not regularly and inadequately trained population. This subjects their joints to distracting repetitive forces that may lead to progressive cartilage damage and subsequently to secondary or posttraumatic OA.

Focal cartilage lesions usually occur at a first stage, often remaining asymptomatic. Untreated or under-treated lesions may lead to OA. The treatment of OA in elder patients is well clarified and accepted to be joint reconstruction *via* an arthroplasty (either hip or knee). However, arthroplasty may be considered a salvage procedure requiring a modification of daily life postoperatively, not participation in contact sports or high impact sports and is subject to revision surgery after a certain period of time. Therefore this treatment option does not apply to the more active and/or younger patients, even those with severe OA.

Therefore, there is increasing need for treating OA with less invasive interventions, with pharmaceutical agents being the most favourite especially for younger age groups. Analgesics and non-steroidal anti-inflammatory drugs are currently extensively used[4-6]. However, they frequently cause serious adverse events, including the gastrointestinal or cardiovascular system. Given also that they rather act as symptomatic treatment, not offering a cure of OA, a long-term use is usually required, increasing the risk of such events[4,5].

An ideal treatment would not only reduce the symptoms but additionally modify the natural history of OA, slowing or even altering the inflammation and destructive effect on the articular cartilage and joint tissues. Such substances that protect the articular cartilage during the course of OA have been termed as "chondroprotective agents" or "chondroprotectors". When these agents appear to alter the course of the disease (*e.g*., by modifying the biochemical cascades that contribute to the OA), they are termed "disease-modifying OA drugs" (DMOADs). Such agents aim to protect the joint cartilage along with the subchondral bone and synovial membrane, which are the main structures of the joint[7-9].

Glucosamine (GL) and chondroitin (CH) are nutritional supplements that have gained widespread use. They are two main categories of agents potentially or theoretically acting as chondroprotectors and/or as DMOADs. Although many studies have been published showing a significant treatment effect, accompanied with remarkable safety, there is still controversy regarding their relative effectiveness compared with placebo or other treatments, their cost-effectiveness and the need for insurance coverage of the therapy cost[10-12]. Due to methodological and bias concerns, these studies have failed to persuade most of the big national insurance committees (like FDA or NICE) or the biggest scientific societies (like EULAR, ACG EULAR or OARSI) to include GL and CH as first line treatment options in their guidelines[13-19]. However despite this, global sales of GL supplements reached almost $2bn in 2008 in United States, after an increase of about 60% compared with 2003, with a forecasted continued growth that would reach $2.3bn in 2013[20].

The scope of this review is to present and critically evaluate the current evidence-based information regarding the administration of GL and CH for the treatment of knee or hip OA. Our focus is to investigate the clinical efficacy and safety after the use of these supplements. Initially we will present the theoretical mechanism of action of these agents, through which they may affect the progress of OA. Next, we will present the clinical evidence, mainly based on the level Ⅰ information from systematic reviews (SRs) of randomised control trials (RCTs). Finally, we will discuss the information along with probable factors that may contribute to a safe conclusion regarding the efficacy and safety of the use of GL and CH for the treatment of osteoarthritis.

BACKGROUND

Molecular structure of articular cartilage and mechanism of primary OA

Articular cartilage has a vast preponderance of extracellular matrix (composed of collagen and proteoglycans), in which cells (chondrocytes) are distributed sparsely. Collagen fibrils (mainly of type Ⅱ collagen) form the framework of articular cartilage[21]. The proteoglycan aggregate is an aggregation of proteoglycan monomers attaching to the filamentous hyaluronan backbone and fills the space of the collagen network[22]. The proteoglycan molecules (also called aggrecans) consist of numerous long-chain glycosaminoglycans (GAGs)

linked to a core protein. Such GAGs (CH sulfate and keratan sulphate) are linear polymers composed of sugar residues[23]. They are composed of repeating units of N-acetylgalactosamine and glucuronic acid (in CH sulphate) and N-acetylglucosamine and galactose (in keratan sulphate). GAGs are negatively charged, so they attract a large quantity of water molecules. More than 70% of the net weight of cartilage consists of water. Synovial fluid produced from synovial cells, lubricates the joint surfaces and also provides cartilage with oxygen and nutrition.

In OA, matrix metalloproteinases (MMPs) and aggrecanases produced by inflamed synovial cells and the diseased chondrocytes result in a gradual degradation of collagen and proteoglycan molecules. Lytic enzymes released as a result of this degradation also enhance synovial inflammation and induce chondrocytes' apoptosis. The inflammation leads to progressive cartilage degradation. The network described above is gradually destructed. Loss of aggrecans from the extracellular matrix leads to a change in the biomechanical properties of the cartilage tissue. This adds to an increased mechanical wear and would result in an accelerated damage of articular cartilage and eventually to OA. This mechanism of OA may be triggered by traumatic lesions and degradation of focal lesions of cartilage, chondrocyte apoptosis and consequent release of lytic enzymes entering the above described cascade of events.

Prostaglandins released by synoviocytes and chondrocytes during this inflammatory cyclic reaction of cartilage degradation are also known to enhance pain and inflammation.

The above suggested mechanism is primarily apparent in primary osteoarthritis, which is characterised by a generalized cellular dysfunction starting with focal degradation in the most loaded areas of the joint articular surface. In secondary cases of osteoarthritis, other factors also contribute to the joint damage. For example in posttraumatic OA a traumatic focal cartilage lesion may trigger this cascade of degradation. In this case the combination of the mechanic break down in the lesion area and the enzymatic degradation of the damaged cartilage finally lead to OA.

In vitro and animal studies

GL: GL is a water-soluble amino monosaccharide and one of the most abundant monosaccharides in the human body. It is present in high quantities in articular cartilage, being a normal constituent of GAGs in cartilage matrix and also in the synovial fluid. It is a constituent of keratan sulphate. There are two forms: Glucosamine sulphate (GS) and glucosamine hydrochloride (GH).

The way that exogenous administration of GL may work in OA is not yet fully defined. It is believed that GL may have an important role in regulating the anabolic processes of cartilage and also in the synthesis of synovial fluid. Additionally it may inhibit the degenerative and catabolic process of OA with its anti-inflammatory and even antioxidant properties.

It is reported that GL may affect the cytokine-mediated pathways regulating inflammation, cartilage degradation, and immune responses[24,25]. It appears to have immune-modulatory activity inhibiting the expression and/or activity of catabolic enzymes such as phospholipase A2, MMPs or aggrecanases[24-27]. GL reduces or regulates interleukin-1 (IL-1) levels in synovial fluid and inhibits the actions of catabolic enzymes in the joint[28-30]. This reduces inflammation and cartilage degradation potentially altering the progression of OA. Except from its anti-catabolic action, it has been suggested that GL sulphate has an anabolic effect by stimulating cultured human chondrocytes to synthesize proteoglycans and has been reported to be a substrate for new CH sulphate synthesis[24,31]. It has also found to inhibit gene expression of OA cartilage *in vitro*[31]. Finally, GL may act by inducing the production of hyaluronic acid by the synovial membrane[31]. Along with its indirect effect on the cartilage metabolism, being a precursor of GAGs, it is also possible that supplementation with GL may help promote GAG synthesis or reduce its degradation.

Animal studies have also supported the anabolic and/or anti-catabolic effect of GL on cartilage. A GL analogue has demonstrated both anti-arthritic and anti-inflammatory properties in rats[32]. Another study reports a positive effect on cartilage, enhancing the rate of new proteoglycan synthesis[33] and others have confirmed the effectiveness of GL in delaying the cartilage degradation and the progression and severity of OA[34]. Long-term oral administration of GL sulphate also reduced the destruction of cartilage and upregulation of MMP-3 mRNA in a model of spontaneous osteoarthritis in Harley guinea pigs[30,35]. However, the preparation used in many of *in vitro* and *in vivo* studies was not a GL sulphate ester but a preparation in which GL and sulphate occurred as two single molecules in crystalline form[36].

CH: CH sulfate is a sulfated GAG being also a major component of the extracellular matrix of articular cartilage. It is found attached to proteins as part of the aggrecan of the cartilage. It plays a major role in creating considerable osmotic pressure that expands the matrix and places the collagen network under tension[37]. It provides cartilage with resistance and elasticity allowing it to resist tensile stresses during various loading conditions[38].

Similarly to GS, the exogenous administration of chondroitin sulphate (CS) has been suggested to act against OA by three main mechanisms; anabolic effect by stimulating the production of extracellular matrix of cartilage, suppression of inflammatory mediators and inhibition of cartilage degeneration[21]. Studies have demonstrated that CS counteracts the action of IL-1b (a factor that induces articular inflammation and

cartilage degeneration), thus playing a chondroprotective role[39,40]. Additionally an effect on subchondral bone had been suggested by reducing the resorptive activity in subchondral bone[41,42].

Proteoglycan content in cartilage was also significantly higher in animals treated with oral or intramuscular administration of CS than that in control animals[43]. It has been shown that CS significantly decreases collagenolytic activity[44]. Other studies suggested that the benefits of CS on degenerative osteoarthritic chondrocytes are larger than those on normal chondrocytes[39,45].

Bioavailability

As described above, both GL and CH are components of the extracellular matrix of articular cartilage. Experimental studies have also suggested an additional action in inflammatory pathways that contribute to OA. Provided this, their external administration has been widely considered as a treatment option for OA.

GL and CH have been used for medicinal purposes for nearly 40 years[46]. However, their bioavailability after oral administration in humans is a subject still under debate. A key issue would be the absorption of these agents through their passing from the gastrointestinal system.

In mammals, the major site of their metabolism and degradation is the liver, but the exact mechanism is unclear[21]. Published information is rather controversial. Early pharmacodynamic studies inferred absorption only indirectly. Laboratory work has suggested that GL is substantially degraded in the gastrointestinal tract[47]. Other studies show that despite its large molecular size, ingested CH is partially absorbed in the intestine and some of it may reach joints[10,48]. A pharmacokinetic study in dogs, showed that GL (hydrochloride) is absorbed with a bioavailability of about 10%-12% from single or multiple doses[49]. In humans, serum GL levels following an oral dose of 1.5 g GL sulfate do not appear to exceed 12 mmol/L. Animal studies have also shown that after oral administration of GL hydrochloride, synovial GL concentrations are higher in joints with synovial inflammation compared to levels attained in healthy joints[50].

Regarding CS, different bioavailability and pharmakokinetic variables have been reported, usually depending on the study methodology or the CS characteristics[51]. A bioavailability of 10%-20% has been reported in earlier studies[52-54]. Study in humans has shown a significant increase in plasma levels (more than 200% compared with pre-dose levels) over a 24-h period[48]. Use of labelled CS has shown a high level of CS, observed in the human synovial fluid and articular cartilage after oral administration[53]. A limitation to the studies provided above is that both GL and CS are drugs of biological origin. Thus, their measurement in biological fluids does not discriminate the drug from endogenous molecules.

CLINICAL EVIDENCE

Based on laboratory and animal studies, it has been suggested that GL and CH may be effective on preserving cartilage in early OA, and hence might slow down its progression. This would result in a relief from symptoms including pain and stiffness. This claim was also based on clinical studies that reported a clinical benefit after oral administration. However, recent SRs have cast doubt on this.

Quite early, in 2000, a large SR of RCTs assessed the efficacy and safety of GL (GS or GH) and CH[55]. Assessing 15 RCTs, the authors found moderate effect sizes for GL (0.44, 95%CI: 0.24-0.64) and large effects for CH (0.96, 95%CI: 0.63-1.3). They also extensively investigated the quality of information provided by these studies. A high risk of bias was reported, with poor methodology and poor reporting among the included trials. In all but two trials there was some level of manufacturer sponsorship, while none of the studies reported independent funding from a governmental or non-for-profit organization. They also found that pooled effect sizes were substantially higher compared to those of lower quality or smaller trials, which seem to exaggerate the efficacy of both GL and CH. A high risk of publication bias was also shown on funnel plots, suggesting a high probability of not reporting of small trials or of those with small or null treatment effect.

Richy *et al*[56] assessed also 15 RCTs, concluding to a superiority of GL and CH in clinical and radiological findings. Although the authors assessed the quality of the included trials, no further analysis was performed to detect any association with the effect sizes.

Wandel *et al*[11] assessed RCTs that compared CS, GS, GH, or the combination of any two with placebo or head to head. Small trials and ones using subtherapeutic doses were excluded. A network meta-analysis of 10 trials was conducted. In 5 trials, GS was compared with placebo, in 3 CS with placebo, and one compared GH, CS and their combination with placebo. In another placebo controlled trial GS was used; however, after 80% of the patients had been treated, the investigators were forced to change into GH because the manufacturer of GS declined to supply matching placebos[57]. Seven of the trials were funded by manufacturers. Joint pain was extracted in nine time-windows starting from "up to 3 mo", up to "22 mo or more". Effect sizes for joint pain were -0.17 (95%CI: -0.28 to -0.05) for GL, -0.13 (95%CI: -0.27 to 0.00) for CH, and -0.19 (95%CI: -0.37 to 0.00) for the combination suggesting a close to null effectiveness of the interventions. Stratified analysis revealed that the estimated differences between supplements and placebo were significantly more pronounced in industry funded trials [by on average, 0.5 cm (0.1 to 0.9 cm) in a 10-cm VAS scale, $P = 0.02$]. The analysis of 6 trials providing outcome on radiological joint space, showed no clinically relevant effect on joint space narrowing for

any of the interventions. No differences were found in adverse events, and withdrawals or drop-outs because of adverse events. The authors concluded that CH, GL, and their combination do not have a clinically relevant effect on perceived joint pain or on joint space narrowing. They suggested that health authorities and health insurers should not cover the costs of these preparations, and new prescriptions to patients who have not received other treatments should be discouraged.

Vlad *et al*[58] analysed 15 RCTs comparing GL (12 GS and 3 GH) with placebo. Industry funding was reported for 11 trials, while 13 studies used an industry-supplied drug. Rottapharm provided GS in 8 trials and contributed to a ninth trial. The authors reported a marked heterogeneity among trials. They found marked differences between subgroups of trials when grouped by various trial characteristics. Overall, they found a pooled effect size of 0.35 (95%CI: 0.56 to 0.14) in favour of GL. However, there was substantial heterogeneity among trials, questioning the reliability of this finding. This heterogeneity remained high in the industry-funded trials but not in the independent trials. The 11 industry-funded trials had a pooled effect size of 0.47 (95%CI: 0.24-0.70) favouring GL; however a null effect size was found when only the 4 non-industry-funded trials were analysed 0.05 (95%CI: -0.32 to 0.41). Trials with Rottapharm products (a GS product) showed an increased effect size compared with trials with other products (P = 0.01.) In general, heterogeneity was absent and effect sizes were smaller in high quality, more recently published and not funded trials, suggesting a high risk of bias for the overall quality of provided information in the related literature. Trials using GS had an effect size favouring the intervention (0.44, 95%CI: 0.18 to 0.70) although GH did not show superiority over placebo. High heterogeneity was found in both cases. The authors concluded that there is sufficient information to conclude that GH lacks efficacy for pain in OA. Among GS trials, marked heterogeneity existed; therefore no definitive conclusion about efficacy is possible.

Reichenbach *et al*[10] assessed 22 RCTs or quasi-RCT trials that compared CH with placebo or no intervention. The authors also reported a low quality of evidence as only a few trials had an adequate generation of allocation sequence (1 study) or adequate concealment (2 studies) or followed an intention to treat analysis (3 studies). The meta-analysis of 20 trials providing pain outcomes suggested a pooled large effect size that favours CH sulphate -0.75 (-0.99 to -0.50), corresponding to a difference of 1.6 cm on a 10 cm VAS. However, the heterogeneity was large (I^2 = 92%) and the funnel plot was asymmetrical suggesting high publication bias. More recent trials tended to be larger and of higher quality and included patients with lower-grade of osteoarthritis than did earlier trials. Stratified analysis found that when the analysis was restricted to methodologically sound trials of adequate sample size, there was a null effect size with low heterogeneity. From 5 trials assessing the difference of mean joint space width, the authors found a mean effect size of 0.18 SD units favouring CH, an effect size that was not clearly clinically significant. The authors finally discouraged the use of CH. In this trial only one time point was assessed per trial, which was criticised.

Another SR assessed the short-term efficacy of several pharmacotherapeutic interventions in osteoarthritic knee pain[59]. Among 63 RCTs assessing different interventions, 7 assessed GS and 6 CS, with minimal daily administered doses of 1500 mg and 800 mg, respectively. Mean pain relief values for GS or CS had no clinical relevance within 4, 6, 8 or 12 wk. Only for CH sulphate, there was a slight increase in efficacy equivalent to a categorical shift from none to perceptible improvement up to 12 wk.

A SR conducted by Lee *et al*[60] included six trials evaluating the effects of CH (4 studies) or GL (2 studies) on narrowing of joint space. They found significant small to moderate protective effects on minimum joint space narrowing, after 3 years of treatment with GS (SMD 0.43, 95%CI: 0.24-0.63, P < 0.001). The same was observed for CH sulphate, which had a small but significant protective effect on minimum joint space narrowing after 2 years (SMD 0.26, 95%CI: 0.13-0.39). This SR concluded that GL and CS may delay radiological progression of OA of the knee after daily administration for over 2 or 3 years. However, the number of RCTs assessed was low and important big studies were missing from the evaluation[61,62]. No clinical assessment was included in the outcomes and no methodological assessment of the included trials was performed. Two of the publications assessing CH where part of the same study, which was not taken into account in the meta-analysis[63,64].

A comprehensive Cochrane SR assessed RCTs of GL[12]. After the update in 2009, 25 RCTs were included (with 4963 patients). The analysis of the literature in this SR showed controversial results. There was evidence to show that GL is more effective in treating pain when compared with placebo showing an estimated relative per cent change from baseline of 22%. There was also superiority in Lequensne Index score (11% relative change from baseline), WOMAC total score and physician global assessment but not in other outcomes like WOMAC pain, stiffness and function subscales, minimum joint space width, patient global assessment. The majority of studies included had some form of relationship with a specific pharmaceutical manufacturer (Rottapharm). Interestingly, the authors found significant differences between the studies related with this manufacturer and the rest of the studies. Thus, studies in which this company's product was compared with placebo showed superiority of GL, even in radiological progression. However, pooled results from studies not using this product or from higher quality studies (with adequate allocation concealment) failed to show any benefit. It was clear though that GL had an

excellent safety profile, with complication rate equal to placebo and significantly less than NSAIDS.

Similarly, a recent SR from Singh *et al*[65], in the Cochrane library, included 42 RCTs that assessed the effectiveness of CH compared with placebo or control treatments. The authors concluded that there was a superiority of CH (alone or in combination with GL) over placebo, in terms of pain relief, in short-term studies. Moreover, CH had a lower risk of adverse events compared with control treatments. A limitation was the generally poor quality of studies available.

Regarding safety, all the SRs confirmed the safe profile of both GL and CH. In the total number of adverse events, withdrawals, or serious adverse events, no difference was found comparing with placebo[10,11,56]. Between trial heterogeneity, when reported for adverse events, was low in all cases[10,11].

DISCUSSION

There are several publications, from case series to RCTs, assessing the effectiveness and safety of GL and CH for the treatment of OA. However, there is criticism regarding the quality and validity of the majority of these studies. Even higher quality level I trials have been criticized for their non-transparent and low quality design. The vast majority have also been conducted by the manufacturing companies, increasing the risk of sponsorship bias. The low number of participants, non-defined source and preparation of the supplements used, short-term of follow up and outcome retrieval, non-defined dosing have also been discussed as sources of bias. Besides, there is increased heterogeneity among trials, mainly due to different dosing, different duration of application, different follow-up times, use of various escape or concomitant treatments (*e.g.,* pain killers, NSAIDS, physiotherapy).

Meta-analysis is the best tool available to collect and summarize all this spare and controversial information and to synthesise it, providing a more secure conclusion on the efficacy and safety of these interventions. The stratified analysis and subgroup analysis give the possibility to detect the effect of factors that are considered to potentially introduce heterogeneity or bias, like sponsorship of the study, inadequate treatment concealment, not binding of the outcome assessors, *etc*.

There are several level I SRs assessing GL and CH. Each of these has different inclusion or exclusion criteria resulting in a variety of number of studies included. The outcomes that are extracted from primary studies and analysed in the meta-analysis also differ in their nature and also in the time points assessed.

Despite the different methodology of these SRs, it seems that almost all conclude to a similar result; CH and GL have an effect size slight better when compared with placebo. However, when only the information from best quality trials are considered, then none of these supplements seem to demonstrate any superiority. Therefore, almost all of these level I reviews conclude to a lack of established efficacy, eventually suggesting that CH or GL should not be used in new patients.

Most of these SRs confirmed that the heterogeneity among trials could not be expected by chance alone. Bigger, methodologically sound independent trials did not show heterogeneity and did also not show relative efficacy of the intervention (either GL or CH)[10]. Cumulative analysis has also shown that newer publications showed smaller effects than did older publications[10,19].

According to the outcome of most of the SRs, there is a substantially increased risk of sponsorship bias in the available RCTs and this bias contributes to increased heterogeneity. It seems that the majority of the studies is financially supported in any form; either the manufacturer conducted the study, or provided with the drug or authors were supported. Sponsored trials showed more favourable results for the interventions although the rest of the studies did show null efficacy. It was also shown from some SRs that when a specific company was involved, the results were more favourable for the intervention. However, we should not exclude the possibility that some of this heterogeneity could be due to the use of different supplement formulations or to different dosing protocols. Such information was not regularly provided so to systematically detect this possibility.

Assumptions about reasons for failure

Animal studies have shown very good results favouring these supplements. However, it seems that these findings do not correlate with clinical level I studies. There are two possible explanations for this inconsistency. One might be the publication bias. It has been shown that studies with negative results are more likely not to be published[66,67]. This may be even more exacerbated in experimental animal studies, as usually protocols are not preregistered and therefore there is usually no obligation to publish any of the results. Another important reason is potentially the concentrations of supplements experimentally used in animals. The plasma concentrations achieved in animal studies can be hundreds times higher than the maximal concentration that can realistically be achieved after oral administration of 1500 mg of GL sulphate in human subjects[68]. Therefore, although a positive effect is noticed even in histological examination of cartilage, such a result cannot realistically be expected for humans[69]. It has been suggested that the therapeutic doses used in humans do not even allow the identification of proteoglycan synthesis as a mechanism of action of GL[69-71]. Therefore, extrapolation of the *in vitro* data directly to the *in vivo* situation should be done with great caution[69].

Pharmakokinetic and bioavailability of these supplements in the human joints after oral administration is certainly an issue that has to be further investigated[72]. There is evidence supporting that both GL and CH reach and retain a certain concentration in plasma

and also in joint fluid and cartilage, after normal doses administered *per os*[50,68,73-75]. However, as previously mentioned, there is no solid evidence to directly prove cartilage synthesis or regeneration in humans, as a result of this concentration.

Regarding dosing, little research has been published, thus no dietary reference intake currently exists for either GL or CH. There is an accepted daily dosage of 1500 mg for GL and 1200 mg for CH, rather empirically adopted, although different dosage schemes have been suggested in the literature[61,76]. This lack of consensus regarding the total daily dose or the dosing scheme may be an additional reason for the controversial and heterogeneous outcomes of related studies. However, the results and conclusions for the effectiveness or safety of GL and CH remain the same, even in SRs that excluded the subtherapeutic doses of GL and CH, which probably rejects this assumption[11,59].

A very important factor in the use of GL or CH is the length of therapy[46]. There are preliminary studies that showed clinical efficacy even at 4-12 wk of treatment[77,78]. However, these studies were of poor quality and high risk of bias and usually involved a rescue treatment with pain killers[46]. In more recent and higher quality trials, effects are not seen before 3 to 6 mo. Nevertheless, in most of the recent studies, the duration has been extended at least to 6 mo.

The selection of the patients and the use of treatment algorithms are probably mandatory. Even in single trials, there is usually not a limitation in specific age groups or OA grading. In 2 years follow up of GAIT trial, patients with more primary OA (Kellgren/Lawrence grade 2), seemed to have the higher potential for disease modification when compared with grade 3 cases, after combined GL and CH administration[62]. However, there is little known for the relative efficacy of any of these supplements in different age groups or different OA grades. Summarizing the outcomes of all these groups includes the assumption of equal action and effectiveness, which is yet not shown.

Felson *et al*[79] highlighted the role of the mechanical environment of an osteoarthritic joint for the success of any pharmacological treatment. Mechanical abnormalities, including joint malalignment, bony remodelling or instability, contributing to or being caused by the OA, may need to be addressed and corrected if possible, before any pharmacological treatment. None of the currently available drugs or supplements could probably have a reversible effect on the joint as a whole. Tissue-level dynamic stresses on cartilage in OA joints may also exceed thresholds that could be reversed by any effective pharmacologic agent. The mechanical factor has not been widely considered in the trials that assess the treatment role of either GL or CH, and this is potentially a reason for the lack of efficacy as it is shown in these trials.

Joint space narrowing has been used as an indicator for the alteration of the OA progression in the knee joint after the use of GL or CH[63,64,80-82]. Meta-analysis of this data has concluded that GL and CH may reduce the joint space narrowing after 2-3 years of continuous administration[60]. The SR of Wandel *et al*[11] additionally analysed 3 more recent RCTs concluding to a null effect size[11,62,83,84]. However, the measurement of joint space was performed by X-rays, which is criticised as a not accurate and reliable tool. In none of these studies the cartilage width was assessed.

Limitations of evidence

The quality and validity of the information provided above, regarding the efficacy and safety of GL or CH, is limited by the quality of the studies available. The low quality of published studies and the high risk of bias which is introduced by several factors (*e.g.*, poor methodology, poor reporting) limit the value of any suggestion or guidelines. The high interest of industry may have potentially impacted the currently available information.

There is evidence from funnel plots suggesting an absence of trials with both small numbers of participants and small or null treatment effects. This may be the result of selective publication of "positive" trials (that favours the new intervention) or of premature termination of trials with negative or null results. The high rate of sponsorship among the RCTs of GL or CH strengthens the possibility of high publication bias. However, this is just an assumption and in any case cannot be considered as evidence.

The pooling of different preparations of these supplements or products with different administration paths may increase the heterogeneity and decrease the validity of the outcomes in any meta-analysis. In many published trials the specific preparation of the supplements is not reported.

In many published meta-analyses, although the overall summary suggested a superiority of the intervention, the subgrouping of higher quality studies revealed a null effect size. In almost all cases only a few studies were of high quality. Therefore, one should argue that the limited number of studies decrease the power of the meta-analysis. This might provide a potential explanation for the trend for null effect sizes in such assessments.

Implications for research

Despite the large number of the available RCTs, there are still several questions not yet answered, first being the efficacy of GL and CH.

There is need for higher quality of information, either from RCTs or SRs. Therefore, more independent (not sponsored) high-quality randomized trials should be conducted. Trials should adhere to methodological standards that aim to reduce the risk of bias introduced (*e.g.*, CONSORT)[85]. SRs play also a mandatory role in evidence based information and should also follow similar standards (*e.g.*, MECIR)[86].

The best dosage scheme is still not yet defined by evidence. The duration of treatment that might provide

(if any) symptoms' relief or cartilage restoration is also still unknown. More advanced tools (*e.g.*, MRI) should be used to assess the joint and to detect for any restoration or regeneration of cartilage. The quality and quantity of cartilage should also be more accurately defined (*e.g.*, with DGEMRIC)[87].

It is still unclear which patients groups (if any) may profit from the use of such supplements. For this reason research, should be focused on assessing specific age groups, with specific OA grading. Inclusion criteria should be carefully and strictly defined. Idiopathic OA patients should be examined separately from secondary cases. By adding confounding factors like different stages of OA or different age groups the heterogeneity is increased, thus limiting the validity of outcomes. A more specific determination of supplements' characteristics and preparations is also mandatory to decrease this heterogeneity.

Implications for practice

There is currently no convincing information on the efficacy of GL or CH as treatment options in OA.

A positive effect of GL and CH on both clinical and radiological findings has been shown. However, only a few high-quality level I trials exist, especially for the assessment of radiological progression of OA. The effect sizes are small and probably not clinically relevant. However, even the validity of these results is limited by the high risk of bias introduced in the studies. Both GL and CH seem to be safe with no serious adverse events reported.

REFERENCES

1 **Jordan JM**, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, Fang F, Schwartz TA, Abbate LM, Callahan LF, Kalsbeek WD, Hochberg MC. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. *J Rheumatol* 2007; **34**: 172-180 [PMID: 17216685]

2 **Roos EM**. Joint injury causes knee osteoarthritis in young adults. *Curr Opin Rheumatol* 2005; **17**: 195-200 [PMID: 15711235 DOI: 10.1097/01.bor.0000151406.64393.00]

3 **Lawrence RC**, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008; **58**: 26-35 [PMID: 18163497 DOI: 10.1002/art.23176]

4 **Towheed TE**, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006; **(1)**: CD004257 [PMID: 16437479 DOI: 10.1002/14651858.CD004257.pub2]

5 **Garner SE**, Fidan DD, Frankish R, Maxwell L. Rofecoxib for osteoarthritis. *Cochrane Database Syst Rev* 2005; **(1)**: CD005115 [PMID: 15654705 DOI: 10.1002/14651858.CD005115]

6 **Wielage RC**, Myers JA, Klein RW, Happich M. Cost-effectiveness analyses of osteoarthritis oral therapies: a systematic review. *Appl Health Econ Health Policy* 2013; **11**: 593-618 [PMID: 24214160 DOI: 10.1007/s40258-013-0061-x]

7 **Manno RL**, Bingham CO, Paternotte S, Gossec L, Halhol H, Giacovelli G, Rovati L, Mazzuca SA, Clegg DO, Shi H, Tajana Messi E, Lanzarotti A, Dougados M. OARSI-OMERACT initiative: defining thresholds for symptomatic severity and structural changes in disease modifying osteoarthritis drug (DMOAD) clinical trials. *Osteoarthritis Cartilage* 2012; **20**: 93-101 [PMID: 22178465 DOI: 10.1016/j.joca.2011.11.013]

8 **Losina E**, Daigle ME, Suter LG, Hunter DJ, Solomon DH, Walensky RP, Jordan JM, Burbine SA, Paltiel AD, Katz JN. Disease-modifying drugs for knee osteoarthritis: can they be cost-effective? *Osteoarthritis Cartilage* 2013; **21**: 655-667 [PMID: 23380251 DOI: 10.1016/j.joca.2013.01.016]

9 **Davies PS**, Graham SM, MacFarlane RJ, Leonidou A, Mantalaris A, Tsiridis E. Disease-modifying osteoarthritis drugs: in vitro and in vivo data on the development of DMOADs under investigation. *Expert Opin Investig Drugs* 2013; **22**: 423-441 [PMID: 23409708 DOI: 10.1517/13543784.2013.770837]

10 **Reichenbach S**, Sterchi R, Scherer M, Trelle S, Bürgi E, Bürgi U, Dieppe PA, Jüni P. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 2007; **146**: 580-590 [PMID: 17438317 DOI: 10.7326/0003-4819-146-8-200704170-00009]

11 **Wandel S**, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 2010; **341**: c4675 [PMID: 20847017 DOI: 10.1136/bmj.c4675]

12 **Towheed TE**, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Wells G. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* 2005; **(2)**: CD002946 [PMID: 15846645 DOI: 10.1002/14651858.CD002946.pub2]

13 **Hochberg MC**, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* (Hoboken) 2012; **64**: 465-474 [PMID: 22563589 DOI: 10.1002/acr.21596]

14 **Jordan KM**, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, Gunther K, Hauselmann H, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Leeb B, Lequesne M, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Serni U, Swoboda B, Verbruggen G, Zimmerman-Gorska I, Dougados M. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003; **62**: 1145-1155 [PMID: 14644851 DOI: 10.1136/ard.2003.011742]

15 Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum* 2000; **43**: 1905-1915 [PMID: 11014340 DOI: 10.1002/1529-0131(200009)43]

16 **Zhang W**, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther KP, Hauselmann HJ, Herrero-Beaumont G, Jordan K, Kaklamanis P, Leeb B, Lequesne M, Lohmander S, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Swoboda B, Varatojo R, Verbruggen G, Zimmermann-Gorska I, Dougados M. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2005; **64**: 669-681 [PMID: 15471891 DOI: 10.1136/ard.2004.028886]

17 **Zhang W**, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007; **15**: 981-1000 [PMID: 17719803 DOI: 10.1016/j.joca.2007.06.014]

18 **Zhang W**, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS,

Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008; **16**: 137-162 [PMID: 18279766 DOI: 10.1016/j.joca.2007.12.013]

19 **Zhang W**, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010; **18**: 476-499 [PMID: 20170770 DOI: 10.1016/j.joca.2010.01.013]

20 **Heller L**. US glucosamine grows slow, lags global sales. [Internet]. 2009. Available from: URL: http://www.nutraingredients-usa.com/Consumer-Trends/US-glucosaminegrows- slow-lags-global-sales

21 **Kubo M**, Ando K, Mimura T, Matsusue Y, Mori K. Chondroitin sulfate for the treatment of hip and knee osteoarthritis: current status and future trends. *Life Sci* 2009; **85**: 477-483 [PMID: 19695267 DOI: 10.1016/j.lfs.2009.08.005]

22 **Nakamura H**. Application of glucosamine on human disease-Osteoarthritis. *Adv Chitinchitosan Sci Their Appl* 2011; **84**: 835-839 [DOI: 10.1016/j.carbpol.2010.08.078]

23 **Black C**, Clar C, Henderson R, MacEachern C, McNamee P, Quayyum Z, Royle P, Thomas S. The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation. *Health Technol Assess* 2009; **13**: 1-148 [PMID: 19903416 DOI: 10.3310/hta13520]

24 **Chan PS**, Caron JP, Orth MW. Short-term gene expression changes in cartilage explants stimulated with interleukin beta plus glucosamine and chondroitin sulfate. *J Rheumatol* 2006; **33**: 1329-1340 [PMID: 16821268]

25 **Imagawa K**, de Andrés MC, Hashimoto K, Pitt D, Itoi E, Goldring MB, Roach HI, Oreffo RO. The epigenetic effect of glucosamine and a nuclear factor-kappa B (NF-kB) inhibitor on primary human chondrocytes--implications for osteoarthritis. *Biochem Biophys Res Commun* 2011; **405**: 362-367 [PMID: 21219853 DOI: 10.1016/j.bbrc.2011.01.007]

26 **Dodge GR**, Jimenez SA. Glucosamine sulfate modulates the levels of aggrecan and matrix metalloproteinase-3 synthesized by cultured human osteoarthritis articular chondrocytes. *Osteoarthritis Cartilage* 2003; **11**: 424-432 [PMID: 12801482 DOI: 10.1016/S1063-4584(03)00052-9]

27 **Piperno M**, Reboul P, Hellio Le Graverand MP, Peschard MJ, Annefeld M, Richard M, Vignon E. Glucosamine sulfate modulates dysregulated activities of human osteoarthritic chondrocytes in vitro. *Osteoarthritis Cartilage* 2000; **8**: 207-212 [PMID: 10806048 DOI: 10.1053/joca.1999.0291]

28 **Calamia V**, Ruiz-Romero C, Rocha B, Fernández-Puente P, Mateos J, Montell E, Vergés J, Blanco FJ. Pharmacoproteomic study of the effects of chondroitin and glucosamine sulfate on human articular chondrocytes. *Arthritis Res Ther* 2010; **12**: R138 [PMID: 20626852 DOI: 10.1186/ar3077]

29 **Largo R**, Alvarez-Soria MA, Díez-Ortego I, Calvo E, Sánchez-Pernaute O, Egido J, Herrero-Beaumont G. Glucosamine inhibits IL-1beta-induced NFkappaB activation in human osteoarthritic chondrocytes. *Osteoarthritis Cartilage* 2003; **11**: 290-298 [PMID: 12681956 DOI: 10.1016/S1063-4584(03)00028-1]

30 **Reginster JY**, Bruyere O, Neuprez A. Current role of glucosamine in the treatment of osteoarthritis. *Rheumatology* (Oxford) 2007; **46**: 731-735 [PMID: 17401134 DOI: 10.1093/rheumatology/kem026]

31 **Uitterlinden EJ**, Jahr H, Koevoet JL, Jenniskens YM, Bierma-Zeinstra SM, Degroot J, Verhaar JA, Weinans H, van Osch GJ. Glucosamine decreases expression of anabolic and catabolic genes in human osteoarthritic cartilage explants. *Osteoarthritis Cartilage* 2006; **14**: 250-257 [PMID: 16300972 DOI: 10.1016/j.joca.2005.10.001]

32 **Jawed H**, Anjum S, Awan SI, Simjee SU. Anti-arthritic effect of GN1, a novel synthetic analog of glucosamine, in the collagen-induced arthritis model in rats. *Inflamm Res* 2011; **60**: 1113-1120 [PMID: 21874354 DOI: 10.1007/s00011-011-0375-9]

33 **Oegema TR**, Deloria LB, Sandy JD, Hart DA. Effect of oral glucosamine on cartilage and meniscus in normal and chymopapain-injected knees of young rabbits. *Arthritis Rheum* 2002; **46**: 2495-2503 [PMID: 12355498 DOI: 10.1002/art.10499]

34 **Wen ZH**, Tang CC, Chang YC, Huang SY, Hsieh SP, Lee CH, Huang GS, Ng HF, Neoh CA, Hsieh CS, Chen WF, Jean YH. Glucosamine sulfate reduces experimental osteoarthritis and nociception in rats: association with changes of mitogen-activated protein kinase in chondrocytes. *Osteoarthritis Cartilage* 2010; **18**: 1192-1202 [PMID: 20510383 DOI: 10.1016/j.joca.2010.05.012]

35 **Taniguchi S**, Ryu J, Seki M, Sumino T, Tokuhashi Y, Esumi M. Long-term oral administration of glucosamine or chondroitin sulfate reduces destruction of cartilage and up-regulation of MMP-3 mRNA in a model of spontaneous osteoarthritis in Hartley guinea pigs. *J Orthop Res* 2012; **30**: 673-678 [PMID: 22058013 DOI: 10.1002/jor.22003]

36 **Verbruggen G**. Chondroprotective drugs in degenerative joint diseases. *Rheumatology* (Oxford) 2006; **45**: 129-138 [PMID: 16278282 DOI: 10.1093/rheumatology/kei171]

37 **Bali JP**, Cousse H, Neuzil E. Biochemical basis of the pharmacologic action of chondroitin sulfates on the osteoarticular system. *Semin Arthritis Rheum* 2001; **31**: 58-68 [PMID: 11503140 DOI: 10.1053/sarh.2000.24874]

38 **Martel-Pelletier J**, Kwan Tat S, Pelletier JP. Effects of chondroitin sulfate in the pathophysiology of the osteoarthritic joint: a narrative review. *Osteoarthritis Cartilage* 2010; **18** Suppl 1: S7-11 [PMID: 20399897 DOI: 10.1016/j.joca.2010.01.015]

39 **Legendre F**, Baugé C, Roche R, Saurel AS, Pujol JP. Chondroitin sulfate modulation of matrix and inflammatory gene expression in IL-1beta-stimulated chondrocytes--study in hypoxic alginate bead cultures. *Osteoarthritis Cartilage* 2008; **16**: 105-114 [PMID: 17625924 DOI: 10.1016/j.joca.2007.05.020]

40 **Jomphe C**, Gabriac M, Hale TM, Héroux L, Trudeau LE, Deblois D, Montell E, Vergés J, du Souich P. Chondroitin sulfate inhibits the nuclear translocation of nuclear factor-kappaB in interleukin-1beta-stimulated chondrocytes. *Basic Clin Pharmacol Toxicol* 2008; **102**: 59-65 [PMID: 17983423 DOI: 10.1111/j.1742-7843.2007.00158.x]

41 **Tsubaki M**, Kato C, Manno M, Ogaki M, Satou T, Itoh T, Kusunoki T, Tanimori Y, Fujiwara K, Matsuoka H, Nishida S. Macrophage inflammatory protein-1alpha (MIP-1alpha) enhances a receptor activator of nuclear factor kappaB ligand (RANKL) expression in mouse bone marrow stromal cells and osteoblasts through MAPK and PI3K/Akt pathways. *Mol Cell Biochem* 2007; **304**: 53-60 [PMID: 17549607 DOI: 10.1007/s11010-007-9485-7]

42 **Kwan Tat S**, Pelletier JP, Lajeunesse D, Fahmi H, Lavigne M, Martel-Pelletier J. The differential expression of osteoprotegerin (OPG) and receptor activator of nuclear factor kappaB ligand (RANKL) in human osteoarthritic subchondral bone osteoblasts is an indicator of the metabolic state of these disease cells. *Clin Exp Rheumatol* 2008; **26**: 295-304 [PMID: 18565252]

43 **Uebelhart D**, Thonar EJ, Zhang J, Williams JM. Protective effect of exogenous chondroitin 4,6-sulfate in the acute degradation of articular cartilage in the rabbit. *Osteoarthritis Cartilage* 1998; **6** Suppl A: 6-13 [PMID: 9743813]

44 **Bassleer CT**, Combal JP, Bougaret S, Malaise M. Effects of chondroitin sulfate and interleukin-1 beta on human articular chondrocytes cultivated in clusters. *Osteoarthritis Cartilage* 1998; **6**: 196-204 [PMID: 9682786 DOI: 10.1053/joca.1998.0112]

45 **Lippiello L**. Glucosamine and chondroitin sulfate: biological response modifiers of chondrocytes under simulated conditions of joint stress. *Osteoarthritis Cartilage* 2003; **11**: 335-342 [PMID: 12744939 DOI: 10.1016/S1063-4584(03)00026-8]

46 **Vangsness CT**, Spiker W, Erickson J. A review of evidence-based medicine for glucosamine and chondroitin sulfate use in knee osteoarthritis. *Arthroscopy* 2009; **25**: 86-94 [PMID: 19111223 DOI: 10.1016/j.arthro.2008.07.020]

47 **Aghazadeh-Habashi A**, Sattari S, Pasutto F, Jamali F. Single dose pharmacokinetics and bioavailability of glucosamine in the rat. *J Pharm Pharm Sci* 2002; **5**: 181-184 [PMID: 12207871]

48 **Volpi N**. Oral bioavailability of chondroitin sulfate (Condrosulf) and its constituents in healthy male volunteers. *Osteoarthritis Cartilage* 2002; **10**: 768-777 [PMID: 12359162 DOI: 10.1053/joca.2002.0824]

49 **Adebowale A**, Du J, Liang Z, Leslie JL, Eddington ND. The bioavailability and pharmacokinetics of glucosamine hydrochloride and low molecular weight chondroitin sulfate after single and multiple doses to beagle dogs. *Biopharm Drug Dispos* 2002; **23**: 217-225 [PMID: 12214321 DOI: 10.1002/bdd.315]

50 **Meulyzer M**, Vachon P, Beaudry F, Vinardell T, Richard H, Beauchamp G, Laverty S. Joint inflammation increases glucosamine levels attained in synovial fluid following oral administration of glucosamine hydrochloride. *Osteoarthritis Cartilage* 2009; **17**: 228-234 [PMID: 18692410 DOI: 10.1016/j.joca.2008.06.018]

51 **Malavaki CJ**, Asimakopoulou AP, Lamari FN, Theocharis AD, Tzanakakis GN, Karamanos NK. Capillary electrophoresis for the quality control of chondroitin sulfates in raw materials and formulations. *Anal Biochem* 2008; **374**: 213-220 [PMID: 18054774 DOI: 10.1016/j.ab.2007.11.006]

52 **Conte A**, de Bernardi M, Palmieri L, Lualdi P, Mautone G, Ronca G. Metabolic fate of exogenous chondroitin sulfate in man. *Arzneimittelforschung* 1991; **41**: 768-772 [PMID: 1772467]

53 **Ronca F**, Palmieri L, Panicucci P, Ronca G. Anti-inflammatory activity of chondroitin sulfate. *Osteoarthritis Cartilage* 1998; **6** Suppl A: 14-21 [PMID: 9743814]

54 **Lauder RM**. Chondroitin sulphate: a complex molecule with potential impacts on a wide range of biological systems. *Complement Ther Med* 2009; **17**: 56-62 [PMID: 19114230 DOI: 10.1016/j.ctim.2008.08.004]

55 **McAlindon TE**, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* 2000; **283**: 1469-1475 [PMID: 10732937 DOI: 10.1001/jama.283.11.1469]

56 **Richy F**, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med* 2003; **163**: 1514-1522 [PMID: 12860572 DOI: 10.1001/archinte.163.13.1514]

57 **McAlindon T**, Formica M, LaValley M, Lehmer M, Kabbara K. Effectiveness of glucosamine for symptoms of knee osteoarthritis: results from an internet-based randomized double-blind controlled trial. *Am J Med* 2004; **117**: 643-649 [PMID: 15501201 DOI: 10.1016/j.amjmed.2004.06.023]

58 **Vlad SC**, LaValley MP, McAlindon TE, Felson DT. Glucosamine for pain in osteoarthritis: why do trial results differ? *Arthritis Rheum* 2007; **56**: 2267-2277 [PMID: 17599746 DOI: 10.1002/art.22728]

59 **Bjordal JM**, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. *Eur J Pain* 2007; **11**: 125-138 [PMID: 16682240 DOI: 10.1016/j.ejpain.2006.02.013]

60 **Lee YH**, Woo JH, Choi SJ, Ji JD, Song GG. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. *Rheumatol Int* 2010; **30**: 357-363 [PMID: 19544061 DOI: 10.1007/s00296-009-0969-5]

61 **Clegg DO**, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, Bradley JD, Bingham CO, Weisman MH, Jackson CG, Lane NE, Cush JJ, Moreland LW, Schumacher HR, Oddis CV, Wolfe F, Molitor JA, Yocum DE, Schnitzer TJ, Furst DE, Sawitzke AD, Shi H, Brandt KD, Moskowitz RW, Williams HJ. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; **354**: 795-808 [PMID: 16495392 DOI: 10.1056/NEJMoa052771]

62 **Sawitzke AD**, Shi H, Finco MF, Dunlop DD, Bingham CO, Harris CL, Singer NG, Bradley JD, Silver D, Jackson CG, Lane NE, Oddis CV, Wolfe F, Lisse J, Furst DE, Reda DJ, Moskowitz RW, Williams HJ, Clegg DO. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial. *Arthritis Rheum* 2008; **58**: 3183-3191 [PMID: 18821708 DOI: 10.1002/art.23973]

63 **Uebelhart D**, Thonar EJ, Delmas PD, Chantraine A, Vignon E. Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. *Osteoarthritis Cartilage* 1998; **6** Suppl A: 39-46 [PMID: 9743819]

64 **Uebelhart D**, Malaise M, Marcolongo R, de Vathaire F, Piperno M, Mailleux E, Fioravanti A, Matoso L, Vignon E. Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo. *Osteoarthritis Cartilage* 2004; **12**: 269-276 [PMID: 15023378 DOI: 10.1016/j.joca.2004.01.004]

65 **Singh JA**, Noorbaloochi S, MacDonald R, Maxwell LJ. Chondroitin for osteoarthritis. *Cochrane Database Syst Rev* 2015; **1**: CD005614 [PMID: 25629804 DOI: 10.1002/14651858.CD005614.pub2]

66 **Dwan K**, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, Decullier E, Easterbrook PJ, Von Elm E, Gamble C, Ghersi D, Ioannidis JP, Simes J, Williamson PR. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS One* 2008; **3**: e3081 [PMID: 18769481 DOI: 10.1371/journal.pone.0003081]

67 **Chan AW**, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004; **291**: 2457-2465 [PMID: 15161896 DOI: 10.1001/jama.291.20.2457]

68 **Aghazadeh-Habashi A**, Jamali F. The glucosamine controversy; a pharmacokinetic issue. *J Pharm Pharm Sci* 2011; **14**: 264-273 [PMID: 21733414 DOI: 10.18433/J3XG6F]

69 **Henrotin Y**, Mobasheri A, Marty M. Is there any scientific evidence for the use of glucosamine in the management of human osteoarthritis? *Arthritis Res Ther* 2012; **14**: 201 [PMID: 22293240 DOI: 10.1186/ar3657]

70 **Biggee BA**, Blinn CM, McAlindon TE, Nuite M, Silbert JE. Low levels of human serum glucosamine after ingestion of glucosamine sulphate relative to capability for peripheral effectiveness. *Ann Rheum Dis* 2006; **65**: 222-226 [PMID: 16079170 DOI: 10.1136/ard.2005.036368]

71 **Mroz PJ**, Silbert JE. Use of 3H-glucosamine and 35S-sulfate with cultured human chondrocytes to determine the effect of glucosamine concentration on formation of chondroitin sulfate. *Arthritis Rheum* 2004; **50**: 3574-3579 [PMID: 15529373 DOI: 10.1002/art.20609]

72 **Owens S**, Wagner P, Vangsness CT. Recent advances in glucosamine and chondroitin supplementation. *J Knee Surg* 2004; **17**: 185-193 [PMID: 15553585]

73 **Meulyzer M**, Vachon P, Beaudry F, Vinardell T, Richard H, Beauchamp G, Laverty S. Comparison of pharmacokinetics of glucosamine and synovial fluid levels following administration of glucosamine sulphate or glucosamine hydrochloride. *Osteoarthritis Cartilage* 2008; **16**: 973-979 [PMID: 18295513 DOI: 10.1016/j.joca.2008.01.006]

74 **Persiani S**, Roda E, Rovati LC, Locatelli M, Giacovelli G, Roda A. Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. *Osteoarthritis Cartilage* 2005; **13**: 1041-1049 [PMID: 16168682 DOI: 10.1016/j.joca.2005.07.009]

75 **Persiani S**, Rotini R, Trisolino G, Rovati LC, Locatelli M, Paganini D, Antonioli D, Roda A. Synovial and plasma glucosamine concentrations in osteoarthritic patients following oral crystalline glucosamine sulphate at therapeutic dose. *Osteoarthritis Cartilage* 2007; **15**: 764-772 [PMID: 17353133 DOI: 10.1016/j.joca.2007.01.019]

76 **Sherman AL**, Ojeda-Correal G, Mena J. Use of glucosamine and chondroitin in persons with osteoarthritis. *PM R* 2012; **4**: S110-S116 [PMID: 22632689 DOI: 10.1016/j.pmrj.2012.02.021]

77 **Bourgeois P**, Chales G, Dehais J, Delcambre B, Kuntz JL, Rozenberg S. Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 x 400 mg/day vs placebo. *Osteoarthritis Cartilage* 1998; **6** Suppl A: 25-30 [PMID: 9743816]

78 **Noack W**, Fischer M, Förster KK, Rovati LC, Setnikar I. Glucosamine sulfate in osteoarthritis of the knee. *Osteoarthritis Cartilage* 1994; **2**: 51-59 [PMID: 11548224 DOI: 10.1016/S1063-4584(05)80006-8]

79 **Felson DT**, Kim YJ. The futility of current approaches to chondroprotection. *Arthritis Rheum* 2007; **56**: 1378-1383 [PMID: 17469094 DOI: 10.1002/art.22526]

80 **Michel BA**, Stucki G, Frey D, De Vathaire F, Vignon E, Bruehlmann P, Uebelhart D. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. *Arthritis Rheum* 2005; **52**: 779-786 [PMID: 15751094 DOI: 10.1002/art.20867]

81 **Pavelká K**, Gatterová J, Olejarová M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2002; **162**: 2113-2123 [PMID: 12374520 DOI: 10.1001/archinte.162.18.2113]

82 **Reginster JY**, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, Giacovelli G, Henrotin Y, Dacre JE, Gossett C. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001; **357**: 251-256 [PMID: 11214126 DOI: 10.1016/S0140-6736(00)03610-2]

83 **Kahan A**, Uebelhart D, De Vathaire F, Delmas PD, Reginster JY. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2009; **60**: 524-533 [PMID: 19180484 DOI: 10.1002/art.24255]

84 **Rozendaal RM**, Koes BW, van Osch GJ, Uitterlinden EJ, Garling EH, Willemsen SP, Ginai AZ, Verhaar JA, Weinans H, Bierma-Zeinstra SM. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Ann Intern Med* 2008; **148**: 268-277 [PMID: 18283204 DOI: 10.7326/0003-4819-148-4-200802190-00005]

85 **Turner L**, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, Dias S, Schulz KF, Plint AC, Moher D. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev* 2012; **11**: MR000030 [PMID: 23152285 DOI: 10.1002/14651858.MR000030.pub2]

86 **Lefebvre C**, Glanville J, Wieland LS, Coles B, Weightman AL. Methodological developments in searching for studies for systematic reviews: past, present and future? *Syst Rev* 2013; **2**: 78 [PMID: 24066664 DOI: 10.1186/2046-4053-2-78]

87 **Vasiliadis HS**, Danielson B, Ljungberg M, McKeon B, Lindahl A, Peterson L. Autologous chondrocyte implantation in cartilage lesions of the knee: long-term evaluation with magnetic resonance imaging and delayed gadolinium-enhanced magnetic resonance imaging technique. *Am J Sports Med* 2010; **38**: 943-949 [PMID: 20185841 DOI: 10.1177/0363546509358266]

P- Reviewer: Garip Y, Malik H, Yao CL **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.12

World J Orthop 2017 January 18; 8(1): 12-20
ISSN 2218-5836 (online)

MINIREVIEWS

Current management of talar osteochondral lesions

Arianna L Gianakos, Youichi Yasui, Charles P Hannon, John G Kennedy

Arianna L Gianakos, Department of Orthopedic Surgery, 2nd Jersey City Medical Center, Jersey City, NJ 07302, United States

Arianna L Gianakos, Youichi Yasui, Charles P Hannon, John G Kennedy, Department of Foot and Ankle, Hospital for Special Surgery, New York, NY 10021, United States

Youichi Yasui, Department of Orthopaedic Surgery, 2nd Teikyo University School of Medicine, Tokyo 173-8606, Japan

Charles P Hannon, 2nd Department of Orthopaedic Surgery, Rush University Medical Center (C.P.H.), Chicago, IL 60612, United States

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: Kennedy JG is a consultant for Arteriocyte, Inc.; Kennedy JG has received research support from the Ohnell Family Foundation, Mr. and Mrs. Michael J Levitt, and Arteriocyte Inc.; Kennedy JG is a board member for the European Society of Sports Traumatology, Knee Surgery, and Arthroscopy, International Society for Cartilage Repair of the Ankle, American Orthopaedic Foot and Ankle Society Awards and Scholarships Committee, International Cartilage Repair Society finance board.

Manuscript source: Invited manuscript

Correspondence to: John G Kennedy, MD, MCh, MMSc, FRCS (Orth), Department of Foot and Ankle, Hospital for Special Surgery, 523 East 72nd Street, Suite 507, New York, NY 10021, United States. kennedyj@hss.edu
Telephone: +1-646-7978880
Fax: +1-646-797896

Received: June 16, 2016
Peer-review started: June 17, 2016
First decision: July 27, 2016
Revised: September 12, 2016
Accepted: October 17, 2016
Article in press: October 18, 2016
Published online: January 18, 2017

Abstract

Osteochondral lesions of the talus (OLT) occur in up to 70% of acute ankle sprains and fractures. OLT have become increasingly recognized with the advancements in cartilage-sensitive diagnostic imaging modalities. Although OLT may be treated nonoperatively, a number of surgical techniques have been described for patients whom surgery is indicated. Traditionally, treatment of symptomatic OLT have included either reparative procedures, such as bone marrow stimulation (BMS), or replacement procedures, such as autologous osteochondral transplantation (AOT). Reparative procedures are generally indicated for OLT < 150 mm^2 in area. Replacement strategies are used for large lesions or after failed primary repair procedures. Although short- and medium-term results have been reported, long-term studies on OLT treatment strategies are lacking. Biological augmentation including platelet-rich plasma and concentrated bone marrow aspirate is becoming increasingly popular for the treatment of OLT to enhance the biological environment during healing. In this review, we describe the most up-to-date clinical evidence of surgical outcomes, as well as both the mechanical and biological concerns associated with BMS and AOT. In addition, we will review the recent evidence for biological adjunct therapies that aim to improve outcomes and longevity of both BMS and AOT procedures.

Key words: Osteochondral lesions of talus; Comprehensive review; Diagnosis; Bone marrow stimulation; Autologous autograft transfer; Biologics

Core tip: Osteochondral lesions of the talus are often missed after acute ankle sprains and fractures. Magnetic resonance imaging is most sensitive in diagnosing these injuries. Bone marrow stimulation (BMS) is effective for lesions < 150 mm^2 in area, but replacement procedures such as autologous osteochondral transplantation or allografts may be required for larger lesions or if BMS fails. Long term studies should attempt to determine the most effective treatment strategy and the critical defect strategy beyond which BMS will not work.

Gianakos AL, Yasui Y, Hannon CP, Kennedy JG. Current management of talar osteochondral lesions. *World J Orthop* 2017; 8(1): 12-20 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/12.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.12

INTRODUCTION

Osteochondral lesions of the talus (OLT) can occur in up to 70% of acute ankle sprains and fractures[1]. OLT have become increasingly recognized with the advancements in cartilage-sensitive diagnostic imaging modalities such as magnetic resonance imaging (MRI). These lesions typically involve a component of the articular surface and/or subchondral bone (SCB)[2]. Although trauma is the primary etiology, non-traumatic causes have been reported including congenital factors, ligamentous laxity, spontaneous necrosis, steroid treatment, embolic disease, and endocrine abnormalities[2,3].

A systematic review by Zengerink *et al*[4] demonstrated that up to 50% of patients failed to resolve their symptoms by conservative treatment. Traditionally, treatment of symptomatic OLT have included either reparative or replacement surgical procedures. Typically, the decision to repair or replace is based primarily on lesion size. Reparative procedures, including bone marrow stimulation (BMS), are generally indicated for OLT < 15 mm in a diameter or 150 mm^2 in area[5]. Replacement strategies, such as osteochondral autologous transplantation (AOT), are used for large lesions or failed primary repair procedures[6]. Although previous clinical literature has demonstrated good to excellent short- and mid-term clinical outcomes, there has been an increase in the concerns regarding the methodological quality of previous clinical studies and deterioration of the ankle joint following surgical interventions.

In this review, we describe the most up-to-date clinical evidence of surgical outcomes, as well as increasing concerns associated with BMS and AOT. In addition, we will review the recent evidence for biological adjunct therapies that have been used to improve outcomes and longevity of both BMS and AOT.

CLINICAL PRESENTATION AND DIAGNOSIS

Most OLT are a sequelae of ankle injuries. Unfortunately, there are no specific physical examination findings that can accurately assess and diagnose OLT, and up to 50% of patients have missed OLT on plain radiographs[7]. It is therefore important to have a high level of suspicion of OLT in patients who have persistent ankle joint pain and a history of ankle injuries.

Patients with OLT frequently present with non-specific chronic ankle pain. Associated symptoms may also include generalized ankle swelling, stiffness, and weakness, which is often exacerbated by prolonged weight-bearing or high impact activities[2]. In the physical examination, a patient's complaint of tenderness or pain may be poorly localized and may not correspond with the location of the OLT[8]. Examiners should perform both anterior drawer and standard inversion maneuvers to detect concomitant lateral ankle instability, and they should also assess hindfoot malalignment, joint flexibility, and joint laxity.

Anteroposterior, mortise, and lateral ankle weight-bearing radiographs are useful when assessing joint alignment and other coexisting abnormalities such as osteophytes and loose bodies. However, more advanced imaging is often recommended, since plain radiographs have been shown to miss up to 50% of OLT[9]. Computed tomography (CT) has excellent ability to detect OLT, accounting for 0.81 sensitivity and 0.99 specificity[7]. Although CT is useful in obtaining detail about bony injury including the condition of SCB, concomitant osteophytes, and loose bodies, it lacks the ability to assess the cartilage compartment of OLT. MRI is the recommended imaging diagnostic modality, with 0.96 sensitivity and 0.96 specificity[7]. MRI is advantageous in that it can show both osseous and soft tissue pathologies that are frequently associated in OLT. Although several scoring systems based on the MRI have been developed for grading of OLT[10-15], it is unclear whether any classification can direct clinical decision making. Research by Ferkel *et al*[11] showed little correlation between MRI grading and clinical outcomes. In a prospective study of 120 ankles, Choi *et al*[12] also found no correlation between any radiological grading and clinical outcome.

TREATMENT

Conservative treatment

Non-operative treatment strategies in asymptomatic patients can include rest and/or restriction of activities along with the use of a non-steroidal anti-inflammatory drug[4]. A systematic review by Zengerink *et al*[4] reported that 45% of patients reported successful outcomes when treated with conservative treatment consisting of weight-bearing as tolerated. The authors also demonstrated that 53% of patients who underwent

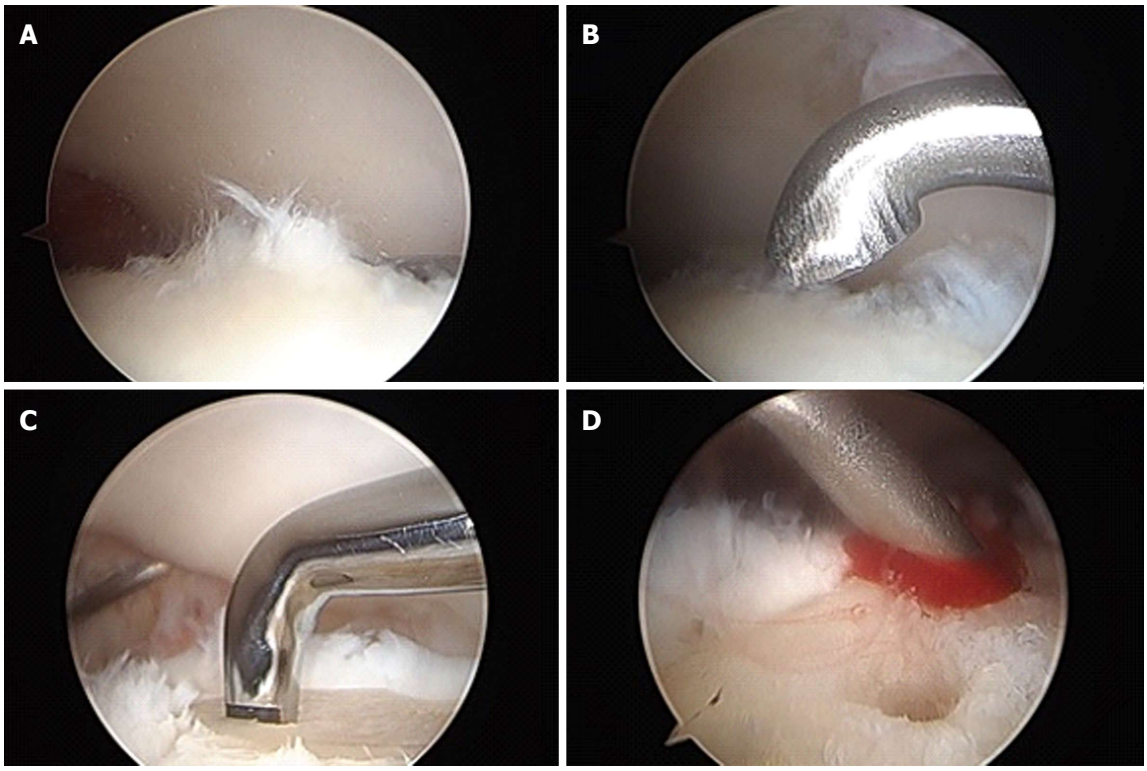


Figure 1 Arthroscopic images of osteochondral lesions of the talus. A: Osteochondral lesion of the talus identified arthroscopically; B: Frayed or fibrillated cartilage is curretted out; C: Subchondral plate is violated with microfracture pick; D: After the subchondral bone plate is violated, bleeding occurs beginning the healing response.

cast immobilization for at least 3 wk up to 4 mo reported successful clinical outcomes. However, success was determined based on symptomatic complaint rather than on the physiological healing of the OLT. In addition, the long-term outcome of these treatment strategies has yet to be established. Recent clinical studies have revealed that OLT of the ankle joint have higher levels of intra-articular inflammatory cytokines than normal ankle joint which may lead to progressive deterioration of global, as well as focal lesions over time[16].

Operative treatment

There are two basic techniques for operative treatment for OLT: Reparative including BMS and replacement procedures including AOT. The decision to either proceed with BMS or AOT is primarily determined by lesion size. Traditionally, lesions of smaller sizes (< 15 mm in diameter or < 150 mm^2 in area) are treated with BMS, while larger lesions are treated with AOT[6]. In addition, there has been recent evidence recommending AOT for patients who previously failed BMS[17].

BMS

BMS is a reparative procedure that aims to stimulate the release of mesenchymal stem cells (MSCs) from the SCB marrow to infill fibrocartilage in the defect. In BMS, unstable cartilage, the calcified layer, and necrotic bone are debrided arthroscopically. A microfracture pick or small diameter drill is then used to penetrate the SCB plate (Figure 1).

While lesion size has been identified as the primary prognostic indicator affecting outcomes after BMS, several other prognostic factors have also been identified. Chuckpaiwong *et al*[5] reported that almost all patients in their series with OLT greater than 15 mm in diameter failed BMS (96.7%; 31/32) while the other patients with lesions less than 15 mm in diameter had 100% success. Choi *et al*[12] demonstrated a risk of failure with lesions greater than 150 mm^2 on MRI. Another important prognostic factor is containment (shoulder *vs* non-shoulder type) of OLT. Choi *et al*[18] demonstrated that patients with shoulder-type OLT were more likely to have a worse clinical outcome than non-shoulder lesions. Because of the nature of BMS, subchondral bone cyst may affect the outcomes. To address this, Lee *et al*[19] performed a randomized control study and found that there were no significant differences in clinical outcomes between patients in the subchondral cyst group and those patients treated with no subchondral cyst component. However, the longevity of these outcomes is of concern due to the lack of mechanical and biological function of SCB required for robust cartilage repair[20].

Several clinical studies have demonstrated that nearly 85% of patients undergoing BMS report good to excellent clinical short- and mid-term outcomes[4,21]. van Bergen *et al*[22] evaluated long term clinical outcomes in 50 patients with at a mean follow-up of 141 mo and reported a mean American Orthopaedic Foot and Ankle Society (AOFAS) score of 88 out of 100 possible points.

Polat *et al*[23] demonstrated that out of 82 patients treated with BMS, 42.6% of patients had no symptoms and 23.1% of patients had pain after walking more than 2 h or after competitive sports activities at a mean follow-up of 121.3 mo.

Despite successful outcomes following BMS for OLT, there have been numerous studies demonstrating cause for concerns including the quality of the studies reporting positive outcomes, mechanical concerns regarding the fibrocartilage repair tissue, and long-term deteriorating clinical outcomes[21]. A systematic review by Hannon *et al*[24] found gross inconsistencies and an underreporting of data in the included 24 clinical studies that report clinical outcomes after BMS for OLT. The authors found that only 46% of clinical studies reported the lesion size and only 25% performed postoperative radiological evaluation. Therefore, the authors concluded that there is not enough data in the current literature to accurately assess the outcome of BMS[24].

Deterioration of reparative fibrocartilage quality has been reported in up to 35% of patients within the first five years of BMS, and only 30% of patients who received BMS have integration of the repair tissue with the surrounding native cartilage at second look arthroscopy 12 mo postoperatively[11,14]. Becher *et al*[25] also demonstrated that although tissue regenerated at the site of microfracture, it was neither intact not homogeneous. In a series of 120 ankles, Choi *et al*[12] has shown deterioration of clinical success rate over time following BMS.

There are numerous factors that may play a role in affecting the durability of the repair tissue following BMS. There is an increased awareness that impairment of SCB following BMS may be a cause of deterioration. Anatomically, the SCB is located under the articular cartilage offering biomechanical and biological support for overlying articular cartilage[26,27]. During BMS, there is gross destruction of cross-talk between the SCB plate and the articular cartilage. This destruction is a result of the surgical trauma and compaction of the SCB plate that occurs with penetration of either a microfracture pic or drilling[27]. In the sheep osteochondral lesion model, Orth *et al*[28] revealed that the SCB plate was not restored at 6 mo after BMS. This finding was supported in the human ankle by Reilingh *et al*[29] which revealed that the SCB were not filled completely in 78.6% (44 of 58) OLT at 1 year after BMS. This inevitable trauma to the SCB may be limited by using a small diameter microfracture pic rather than drilling or using larger diameter conventional microfracture pics[27].

Mechanical and biological insufficiency may be part of the reasons for deterioration of fibrocartilage. Marrow stimulating techniques attempt to fill talar lesions with precursor cells and cytokines, resulting in a fibrin clot that will ultimately lead to fibrocartilaginous type-1 collagen formation[10,24]. This cartilage consists of collagen that has different biomechanical properties than the native hyaline cartilage containing type-II collagen. It has been demonstrated that fibrocartilage has inferior stiffness, resilience, and wear properties and therefore is at risk of degeneration[30,31].

AOT

AOT replaces cartilage by transplanting a cylindrical osteochondral graft from a non weightbearing portion of the knee into a defect site on the talus (Figure 2). AOT is indicated in patients with lesion sizes greater than 15 mm in diameter or 150 mm^2, or in cases of failed previous BMS[4,6]. Kim *et al*[32] reported prognostic factors affecting outcomes of AOT and found that patient age, sex, body mass index, duration of symptoms, location of OLT, and the existence of a subchondral cyst did not significantly influence clinical outcomes of AOT. By Haleem *et al*[33] reported that the size of the OLT is also not a significant predictor of outcomes and multiple grafts may be used without adversely affecting the outcome.

Several studies have reported good clinical outcomes following AOT at both short- and mid-term follow-up. A case series on 85 patients who underwent AOT found improved Foot and Ankle Outcome Score (FAOS) at 47.2 mo follow-up and improved Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores post-operatively at 24.8 mo follow-up[34]. One study by Haleem *et al*[33] compared clinical and radiological MRI outcomes of OLT treated by single-plug *vs* double-plug AOT at 5-year follow-up. They found treatment with double-plug AOT did not show inferior clinical or radiological outcomes when compared to single-plug AOT in the intermediate term. Good outcomes are not limited to the general population only, and excellent outcomes have been reported in the athletic population at midterm follow-up. Fraser *et al*[35] reported improved AOFAS scores and found at final follow up of 24 mo, 90% of professional athletes and 87% of recreational athletes were able to return to pre-injury activity levels. Despite its apparent success and favorable short- and medium-term outcome profile, there has been no study to our knowledge that has described long-term (10+ years) outcomes after AOT.

AOT outcome studies however should be evaluated carefully. Hannon *et al*[24] showed that outcomes and clinical variables were reported in less than 73% and 67% of studies respectively. Therefore, the data between studies reported have been incongruent and limit cross sectional comparison

AOT has good clinical outcomes, but there are some mechanical concerns with the procedure such as formation of post-operative cysts, morbidity associated with accessing the ankle joint through osteotomies, and pressures on the graft due to malalignment. It has been suggested that biomechanical success may be limited by the alignment of the graft. Fansa *et al*[36] demonstrated increased contact pressure on the graft surface by 7-fold with a 1.0 mm of graft protrusion above the level of the native cartilage. Other mechanical considerations have also been an area of concern with AOT. The use of a medial malleolar osteotomy has raised concerns for

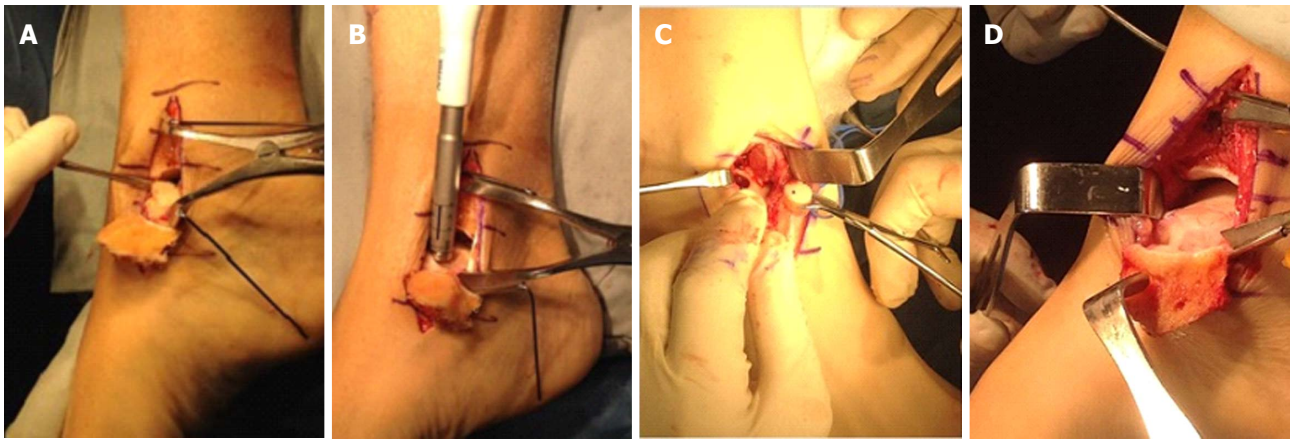


Figure 2 Autologous osteochondral transplantation procedure. A: Medial exposure of the talus; B: Preparation of the defect site; C: Insertion of cylindrical osteochondral plug into the prepared osteochondral lesions of the talus defect site; D: Exposure of the medial talus *via* the chevron-type medial malleolar osteotomy.

increasing the risk of mal/non-union. However, current evidence suggests adequate osteotomy, both medially and laterally, as well as cartilaginous healing in the short- to mid-term follow-up. Lamb *et al*[37] demonstrated that a Chevron-type medial malleolar osteotomy had overall improved healing and fixation, with evidence of fibrocartilaginous tissue present at the superficial osteotomy interface. In addition, at a mean follow-up of 64 mo, a retrospective case series by Gianakos *et al*[38] demonstrated that an anterolateral tibial osteotomy resulted in T2 mapping relaxation times similar to both superficial and deep interfaces of the native cartilage and had overall improved FAOS and MOCART scores and. However, it is known that ankle fractures may cause activation of intra-articular inflammatory cytokines, which may lead to progressive deterioration of OLT over time, and this may theoretically occur with malleolar osteotomy[16]. There have been reports demonstrating the potential of poor integration of the AOT surface with the native tissue, cyst formation around the graft site, and deterioration of the graft cartilage as potential consequences following AOT procedure. However, a case series by Savage-Elliott *et al*[39] demonstrated that although increasing age was related to increased cyst prevalence, the clinical impact of cyst formation was not found to be significant at a mean short-term follow up of 15 mo after surgery.

Lastly, concerns over donor site morbidity have gained increasing attention. Valderrabano *et al*[40] reported on the outcomes of 12 patients undergoing AOT, of whom 50% experienced donor site morbidity with all patients showing MRI signs of cartilage change, joint space narrowing, or cystic changes in untreated donor sites. These results have been challenged by similar reports. Yoon *et al*[17] found in 22 patients a 9% early donor site morbidity with 100% resolution at 48 mo follow-up. Fraser *et al*[41] performed a retrospective analysis on 39 patients who underwent AOT and reported that at 24 mo follow-up, donor site morbidity was present in only 5% of patients and that Lysholm scores were at 99.4 for the entire cohort. Therefore, OLT treated with AOT can have a low incidence of donor site morbidity with good functional outcomes.

Although the overall success of AOT for OLT may be limited by a combination of factors, evidence in the literature suggests that AOT is effective short- and mid-term follow-up, particularly for large lesions that may not be managed by other forms of treatment.

Osteochondral allograft transplantation

Osteochondral allograft transplantation is a technique that has been employed for the treatment of OLT and involves replacing defects in bone and articular cartilage with cadaveric donor specimens[42]. Some surgeons prefer this procedure over AOT because it avoids donor site morbidity[24]. Although frozen grafts may be used, the decline in the viability of chondrocytes within the graft tissue has led to an increase in the use of fresh allografts.

Reported success rates are highly variable within the literature. El-Rashidy *et al*[43] performed one of the largest studies published on patients who received small cylindrical allografts and reported positive outcomes in 28 of 38 patients at a mean follow-up of 37.7 mo. Raikin[44] evaluated patients who received bulk allografts and demonstrated improved AOFAS scores in 15 patients at a mean follow-up of 44 mo. Lastly, Haene *et al*[45] reported in a case series that only ten of 17 cases who underwent allograft transplantation had good or excellent results at an average follow-up of 4.1 years. Although clinical evidence suggests osteochondral allograft transplantation to be effective in the treatment of larger OLT, this evidence is limited as it consists primarily of case series with reported variable success rates.

Autologous chondrocyte implantation

Autologous chondrocyte implantation (ACI) is a cell-based, two-stage procedure that can be used as an alternative to osteochondral grafting techniques.

This technique involves harvesting healthy articular cartilage for chondrocyte cultures, which are grown for approximately 30 d[46]. These cultures are implanted into the defect site. The aim of ACI is to promote the development of hyaline-like repair tissue. ACI is typically indicated for full-thickness cartilage defects with an intact SCB plate with stable edges of the surrounding cartilage[47].

A systematic review by Harris *et al*[48] analyzed 82 studies (5276 subjects; 6080 defects) and reported a low failure rate of 1.5%-7.7% following ACI in the knee. Similar outcomes have been shown in the ankle. A meta-analysis by Niemeyer *et al*[49] reported a clinical success rate of 89.9% in 213 patients following ACI. Gobbi *et al*[50] reported no difference in AOFAS scores following chondroplasty, microfracture, and AOT. Disadvantages of ACI include the cost of culturing hyaline cells, the need for two surgical procedures, hypertrophy of the graft and the durability of the graft[2].

Although many studies have published promising results, the available evidence to date is of poor quality due to the level of evidence, low patient number, and use of variable outcome parameters[47]. Therefore, randomized clinical trials are necessary to determine the superiority of ACI over other more established techniques.

Matrix-induced autologous chondrocyte implantation

Matrix-induced autologous chondrocyte implantation (MACI) is a second generation of ACI whereby cells are embedded into a bioabsorbable matrix[24]. This membrane is placed over the talar cartilage defect. This procedure avoids periosteal graft harvesting and allows for a more even cell distribution[51]. In addition, a fibrin sealant can be utilized to secure the defect, reducing the need for suture fixation.

Evidence in the literature has demonstrated arthroscopic MACI as a safe alternative for the treatment of OLT with good overall clinical and radiologic results. Aurich *et al*[52] reported in a case series of 19 patients, significant improvement in AOFAS clinical scores following MACI at a mean follow-up of 24 mo. Giannini *et al*[53] also reported positive clinical and histologic outcome scores at 36 mo post-operatively.

Evidence has demonstrated MACI to be a promising new treatment method for large OLT. Future research should attempt to compare radiological, clinical, and histological MACI to conventional treatment.

BIOLOGIC AUGUMENTATION FOR CARTILAGE REPAIR

Platelet-rich plasma

Platelet-rich plasma (PRP) is an autologous blood product that contains at least twice the concentration of platelets compared to baseline values, or > 1.1 × 10^6 platelets/μL[54]. Platelets contain numerous growth factors and cytokines which have been shown to induce human-MSC proliferation and promote tissue healing[55]. There has been evidence in the literature that demonstrates positive effects of PRP on cartilage repair. Smyth *et al*[56] showed in a systematic review that 18 of 21 (85.7%) basic science papers reported positive effects of PRP on cartilage repair. Additionally, Smyth *et al*[57] found in a rabbit model, that application of PRP at time of AOT improved the integration of the osteochondral graft at the cartilage interface and decreased graft degeneration. In clinical studies, Guney *et al*[58] performed a randomized control trial in 19 OLT patients and reported that BMS with PRP had better functional outcomes when compared with BMS alone. Görmeli *et al*[59] compared the effect of PRP and HA following BMS for OLT and found at 15.3-mo follow-up, clinical improvement after PRP with HA when compared to HA or saline injection alone.

Despite successful reported outcome following PRP adjuvants, the effect of PRP on OLT is still controversial because of several concerns. Currently there has been no proposed standard method for PRP harvesting. There are a variety of commercially-available centrifugation systems with various timing protocols and activation methods[60]. In addition, plasma contains differing concentrations of platelets, cells, growth factors, and cytokine, which are variable even within a single individual[60]. Several studies have evaluated the anti-inflammatory effects of different leukocyte concentrated PRP on cartilage repair[61,62]. However, to our knowledge, there has be no study that has investigated the effect of leukocyte concentration in PRP in the treatment of ankle OLT. In conclusion, the published literature suggests that utilizing PRP in the operative treatment for OLT can improve clinical and functional outcomes. The evidence for PRP is promising; however, well-designed clinical trials are necessary to determine its efficacy in the clinical setting.

Concentrated bone marrow aspirate

Concentrated Bone Marrow Aspirate (cBMA) is a blood product produced by centrifuging bone marrow typically aspirated from the iliac crest[63]. cBMA contains a variety of bioactive cytokines, as well as MSCs, which have the ability to undergo chondrocyte differentiation. In addition, most recent studies have shown that cBMA includes an abundant concentration of interleukin-1 receptor antagonist proteins (IL-1Ra), which are the primary anti-inflammatory cytokines[63].

A few studies have demonstrated the ability of cBMA to promote the chondrogenic cascade which can be beneficial in the treatment of osteochondral lesions. Improved cartilage healing has been demonstrated in the equine model, with improvements histologically and radiographically in groups receiving cBMA at the time of BMS[64]. In addition, similar results were reported in a goat model when using BMS combination with cBMA and HA[65]. Clinically, Hannon *et al*[66] reported that mean FAOS improved significantly pre- to post-

operatively at 48.3 mo in groups receiving cBMA with BMS. They also demonstrated that groups with cBMA had improved integration of the repair tissue with MRI demonstrating less fissuring and fibrillation. Kennedy *et al*[6] demonstrated improved restoration of radius curvature and color stratification similar to that of native cartilage on MRI using T2 mapping in patients treated with cBMA and AOT. Overall, current evidence suggests that cBMA can improve cartilage repair in OLT, but future clinical research and clinical trials are necessary for better comparison of outcomes with other biological adjuncts.

CONCLUSION

OLT present a challenge and optimal treatment remains controversial. Although future randomized clinical trials are needed to establish evidence of the most effective treatment, both reparative and replacement procedures remain feasible options. The literature supports treatment with BMS for lesions of smaller sizes, whereas treatment with AOT may be utilized for larger or cystic lesions. Cell-based techniques and allograft transplantation may be utilized in failed primary procedures. Although biologic augmentation offers promising results, well-designed clinical trials are necessary to determine efficacy in the clinical setting.

REFERENCES

1 **Hintermann B**, Regazzoni P, Lampert C, Stutz G, Gächter A. Arthroscopic findings in acute fractures of the ankle. *J Bone Joint Surg Br* 2000; **82**: 345-351 [PMID: 10813167 DOI: 10.1302/0301-620X.82B3.10064]

2 **O'Loughlin PF**, Heyworth BE, Kennedy JG. Current concepts in the diagnosis and treatment of osteochondral lesions of the ankle. *Am J Sports Med* 2010; **38**: 392-404 [PMID: 19561175 DOI: 10.1177/0363546509336336]

3 **Gardiner TB**. Osteochondritis dissecans in three members of one family. *J Bone Joint Surg Br* 1955; **37-B**: 139-141 [PMID: 14353962]

4 **Zengerink M**, Szerb I, Hangody L, Dopirak RM, Ferkel RD, van Dijk CN. Current concepts: treatment of osteochondral ankle defects. *Foot Ankle Clin* 2006; **11**: 331-359, vi [PMID: 16798515 DOI: 10.1016/j.fcl.2006.03.008]

5 **Chuckpaiwong B**, Berkson EM, Theodore GH. Microfracture for osteochondral lesions of the ankle: outcome analysis and outcome predictors of 105 cases. *Arthroscopy* 2008; **24**: 106-112 [PMID: 18182210 DOI: 10.1016/j.arthro.2007.07.022]

6 **Kennedy JG**, Murawski CD. The Treatment of Osteochondral Lesions of the Talus with Autologous Osteochondral Transplantation and Bone Marrow Aspirate Concentrate: Surgical Technique. *Cartilage* 2011; **2**: 327-336 [PMID: 26069591 DOI: 10.1177/1947603511400726]

7 **Verhagen RA**, Maas M, Dijkgraaf MG, Tol JL, Krips R, van Dijk CN. Prospective study on diagnostic strategies in osteochondral lesions of the talus. Is MRI superior to helical CT? *J Bone Joint Surg Br* 2005; **87**: 41-46 [PMID: 15686236]

8 **Stone JW**. Debridement with stimulation of the base. The Foot and Ankle: AANA Advanced Arthroscopic Surgical Techniques, 2016: 9-17

9 **Loomer R**, Fisher C, Lloyd-Smith R, Sisler J, Cooney T. Osteochondral lesions of the talus. *Am J Sports Med* 1993; **21**: 13-19 [PMID: 8427354 DOI: 10.1177/036354659302100103]

10 **McGahan PJ**, Pinney SJ. Current concept review: osteochondral lesions of the talus. *Foot Ankle Int* 2010; **31**: 90-101 [PMID: 20067729 DOI: 10.3113/FAI.2010.0090]

11 **Ferkel RD**, Zanotti RM, Komenda GA, Sgaglione NA, Cheng MS, Applegate GR, Dopirak RM. Arthroscopic treatment of chronic osteochondral lesions of the talus: long-term results. *Am J Sports Med* 2008; **36**: 1750-1762 [PMID: 18753679 DOI: 10.1177/0363546508316773]

12 **Choi WJ**, Park KK, Kim BS, Lee JW. Osteochondral lesion of the talus: is there a critical defect size for poor outcome? *Am J Sports Med* 2009; **37**: 1974-1980 [PMID: 19654429 DOI: 10.1177/0363546509335765]

13 **Mintz DN**, Tashjian GS, Connell DA, Deland JT, O'Malley M, Potter HG. Osteochondral lesions of the talus: a new magnetic resonance grading system with arthroscopic correlation. *Arthroscopy* 2003; **19**: 353-359 [PMID: 12671617 DOI: 10.1053/jars.2003.50041]

14 **Lee KB**, Bai LB, Park JG, Yoon TR. A comparison of arthroscopic and MRI findings in staging of osteochondral lesions of the talus. *Knee Surg Sports Traumatol Arthrosc* 2008; **16**: 1047-1051 [PMID: 18779951 DOI: 10.1007/s00167-008-0607-x]

15 **Hepple S**, Winson IG, Glew D. Osteochondral lesions of the talus: a revised classification. *Foot Ankle Int* 1999; **20**: 789-793 [PMID: 10609707 DOI: 10.1177/107110079902001206]

16 **Henkelmann R**, Schmal H, Pilz IH, Salzmann GM, Dovi-Akue D, Südkamp NP. Prospective clinical trial of patients who underwent ankle arthroscopy with articular diseases to match clinical and radiological scores with intra-articular cytokines. *Int Orthop* 2015; **39**: 1631-1637 [PMID: 25947905 DOI: 10.1007/s00264-015-2797-4]

17 **Yoon HS**, Park YJ, Lee M, Choi WJ, Lee JW. Osteochondral Autologous Transplantation Is Superior to Repeat Arthroscopy for the Treatment of Osteochondral Lesions of the Talus After Failed Primary Arthroscopic Treatment. *Am J Sports Med* 2014; **42**: 1896-1903 [PMID: 24907287 DOI: 10.1177/0363546514535186]

18 **Choi WJ**, Choi GW, Kim JS, Lee JW. Prognostic significance of the containment and location of osteochondral lesions of the talus: independent adverse outcomes associated with uncontained lesions of the talar shoulder. *Am J Sports Med* 2013; **41**: 126-133 [PMID: 22859663 DOI: 10.1177/0363546512453302]

19 **Lee KB**, Park HW, Cho HJ, Seon JK. Comparison of Arthroscopic Microfracture for Osteochondral Lesions of the Talus With and Without Subchondral Cyst. *Am J Sports Med* 2015; **43**: 1951-1956 [PMID: 25989800 DOI: 10.1177/0363546515584755]

20 **Goldring SR**. Alterations in periarticular bone and cross talk between subchondral bone and articular cartilage in osteoarthritis. *Ther Adv Musculoskelet Dis* 2012; **4**: 249-258 [PMID: 22859924 DOI: 10.1177/1759720X12437353]

21 **Murawski CD**, Kennedy JG. Operative treatment of osteochondral lesions of the talus. *J Bone Joint Surg Am* 2013; **95**: 1045-1054 [PMID: 23780543 DOI: 10.2106/JBJS.L.00773]

22 **van Bergen CJ**, Kox LS, Maas M, Sierevelt IN, Kerkhoffs GM, van Dijk CN. Arthroscopic treatment of osteochondral defects of the talus: outcomes at eight to twenty years of follow-up. *J Bone Joint Surg Am* 2013; **95**: 519-525 [PMID: 23515986 DOI: 10.2106/JBJS.L.00675]

23 **Polat G**, Erşen A, Erdil ME, Kızılkurt T, Kılıçoğlu Ö, Aşık M. Long-term results of microfracture in the treatment of talus osteochondral lesions. *Knee Surg Sports Traumatol Arthrosc* 2016; **24**: 1299-1303 [PMID: 26831855 DOI: 10.1007/s00167-016-3990-8]

24 **Hannon CP**, Smyth NA, Murawski CD, Savage-Elliott I, Deyer TW, Calder JD, Kennedy JG. Osteochondral lesions of the talus: aspects of current management. *Bone Joint J* 2014; **96-B**: 164-171 [PMID: 24493179 DOI: 10.1302/0301-620X.96B2.31637]

25 **Becher C**, Driessen A, Hess T, Longo UG, Maffulli N, Thermann H. Microfracture for chondral defects of the talus: maintenance of early results at midterm follow-up. *Knee Surg Sports Traumatol Arthrosc* 2010; **18**: 656-663 [PMID: 20130840 DOI: 10.1007/s00167-009-1036-1]

26 **Sharma AR**, Jagga S, Lee SS, Nam JS. Interplay between cartilage and subchondral bone contributing to pathogenesis of osteoarthritis. *Int J Mol Sci* 2013; **14**: 19805-19830 [PMID: 24084727 DOI:

10.3390/ijms141019805]
27 **Gianakos AL**, Yasui Y, Fraser EJ, Ross KA, Prado MP, Fortier LA, Kennedy JG. The Effect of Different Bone Marrow Stimulation Techniques on Human Talar Subchondral Bone: A Micro-Computed Tomography Evaluation. *Arthroscopy* 2016; **32**: 2110-2117 [PMID: 27234650 DOI: 10.1016/j.arthro.2016.03.028]
28 **Orth P**, Meyer HL, Goebel L, Eldracher M, Ong MF, Cucchiarini M, Madry H. Improved repair of chondral and osteochondral defects in the ovine trochlea compared with the medial condyle. *J Orthop Res* 2013; **31**: 1772-1779 [PMID: 23813860 DOI: 10.1002/jor.22418]
29 **Reilingh ML**, van Bergen CJ, Blankevoort L, Gerards RM, van Eekeren IC, Kerkhoffs GM, van Dijk CN. Computed tomography analysis of osteochondral defects of the talus after arthroscopic debridement and microfracture. *Knee Surg Sports Traumatol Arthrosc* 2016; **24**: 1286-1292 [PMID: 26713327 DOI: 10.1007/s00167-015-3928-6]
30 **Furukawa T**, Eyre DR, Koide S, Glimcher MJ. Biochemical studies on repair cartilage resurfacing experimental defects in the rabbit knee. *J Bone Joint Surg Am* 1980; **62**: 79-89 [PMID: 7351420]
31 **Nehrer S**, Spector M, Minas T. Histologic analysis of tissue after failed cartilage repair procedures. *Clin Orthop Relat Res* 1999; **(365)**: 149-162 [PMID: 10627699 DOI: 10.1097/00003086-199908000-00020]
32 **Kim YS**, Park EH, Kim YC, Koh YG, Lee JW. Factors associated with the clinical outcomes of the osteochondral autograft transfer system in osteochondral lesions of the talus: second-look arthroscopic evaluation. *Am J Sports Med* 2012; **40**: 2709-2719 [PMID: 23097298 DOI: 10.1177/0363546512461132]
33 **Haleem AM**, Ross KA, Smyth NA, Duke GL, Deyer TW, Do HT, Kennedy JG. Double-Plug Autologous Osteochondral Transplantation Shows Equal Functional Outcomes Compared With Single-Plug Procedures in Lesions of the Talar Dome: A Minimum 5-Year Clinical Follow-up. *Am J Sports Med* 2014; **42**: 1888-1895 [PMID: 24948585 DOI: 10.1177/0363546514535068]
34 **Flynn S**, Ross KA, Hannon CP, Yasui Y, Newman H, Murawski CD, Deyer TW, Do HT, Kennedy JG. Autologous Osteochondral Transplantation for Osteochondral Lesions of the Talus. *Foot Ankle Int* 2016; **37**: 363-372 [PMID: 26666678 DOI: 10.1177/1071100715620423]
35 **Fraser EJ**, Harris MC, Prado MP, Kennedy JG. Autologous osteochondral transplantation for osteochondral lesions of the talus in an athletic population. *Knee Surg Sports Traumatol Arthrosc* 2016; **24**: 1272-1279 [PMID: 25962962 DOI: 10.1007/s00167-015-3606-8]
36 **Fansa AM**, Murawski CD, Imhauser CW, Nguyen JT, Kennedy JG. Autologous osteochondral transplantation of the talus partially restores contact mechanics of the ankle joint. *Am J Sports Med* 2011; **39**: 2457-2465 [PMID: 21868691 DOI: 10.1177/0363546511419811]
37 **Lamb J**, Murawski CD, Deyer TW, Kennedy JG. Chevron-type medial malleolar osteotomy: a functional, radiographic and quantitative T2-mapping MRI analysis. *Knee Surg Sports Traumatol Arthrosc* 2013; **21**: 1283-1288 [PMID: 22588694 DOI: 10.1007/s00167-012-2050-2]
38 **Gianakos AL**, Hannon CP, Ross KA, Newman H, Egan CJ, Deyer TW, Kennedy JG. Anterolateral tibial osteotomy for accessing osteochondral lesions of the talus in autologous osteochondral transplantation: functional and t2 MRI analysis. *Foot Ankle Int* 2015; **36**: 531-538 [PMID: 25576475 DOI: 10.1177/1071100714563308]
39 **Savage-Elliott I**, Smyth NA, Deyer TW, Murawski CD, Ross KA, Hannon CP, Do HT, Kennedy JG. Magnetic Resonance Imaging Evidence of Postoperative Cyst Formation Does Not Appear to Affect Clinical Outcomes After Autologous Osteochondral Transplantation of the Talus. *Arthroscopy* 2016; **32**: 1846-1854 [PMID: 27453454]
40 **Valderrabano V**, Leumann A, Rasch H, Egelhof T, Hintermann B, Pagenstert G. Knee-to-ankle mosaicplasty for the treatment of osteochondral lesions of the ankle joint. *Am J Sports Med* 2009; **37** Suppl 1: 105S-111S [PMID: 19841140 DOI: 10.1177/0363546509351481]
41 **Fraser EJ**, Savage-Elliott I, Yasui Y, Ackermann J, Watson G, Ross KA, Deyer T, Kennedy JG. Clinical and MRI Donor Site Outcomes Following Autologous Osteochondral Transplantation for Talar Osteochondral Lesions. *Foot Ankle Int* 2016; **37**: 968-976 [PMID: 27177889 DOI: 10.1177/1071100716649461]
42 **Fuchs DJ**, Kadakia AR. Osteochondral allograft transplantation in the ankle: A review of current practice. *Orthop Res Rev* 2015; **7**: 95-105
43 **El-Rashidy H**, Villacis D, Omar I, Kelikian AS. Fresh osteochondral allograft for the treatment of cartilage defects of the talus: a retrospective review. *J Bone Joint Surg Am* 2011; **93**: 1634-1640 [PMID: 21915579 DOI: 10.2106/jbjs.j.00900]
44 **Raikin SM**. Fresh osteochondral allografts for large-volume cystic osteochondral defects of the talus. *J Bone Joint Surg Am* 2009; **91**: 2818-2826 [PMID: 19952243 DOI: 10.2106/JBJS.I.00398]
45 **Haene R**, Qamirani E, Story RA, Pinsker E, Daniels TR. Intermediate outcomes of fresh talar osteochondral allografts for treatment of large osteochondral lesions of the talus. *J Bone Joint Surg Am* 2012; **94**: 1105-1110 [PMID: 22717829 DOI: 10.2106/JBJS.J.02010]
46 **Peterson L**, Vasiliadis HS, Brittberg M, Lindahl A. Autologous chondrocyte implantation: a long-term follow-up. *Am J Sports Med* 2010; **38**: 1117-1124 [PMID: 20181804]
47 **Baums MH**, Schultz W, Kostuj T, Klinger HM. Cartilage repair techniques of the talus: An update. *World J Orthop* 2014; **5**: 171-179 [PMID: 25035819 DOI: 10.5312/wjo.v5.i3.171]
48 **Harris JD**, Siston RA, Brophy RH, Lattermann C, Carey JL, Flanigan DC. Failures, re-operations, and complications after autologous chondrocyte implantation--a systematic review. *Osteoarthritis Cartilage* 2011; **19**: 779-791 [PMID: 21333744 DOI: 10.1016/j.joca.2011.02.010]
49 **Niemeyer P**, Salzmann G, Schmal H, Mayr H, Südkamp NP. Autologous chondrocyte implantation for the treatment of chondral and osteochondral defects of the talus: a meta-analysis of available evidence. *Knee Surg Sports Traumatol Arthrosc* 2012; **20**: 1696-1703 [PMID: 22037894]
50 **Gobbi A**, Francisco RA, Lubowitz JH, Allegra F, Canata G. Osteochondral lesions of the talus: randomized controlled trial comparing chondroplasty, microfracture, and osteochondral autograft transplantation. *Arthroscopy* 2006; **22**: 1085-1092 [PMID: 17027406 DOI: 10.1016/j.arthro.2006.05.016]
51 **Mitchell ME**, Giza E, Sullivan MR. Cartilage transplantation techniques for talar cartilage lesions. *J Am Acad Orthop Surg* 2009; **17**: 407-414 [PMID: 19571296 DOI: 10.5435/00124635-200907000-00001]
52 **Aurich M**, Bedi HS, Smith PJ, Rolauffs B, Mückley T, Clayton J, Blackney M. Arthroscopic treatment of osteochondral lesions of the ankle with matrix-associated chondrocyte implantation: early clinical and magnetic resonance imaging results. *Am J Sports Med* 2011; **39**: 311-319 [PMID: 21068444 DOI: 10.1177/0363546510381575]
53 **Giannini S**, Buda R, Vannini F, Di Caprio F, Grigolo B. Arthroscopic autologous chondrocyte implantation in osteochondral lesions of the talus: surgical technique and results. *Am J Sports Med* 2008; **36**: 873-880 [PMID: 18227232 DOI: 10.1177/0363546507312644]
54 **Miller Y**, Bachowski G, Benjamin R. Practice guidelines for blood transfusion: a compilation from recent peer-reviewed literature. 2th ed. Washington: American Red Cross, 2007: 56. Available from: URL: http://www.sld.cu/galerias/pdf/sitios/anestesiologia/practical_guidelines_blood_transfusion.pdf
55 **Fortier LA**, Barker JU, Strauss EJ, McCarrel TM, Cole BJ. The role of growth factors in cartilage repair. *Clin Orthop Relat Res* 2011; **469**: 2706-2715 [PMID: 21403984 DOI: 10.1007/s11999-011-1857-3]
56 **Smyth NA**, Murawski CD, Fortier LA, Cole BJ, Kennedy JG. Platelet-rich plasma in the pathologic processes of cartilage: review of basic science evidence. *Arthroscopy* 2013; **29**: 1399-1409 [PMID: 23669235 DOI: 10.1016/j.arthro.2013.03.004]
57 **Smyth NA**, Haleem AM, Murawski CD, Do HT, Deland JT, Kennedy JG. The effect of platelet-rich plasma on autologous osteochondral transplantation: an in vivo rabbit model. *J Bone Joint Surg Am* 2013; **95**: 2185-2193 [PMID: 24352772 DOI: 10.2106/

JBJS.L.01497]
58 **Guney A**, Yurdakul E, Karaman I, Bilal O, Kafadar IH, Oner M. Medium-term outcomes of mosaicplasty versus arthroscopic microfracture with or without platelet-rich plasma in the treatment of osteochondral lesions of the talus. *Knee Surg Sports Traumatol Arthrosc* 2016; **24**: 1293-1298 [PMID: 26493549 DOI: 10.1007/s00167-015-3834-y]
59 **Görmeli G**, Karakaplan M, Görmeli CA, Sarıkaya B, Elmalı N, Ersoy Y. Clinical Effects of Platelet-Rich Plasma and Hyaluronic Acid as an Additional Therapy for Talar Osteochondral Lesions Treated with Microfracture Surgery: A Prospective Randomized Clinical Trial. *Foot Ankle Int* 2015; **36**: 891-900 [PMID: 25825393 DOI: 10.1177/1071100715578435]
60 **Castillo TN**, Pouliot MA, Kim HJ, Dragoo JL. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. *Am J Sports Med* 2011; **39**: 266-271 [PMID: 21051428 DOI: 10.1177/0363546510387517]
61 **Riboh JC**, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of Leukocyte Concentration on the Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis. *Am J Sports Med* 2016; **44**: 792-800 [PMID: 25925602 DOI: 10.1177/0363546515580787]
62 **Osterman C**, McCarthy MB, Cote MP, Beitzel K, Bradley J, Polkowski G, Mazzocca AD. Platelet-Rich Plasma Increases Anti-inflammatory Markers in a Human Coculture Model for Osteoarthritis. *Am J Sports Med* 2015; **43**: 1474-1484 [PMID: 25716226 DOI: 10.1177/0363546515570463]
63 **Cassano JM**, Kennedy JG, Ross KA, Fraser EJ, Goodale MB, Fortier LA. Bone marrow concentrate and platelet-rich plasma differ in cell distribution and interleukin 1 receptor antagonist protein concentration. *Knee Surg Sports Traumatol Arthrosc* 2016 Feb 1; Epub ahead of print [PMID: 26831858 DOI: 10.1007/s00167-016-3981-9]
64 **Fortier LA**, Potter HG, Rickey EJ, Schnabel LV, Foo LF, Chong LR, Stokol T, Cheetham J, Nixon AJ. Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. *J Bone Joint Surg Am* 2010; **92**: 1927-1937 [PMID: 20720135 DOI: 10.2106/JBJS.I.01284]
65 **Saw KY**, Hussin P, Loke SC, Azam M, Chen HC, Tay YG, Low S, Wallin KL, Ragavanaidu K. Articular cartilage regeneration with autologous marrow aspirate and hyaluronic Acid: an experimental study in a goat model. *Arthroscopy* 2009; **25**: 1391-1400 [PMID: 19962065 DOI: 10.1016/j.arthro.2009.07.011]
66 **Hannon CP**, Ross KA, Murawski CD, Deyer TW, Smyth NA, Hogan MV, Do HT, O'Malley MJ, Kennedy JG. Arthroscopic Bone Marrow Stimulation and Concentrated Bone Marrow Aspirate for Osteochondral Lesions of the Talus: A Case-Control Study of Functional and Magnetic Resonance Observation of Cartilage Repair Tissue Outcomes. *Arthroscopy* 2016; **32**: 339-347 [PMID: 26395409 DOI: 10.1016/j.arthro.2015.07.012]

P- Reviewer: Angoules A, Fenichel I, Guerado E, Ohishi T
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.21

World J Orthop 2017 January 18; 8(1): 21-29
ISSN 2218-5836 (online)

MINIREVIEWS

Foot and ankle history and clinical examination: A guide to everyday practice

Sulaiman Alazzawi, Mohamed Sukeik, Daniel King, Krishna Vemulapalli

Sulaiman Alazzawi, Trauma and Orthopaedic Department, Royal London Hospital, London E1 1BB, United Kingdom

Mohamed Sukeik, Trauma and Orthopaedic Department, the Royal National Orthopaedic Hospital Brockley Hill, Stanmore, Middlesex HA7 4LP, United Kingdom

Daniel King, Krishna Vemulapalli, Trauma and Orthopaedic Department, Queens Hospital, Romford, Essex RM7 0AG, United Kingdom

Author contributions: Alazzawi S and Sukeik M performed the majority of the writing, prepared the figures and tables; King D performed literature review and provided the input in writing the paper; Vemulapalli K designed the outline, coordinated the writing and edited the paper.

Conflict-of-interest statement: None.

Manuscript source: Invited manuscript

Correspondence to: Sulaiman Alazzawi, Specialty Registrar, Trauma and Orthopaedic Department, Royal London Hospital, Whitechapel Road, Whitechapel, London E1 1BB, United Kingdom. salazzawi2@gmail.com
Telephone: +44-20-73777000

Received: September 18, 2016
Peer-review started: September 20, 2016
First decision: October 21, 2016
Revised: November 7, 2016
Accepted: November 27, 2016
Article in press: November 29, 2016
Published online: January 18, 2017

Abstract

This review summarises the key points in taking a history and performing a comprehensive clinical examination for patients with foot and/or ankle problems. It is a useful guide for residents who are preparing for their specialty exams, as well as family doctors and any other doctor who has to deal with foot and ankle problems in adults.

Key words: Foot; Ankle; History; Examination and clinical assessment

Core tip: Patients present with foot and ankle problems can have either single or multiple pathologies. Obtaining adequate history and performing good clinical examination is a key in reaching the accurate diagnosis. Adjuvant tools like radiological images can be used to confirm what has been clinically suspected.

Alazzawi S, Sukeik M, King D, Vemulapalli K. Foot and ankle history and clinical examination: A guide to everyday practice. *World J Orthop* 2017; 8(1): 21-29 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/21.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.21

INTRODUCTION

Patients commonly present with foot and ankle problems, either in primary or secondary care clinics. However, many physicians find it challenging to assess these patients[1]. This is probably related to the complexity and multiplicity of joints in this part of the body.

There are 26 bones, 33 Joints and more than 100

ligaments, tendons and muscles in each foot[2]. On average, we walk 10000 steps per day, 1000000 steps per year and 115000 miles in our lifetime. The foot stands 3-4 times body weight during running.

This review summarises the keys points in taking a full history and performing a systematic clinical examination for patients with foot and ankle problem. It is a useful guide for residents who are preparing for their specialty exams, but also for any doctor who may have to deal with these problems in practice.

HISTORY

The common reasons for patient's presenting to the foot and ankle clinic are: Pain, swelling, deformity, stiffness, instability and/or abnormal gait[2]. For new patients or when the diagnosis has not been confirmed before, we recommend that the examiner should not read the previous notes prior seeing the patient. This good practice allows the examiner to have more lateral thinking, with fresh eyes looking into the problem.

Pain

Ask the patient to finger point to the exact site of the maximum pain. If the pain was diffuse and not localized to one spot, try to identify the area/side of maximum discomfort. Correlate the site with the anatomical location as described in Table 1. Ask about the radiation of pain and quality or nature of it (sharp, dull or burning), whether it is related to weight bearing (degenerative changes, stress fracture or Inflammatory conditions like plantar fasciitis), the radiation (towards the toes or up the leg), severity of the pain (0-10), prevents activity, waking up during the night, time (early morning or night pain which disturbs the sleep), duration, pattern (constant/intermittent), aggravating factors (like walking distance, walking on flat or uneven floor; Going up and down the stairs; relation with shoes), and any alleviating factors (rest, analgesia, preferred type of foot wear)[3].

The chronicity and the severity of the pain can help to establish whether there is an element of central sensitization where by the patient becomes more sensitive and experiences more pain with less provocation. Factors like sleep deprivation and depression can drive central sensitization[4]. Finally, it is important to clarify what is the patients' belief about their foot pain.

Deformity

Enquire about the duration and when the patient or their family member first noticed the deformity, which area it involves, is it progressing, and whether it associated with other symptoms (for example, skin ulcer, pain, recurrent infection, rapid wear of shoes, or cosmetic).

Table 1 Correlations between the anatomical site of the pain and the possible underlying causes[6]

Location of pain	Common possible pathology	
Anterior ankle pain	Degenerative disease	Impingement Ankle joint capsule injury ex. Sport injury with maximum ankle joint plantar flexion
Medial pain below the medial malleolus	Sinus tarsi syndrome Subtalar degenerative changes Tarsal coalition of mid facet	Spring ligament or deltoid ligament pathology Tibialis posterior pathology or medial impingement
Postero-medial pain	Tibialis posterior tendonitis	Flexor hallucis longus Tarsal tunnel syndrome
Posterior pain	Achilles tendinopathy Posterior impingement	Os trigonum pathology
Postero-lateral pain	Peroneal tendon	
Lateral pain	Stress fracture of distal fibula ATFL injury Lateral impingement	Sinus tarsi syndrome Subtalar pathology Calcaneal fracture malunion
Heel pain	Plantar fasciitis Calcaneal stress fracture Entrapment of first branch of lateral plantar nerve	Fat pad atrophy/contusion Tarsal tunnel syndrome Foreign body reaction Plantar fascia rupture
Mid foot pain	Degenerative disease Post traumatic arthritis	Tarsal bones stress fracture Ligament injury ex Lisfranc injury Insertional tendinopathy of peroneal brevis
Forefoot pain	Metatarsalgia Morton neuropathy Stress fracture Freiberg disease	Metatarsophalangeal joint synovitis Nail pathology
Forefoot pain - big toe	Hallux valgus/rigidus Inflamed bunion	Sesamoiditis Sesamoid fracture
Forefoot pain - 2nd, 3rd and 4th toe	Claw toe Hammer toe	Mallet toe
Forefoot pain - little toe	Inflamed bunionette	

ATFL: Anterior inferior tibiofibular ligament.

Swelling

It is important to establish whether the swelling is localized to one area or the whole leg or ankle, whether it is uni- or bilateral, associated with activities, as well as the frequency and the duration of swelling. Generalized bilateral swelling that involves the whole foot and ankle is usually related to more systematic pathology, such as cardiac or renal problems. Swelling which includes the area only around the ankle joint may be related to the tibio-talar joint (for example, degenerative changes or inflammatory arthropathy). On other hand, localized swelling is more likely result from a specific local pathology. As an example, swelling anterior to the distal fibula may indicate chronic injury of the anterior inferior tibio fibular ligament (ATFL) and swelling posterior to the distal fibula may indicate peroneal tendon pathology[5]. Acute painful or painless swelling with or

Table 2 Important points not to miss during the history taking[6]

Important key points not to be missed in general medical history
Age
Occupation
Participation in sports
History of lower back pain
History of problems with other joints (for example, hip and knee)
Diabetes
Peripheral neuropathy
Peripheral vascular disease
Inflammatory arthropathy
Rheumatoid arthritis
Vasculitis

without the deformity of the mid foot deformity could result from Charcot neuropathy.

Instability

Enquire as to when the first episode of instability or sprain occurred, how often it happens and what can precipitate it[6].

History of trauma

History of trauma with details of immediate symptoms and treatment, surgery, injections or infection with date and details of any identified.

Associated symptoms

It is important to look out for red flags symptoms such as night sweating, temperature or weight loss, which may be related to an infection or neoplasm. Neurological symptoms like numbness, limb weaknesses or burning sensation are usually related either to spinal problem or peripheral neuropathy.

General medical history

It is important to cover all the key points that are summarised in Table 2.

CLINCIAL EXAMINATION

The examination begins from the first moment of meeting the patient by observing the gait and whether he/she uses any walking aids. The patient should be adequately exposed and ideally patients should wear shorts with bare feet. Ask for chaperone if appropriate.

Inspection of the patients footwear, insole, and walking aides

Start by examining the patient shoes and whether they are commercial or surgical shoes. Look at the pattern of the wear, which usually involves the outside of the shoe heel. Different patterns of wear indicate abnormal contact of the foot with the ground. Early lateral, proximal, and mid shoe wear, indicates a supination deformity; wear on the medial border indicates a pronation deformity[2]. In case of absence of any wear, it may simply reflect new or unused pair of foot wears. Look for any orthosis or walking aides. Inspect any insole and ask the patient which type of insole is comfortable and which type is painful.

Table 3 Correlations between the different gait patterns and the functional assessment

Examination of gait	Assessing the following aspects
Tiptoe walking	Ankle flexibility
	Posterior impingement
	Achilles/tibialis post function
	Midfoot function
	MTPJ problems
	Fractures (Stress)
	S1/2 function
Heel walking	Ankle mobility
	Anterior impingement
	Tibialis anterior function
	L4/5
	EHL/EDL function
	Plantar fasciitis/heel problems
Inner borders (inversion)/ outer borders (eversion) foot walking	Sub talar mobility
	Tibialis posterior function
	Peroneal tendons function
	5th ray problems
	Medial and lateral gutter impingement
	1st ray problem

Examination in a standing position

In most clinical setting the patient is sitting on the chair at the start of the examination. First ask the patient to stand up, and assess the alignment of the lower limbs as a whole. In particular look for any excessive varus or valgus knee deformity. Inspect the alignment of the spine in case of scoliosis, and look for any pelvic tilt. Inspect for any thigh or calf muscles wasting[7].

Look from the side for the feet arches (is there any pes cavus or pes planus), any swelling or scars. Inspect for any big toe deformity (hallus valgus, hallux valgus interphalangeus or hallus varus), lesser toes deformity (mallet toe, hammer toes, claw toes)[1]. In normal ankle, you should not be able to see the heel pad on the medial side when you inspect from the front. If this was visible then it is called "peek a boo" sign which exists with pes cavus[2]. It is important to compare both sides as a false-positive sign may be caused by a very large heel pad or significant metatarsus adductus[8].

Inspect the ankle from the back for any bony bumps like calcaneal boss[1]. The normal ankle alignment is neutral. Also notice if there is a "too many toes" sign. In a normal foot you should not be able to see more than 5th and 4th toes when you look at it from behind. If there were more toes visible (3rd or 3rd and 2nd), then it is called "too many toes" sign which can indicate an increased heel valgus angle.

Ask the patient to stand onto tiptoes. Both ankles should turn into varus. This indicates normal subtalar movement and, in case of flat feet, if a medial arch

Table 4 Different types of abnormal gaits

Type of the gait	Physical findings and observations	Possible cause
Antalgic gait	Short stance phase of the affected side Decrease of the swing phase of the normal side	Pain on weight bearing could be any reason from Back pathology to toe problem, *e.g.*, degenerative hip joint
Ataxic (stamping) gait	Unsteady and uncoordinated walk with a wide base	Cerebral cause Tabes dorsalis
Equinus (tiptoes) gait	Walking on tiptoes	Weak dorsiflexion and/or plantar contractures
Equinovarous gait	Walking on the out border of the foot	CETV
Hemiplegic (circumductory) gait	Moving the whole leg in a half circle path	Spastic muscle
Rocking horse (gluteus maximum) gait	The body shift backward at heel strike then move forward	Weak or hypotonic gluteus maximum
Quadriceps gait	The body leans forward with hyperextension of the knee in the affected side	Radiculopathy or spinal cord pathology
Scissoring gait	One leg crosses over the other	Bilateral spastic adductors
Short leg (Equinus) gait (more than 3 cm)	Minimum: Dropping the pelvis on the affected side Moderate: Walks on forefoot of the short limb Severe: Combination of both	Leg length discrepancy
Steppage gait (high stepping - slapping - foot drop)	No heel strike The foot lands on the floor with a sound like a slap	Foot drop Polio Tibialis anterior dysfunction
Trendelenburg (lurching) gait	Trunk deviation towards the normal side When the foot of the affected side leaves the floor, the pelvis on this side drops	Weak gluteus medius
Waddling gait	Lateral deviation of the trunk with an exaggerated elevation of the hip	Muscular dystrophy

Table 5 Movements of the ankle joint and possible causes of restrictions[3,9]

Movement	Normal range of motion	Possible causes of restriction
Dorsiflexion	0-20 degrees	Tight Achilles tendon Tightness of the posterior ligaments Loss of flexibility in the ankle syndesmosis Impingement of anterior soft tissue or osteophytes
Plantar flexion	0-50 degrees	Anterior capsule/ligaments contractures Posterior impingement
Inversion	0-35 degrees	Tension in the joint capsules and the lateral ligaments[1]
Eversion	0-15 degrees	Tension in the joint capsules and the medial ligaments[1]

[1]Inversion and eversion is mostly the motion of subtalar joint, the most common causes of restriction including subtalar arthritis, tarsal coalitions or calcaneal fracture malunion.

forms on standing on tip toes then this is a flexible pes planus[1].

Gait: Enquire if the patient can walk without a support and be prepared to provide support for elderly patients and those who may unsteady on their feet. Ask the patient to walk as per their normal gait. Observing the gait from the front and the back help to assess the shoulder and pelvic tilt. Looking from at the hip movements, knee movements, initial contact, three rockers, stride length, cadence and antalgesia.

The patient should then be asked to walk on his/her tiptoes, then heels, inner borders and finally the outer borders of the feet. Correlate your finding with possible causes as described in Tables 3 and 4. Beware not to miss a foot drop.

Examination in a sitting position

By this stage, a fair idea of the possible diagnosis may have been established. Hence, you should be able to direct the rest of the examination accordingly. We recommend at this stage to ask the patient to sit on the examining couch, with the legs hanging loosely from the side. Raise the bed so the patient's foot is at the level of the examiner's hand, and sit on a chair opposite the patient.

Look: Start with meticulous inspection of the sole then the rest of the foot. Look for skin discoloration, scar, ulcer, lack of hair (circulatory changes), nails, any skin thickening (callosity), hard/soft corns and any signs of infection[7].

Feel: First ask the patient if there are any areas which are painful to touch, so you can try to avoid causing pain during the examination. Then you start with gentle feel of the skin temperature, always comparing to the other side.

The second part of the palpation is to establish area of tenderness. Always follow a systematic method of palpation so you will not miss any part. We recommend to start the palpation for tenderness from proximal fibula, Achilles tendon, distal fibula, peroneal tendons, PTFL, CFL, ATFL, AITFL, Sinus tarsi, Calcaneum, Calcaneocuboid (CC) joint, Cuboid, lesser Metatarsals, Phalanges, 1st IP and MTP joint, 1st ray, TMT joints, Cuneiforms, Navicular, TN joint, Talus, Ankle

Table 6 Examination techniques of muscles functions[3]

Muscle	Ankle position	Manoeuvre of the test
Tibialis Anterior	Maximum Dorsiflexion and inversion	Try to plantar flex the ankle with your hand and ask the patient to resist, use your second hand on the tendon to feel the contraction (Figure 1)
Tibialis posterior	Plantar flexion and inversion	Patient inverts the foot in full plantar flexion whilst the examiner pushes laterally against the medial border of the patient's foot (in an attempt to evert the foot). The examiner needs to use second hand on the tendon to feel the contraction (Figure 2)
Peroneal longus and peroneal brevis	Plantar flexion and eversion	Patient everts the foot in full plantar flexion and the examiner pushes medially against the lateral border of the patient's foot (in an attempt to invert the foot) (Figure 3)
Extensor hallucis longus	Neutral	Patient extends the great toe and the examiner try to planter flex it (Figure 4)
Extensor digitorum longus	Neutral	Patient extends the lesser toes toe and the examiner try to planter flex it[1] (Figure 5)
Flexor hallucis longus and flexor digitorum longus	Neutral	Patient curls the toes downward and the examiner tries to dorsiflex them[1]

[1]It can be difficult to neutralize the intrinsic muscles completely.

Table 7 Examination techniques of performing the foot and ankle special tests[2,3,9,10]

Name of the test	Purpose of the test	Maneuver
Anterior drawer test	Lateral ligament complex	The leg hangs loosely off the table The examiner hold the patient's leg just above the ankle joint with one hand The examiner uses the other hand to hold the ankle in plantar flexion and try to gently to pull the ankle forward - anterior translation (Figure 6) Look at the skin over the anterolateral dome of the talus to watch for anterior motion of the talus with this maneuver - sulcus sign
Inversion stress test	Stability of the lateral ankle ligaments (ATFL)	The knee is flexed 90 degree With one hand perform inversion stress by pushing the calcaneus and talus into inversion while holding the leg form the medial side with the other hand (Figure 7) The test is positive when there is excessive inversion and/or pain
Calf compression or "squeeze" test	Syndesmotic injury	The leg hangs loosely off the table - knee flexed The examiner uses both hand to squeeze at midpoint of the tibia and fibula Pain caused by this maneuver indicates Syndesmotic injury
External rotation stress	Syndesmotic injury	The leg hangs loosely off the table - knee flexed and foot fully dorsiflexed The examiner uses one hand to stabilize the lower leg With the other hand they externally rotate the foot Pain caused by this maneuver indicates Syndesmotic injury
Coleman block test	To assess the flexibility of the hindfoot, *i.e.*, whether the cavus foot is caused by the forefoot or the hindfoot	A block is placed under the lateral border of the patients foot The medial forefoot is allowed to hang over the side The first metatarsal will be able to drop below the level of the block, *i.e.*, eliminate the contribution by the first ray (Figure 8) With a flexible hindfoot, the heel will fall into valgus or neutral termed forefoot-driven hindfoot varus In case of rigid hindfoot or hindfoot-driven hindfoot varus the heel will remain in varus, and no correction will be happen
Semmes-weinstein monofilament test	To assess the degree of sensory deficit	Pressure testing using a 10 g Semmes-Weinstein mono- filament. Especially useful in diabetic charcot feet (Figure 9)

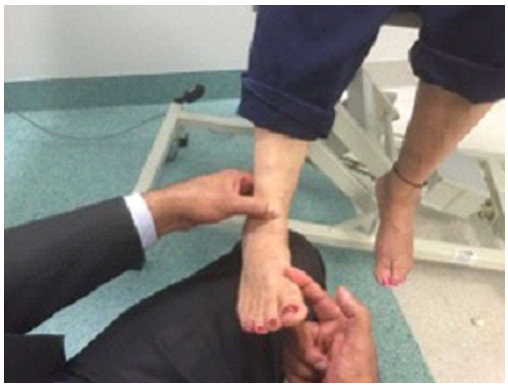


Figure 1 Test for tibialis anterior muscle.

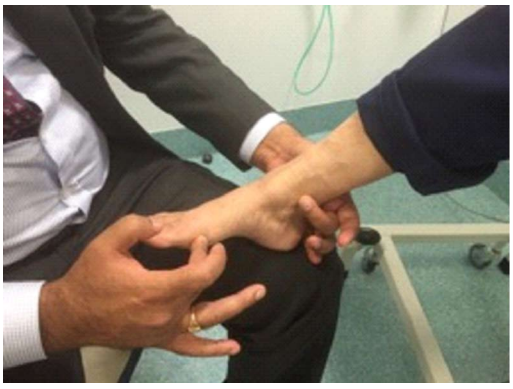


Figure 2 Test for tibialis posterior muscle.

Table 8 Examination techniques of performing the foot and ankle special tests[2,3,9,10]

Name of the test	Purpose of the test	Manoeuvre
Silfverskiold test	Differentiate between a tight gastrocnemius and a tight soleus muscle	The leg hangs loosely off the table - knee flexed Dorsiflex the ankle to the maximum Patient should then extend their knee Repeat the ankle dorsiflexion (Figure 10) If there was more ankle dorsiflexion with the knee flexed then there is gastrocnemius tightness
Thompson's test	Achilles' tendon rupture	Patient lies is prone on the bed or kneel on a chair The examiner gently squeeze the gastrocsoleus muscle (calf) If the tendon is intact, then the foot passively plantar flexes when the calf is squeezed
Test for tarsal tunnel syndrome	Compressions of the posterior tibial nerve underneath the flexor retinaculum at the tarsal tunnel	Tap inferior to the inferior to the medial malleolus to produce Tinel's sign
Test for flat foot	Differentiate between flexible *vs* rigid	Ask patient to stand on tiptoes If the medial arch forms and heel going into varus then it is flexible flat foot Beware of rupture tibialis posterior tendon or tarsal coalition
Test for stress fractures	Stress fractures	Place a tuning fork onto the painful area If it increases the pain, then it is positive Other test: One spot tenderness on palpation with finger
Babinski's response	Upper motor neuron disease	Scratch the lateral border of the sole of the foot A positive response is dorsiflexion of the great toe
Oppenheim's test	Upper motor neuron disease	Run a knuckle or fingernail up the anterior tibial surface A positive response is dorsiflexion of the great toe
Mulder's test	Morton's neuroma	A mass felt or audible Click is elicited by palpating (grasping) the forefoot (web space) with the index finger and thumb of the examiner

joint, Medial malleolus, Tibialis post, Tibialis anterior, extensors and other flexors and finally plantar fascia.

Move: Start with active movement by asking the patient to perform dorsiflexion, plantar flexion, inversion, and eversion. Always compare both sides (Table 5).

This will be followed by passive movement of dorsiflexion: As the patient is already sitting, the knee is flexed to 90 degrees then repeat the test with knee straight (Silfverskiold test). Keep the foot in a neutral position (0 degree of inversion and eversion), hold the back of the leg with one hand and use the palm of the other hand to push the sole of the examined foot[9].

Table 9 Three common pathologies and the related necessary clinical tests[7]

Special pathology	Required tests
Pes cavus	Claw toes Examine peroneal tendons Tibialis anterior and posterior Coleman block test Examine the Achilles tendon Full lower and upper limb neurological examination Hand - inspect for muscle wasting Spine
Pes planus	Single leg sustained tip toe test Testing tibialis posterior power Too many toes sign Examine the Achilles tendon
Hallux valgus/ rigidus	Dorsal osteophyte Passive ROM Grind tests Correct the deformity Examine the Achilles tendon

Table 10 Medical Research Council scale to assess the strength of muscle[8]

Grade	Description
Grade 0	No contraction
Grade 1	Flicker or trace of contraction
Grade 2	Active movement with gravity eliminated
Grade 3	Active movement against gravity
Grade 4	Active movement against gravity and resistance
Grade 5	Normal power

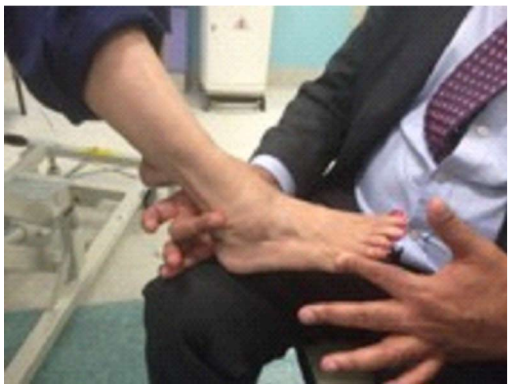
Now move the palm of the hand to the dorsum of the examined foot to produce the passive plantar flexion.

Supination and pronation are triplanar movements. Supination is the combination of Inversion, Plantarflexion and adduction. Pronation is the combination of Eversion, Dorsiflexion and Abduction.

Inversion: Place one hand over the back of the leg and use your other hand to grasp the calcaneus between your index finger and thumb and use your forearm to fully dorsiflex and lock the talus in the ankle. Rotate the calcaneus in a medial direction to test for inversion and move your hand in a lateral direction to test for Eversion[9].

Midfoot movements: Stabilize the calcaneus and talus with one hand and use the other hand to move the foot medially to test for Adduction). Move the foot laterally to test for the abduction[9]. It is also important to examine the motion of midfoot (transverse tarsal joint) on sagittal plane (specially for patients with end stage ankle arthritis). The motion of 1st TMT joint should be examined as well (for patients with hallux valgus or flexible flatfoot).

Forefoot movements (metatarsophalangeal and interphalangeal joints): You should test the



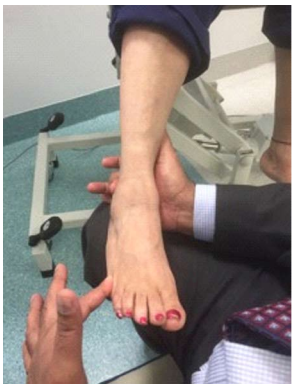


Figure 3 Test for the peroneal tendons.

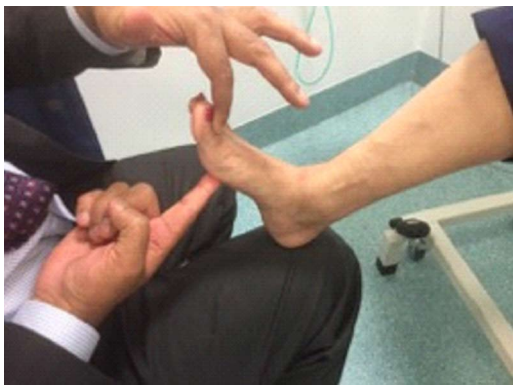


Figure 4 Test for extensor hallucis longus.

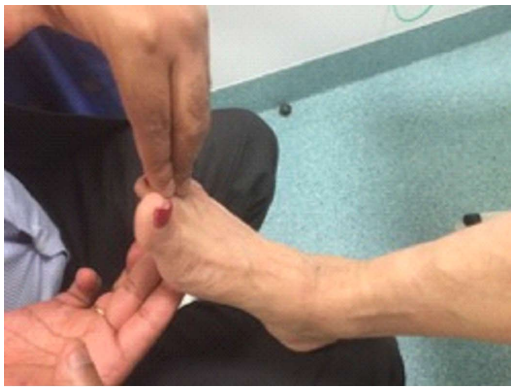


Figure 5 Test for extensor digitorum longus.

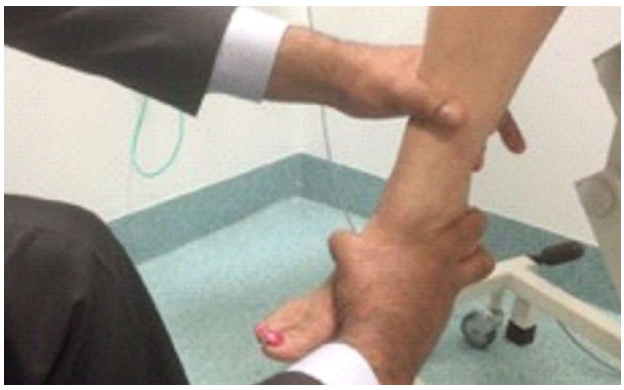


Figure 6 Anterior drawer test.

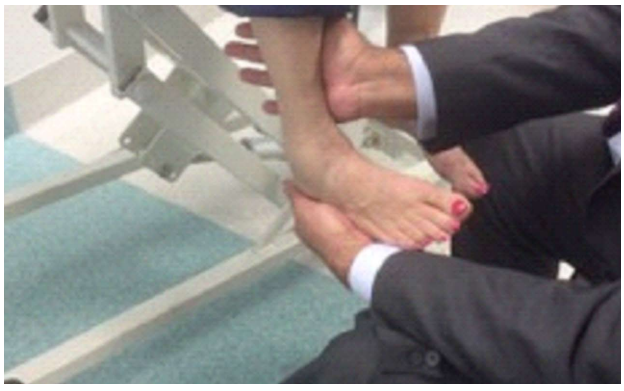


Figure 7 Inversion stress test.

movement in each joint separately. If there is any deformity, try to find whether it is correctable or not (for example, a fixed flexion deformity).

The examination of muscular function and the special tests should be the next step of the assessment. Both of these aspects are summarised in Tables 6, 7, 8 and 9. The strength of each muscle is assessed using the medical research council (MRC) scale Table 10.

The examination of the foot and ankle is not complete until you perform neurovascular examination, an examination of the spine (deformity like scoliosis, hair tuft on the lower back), leg length, hip joint examination and knee joint examination.

Finally, it is important to consider Functional testing which is important and needs to be appropriate to the level and background of the patient for instance, a single leg squat or squat jump for higher level athletes may indicate issues not obvious with more static tests.

CONCLUSION

The assessment of foot and ankle pathology can

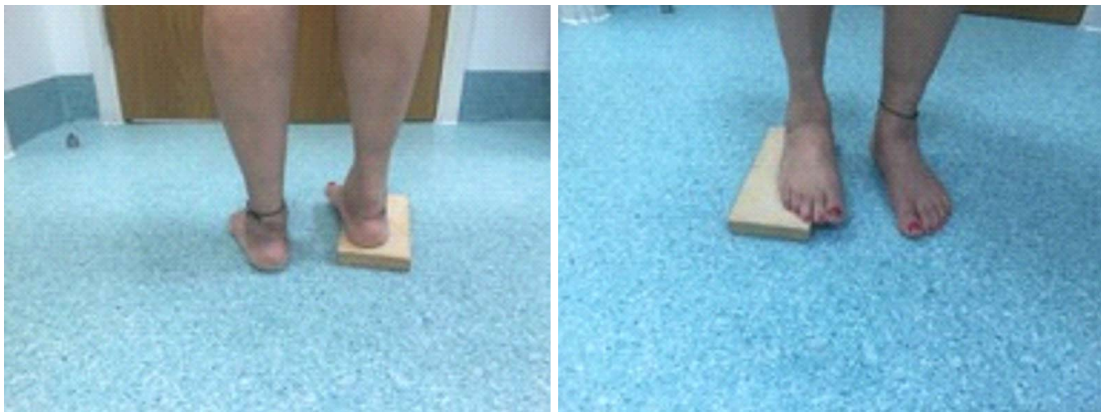


Figure 8 Coleman block test.

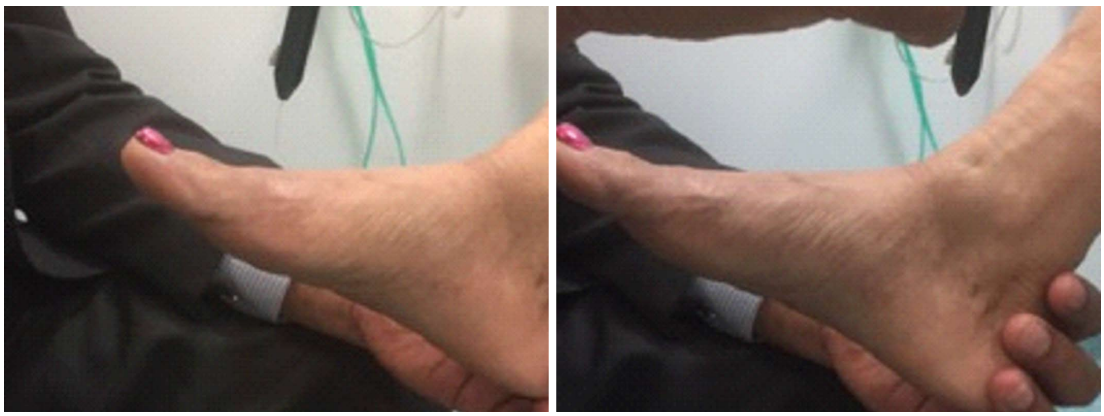


Figure 9 Semmes - weinstein monofilament test.

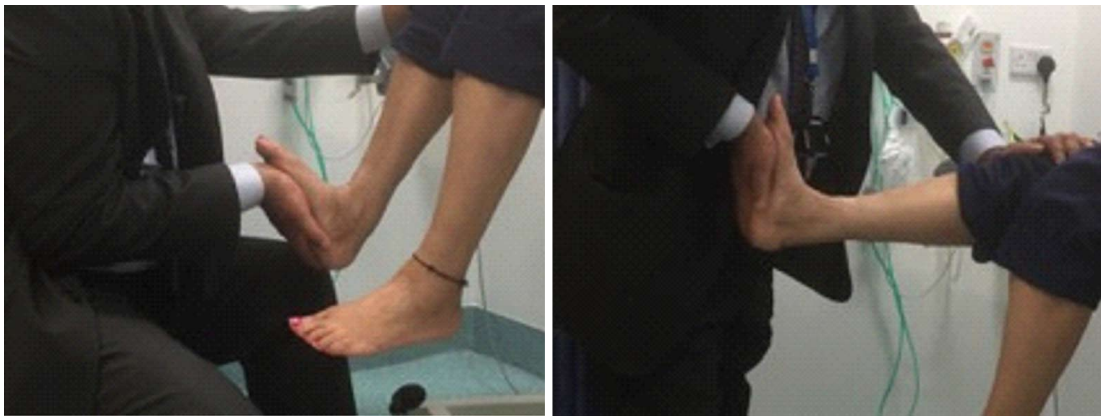


Figure 10 Silfverskiold test.

be challenging, hence the importance of following a systematic method for its clinical assessment. We have described here one way of performing the clinical examination. It has been built using the best available evidence, and has been tested and evolved through the experience of the senior author. We recommend this approach for residents who are preparing for their specialty exams, for clinicians in family or sports medicine, and for any physician who has to deal with foot and ankle patients.

REFERENCES

1 **Papaliodis DN**, Vanushkina MA, Richardson NG, DiPreta JA. The foot and ankle examination. *Med Clin North Am* 2014; **98**: 181-204 [PMID: 24559868 DOI: 10.1016/j.mcna.2013.10.001]

2 **Coughlin MJ**, Saltzman CL, Anderson RB. Mann's surgery of the foot and ankle. Amsterdam: Elsevier Saunders, 2014: 2186

3 **Reider B**. The Orthopaedic Physical Examination. 2nd ed. Amsterdam: Elsevier Saunders, 2005: 383

4 **Finan PH**, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J Pain* 2013; **14**: 1539-1552 [PMID: 24290442 DOI: 10.1016/j.jpain.2013.08.007]

5 **Simpson MR**, Howard TM. Tendinopathies of the foot and ankle. *Am Fam Physician* 2009; **80**: 1107-1114 [PMID: 19904895]
6 **Harris N**, Ali F. Examination Techniques in Orthopaedics. England: Cambridge University Press, 2014
7 **Roberts PJ**, Tandon S, Wade RH. Clinical Examination for FRCS (Trauma & Orthopaedics). 1st ed. Oswestry: The Institute of Orthopaedics (Oswestry) Publishing Group, 2002: 149
8 **Thevendran G**, Younger AS. Examination of the varus ankle, foot, and tibia. *Foot Ankle Clin* 2012; **17**: 13-20 [PMID: 22284549 DOI: 10.1016/j.fcl.2011.11.006]
9 **Gross J**, Fetto J, Rosen E. Musculoskeletal Examination 3rd ed. New Jersey: Wiley-Blackwell, 2009: 463
10 **Davies H**, Blundell C. Clinical examination of the foot and ankle. *Orthopaedics and Trauma* 2011; **25**: 287-292 [DOI: 10.1016/j.mporth.2011.07.007]

P- Reviewer: Chen GS, Papanas N **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.30

World J Orthop 2017 January 18; 8(1): 30-35
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Case Control Study

Digital templating in total hip arthroplasty: Additional anteroposterior hip view increases the accuracy

Sophia K Stigler, Franz J Müller, Sebastian Pfaud, Michael Zellner, Bernd Füchtmeier

Sophia K Stigler, Franz J Müller, Sebastian Pfaud, Michael Zellner, Bernd Füchtmeier, Clinic for Trauma, Orthopaedic and Sports Medicine, Hospital Barmherzige Brüder, 93049 Regensburg, Germany

Author contributions: Stigler SK collected, analysed the data and wrote the manuscript; Müller FJ contributed in final editing of the manuscript; Stigler SK, Müller FJ, Pfaud S, Zellner M corrected the manuscript; Füchtmeier B designed and supervised the study, acquired the data; all authors approved the definite version of the manuscript.

Institutional review board statement: Institutional review board approval.

Informed consent statement: An informed consent statement was given.

Conflict-of-interest statement: All authors declare that there is no conflict of interest. For this work no benefits in any form were received.

Data sharing statement: No data sharing is required.

Manuscript source: Unsolicited manuscript

Correspondence to: Dr. med. Franz Müller, habil., Clinic for Trauma, Orthopaedic and Sports Medicine, Hospital Barmherzige Brüder, Prüfeninger Str. 86, 93049 Regensburg, Germany. franz.mueller@barmherzige-regensburg.de
Telephone: +49-941-3692251
Fax: +49-941-3692255

Received: July 17, 2016
Peer-review started: July 18, 2016
First decision: September 2, 2016
Revised: September 21, 2016
Accepted: December 1, 2016
Article in press: December 2, 2016
Published online: January 18, 2017

Abstract

AIM

To analyze planning total hip arthroplasty (THA) with an additional anteroposterior hip view may increases the accuracy of preoperative planning in THA.

METHODS

We conducted prospective digital planning in 100 consecutive patients: 50 of these procedures were planned using pelvic overview only (first group), and the other 50 procedures were planned using pelvic overview plus antero-posterior (a.p.) hip view (second group). The planning and the procedure of each patient were performed exclusively by the senior surgeon. Fifty procedures with retrospective analogues planning were used as the control group (group zero). After the procedure, the planning was compared with the eventually implanted components (cup and stem). For statistic analysis the χ^2 test was used for nominal variables and the *t* test was used for a comparison of continuous variables.

RESULTS

Preoperative planning with an additional a.p. hip view (second group) significantly increased the exact component correlation when compared to pelvic overview only (first group) for both the acetabular cup and the femoral stem (76% cup and 66% stem *vs* 54% cup and 32% stem). When considering planning ± 1 size, the accuracy in the second group was 96% (48 of 50 patients) for the cup and 94% for the stem (47 of 50

patients). In the analogue control group (group zero), an exact correlation was observed in only 1/3 of the cases.

CONCLUSION

Digital THA planning performed by the operating surgeon and based on additional a.p. hip view significantly increases the correlation between preoperative planning and eventual implant sizes.

Key words: Digital; Templating; Preoperative planning; Hip view; Total hip arthroplasty

Core tip: Preoperative planning is an essential practice carried out prior to total hip arthroplasty (THA). However, the accuracy of digital preoperative planning in THA is variable and often lacks sufficient precision. Our prospective study analysed that preoperative planning with an additional antero-posterior hip view significantly increased the exact component correlation when compared to pelvic overview only for both the acetabular cup and the femoral.

Stigler SK, Müller FJ, Pfaud S, Zellner M, Füchtmeier B. Digital templating in total hip arthroplasty: Additional anteroposterior hip view increases the accuracy. *World J Orthop* 2017; 8(1): 30-35 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/30.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.30

INTRODUCTION

Preoperative planning for elective total hip arthroplasty (THA) is of paramount importance, irrespective of the level of difficulty. Not only does it prevent complications, but it also helps to optimise important geometric parameters such as leg length, centre of rotation, and femoro-acetabular offset adjustment by determining such components[1-4].

Previously, conventional X-ray images and measuring templates were used for this purpose. However, according to the literature, these practices resulted in low levels of correlation with the sizes of the eventually implanted devices in most cases[2]. With the increasing use of digital radiography, more and more digital planning software programmes are being offered, which, in theory, should deliver higher precision. However, it has been reported that there were only a few cases for which digital planning has resulted in more than low correlation between planning and implanted sizes[4-6].

Therefore, we conducted a comparative case-control study based on the null hypothesis that planning precision regarding the eventually implanted components can be increased with an additional antero-posterior (a.p.) hip view. This was based on the fact that the a.p. hip view with a central X-ray beam (directed to the proximal femur) reduces parallax shifts and rotational deviations[7].

MATERIALS AND METHODS

Since 2014, we have exclusively performed preoperative THA planning in our hospital using digital software (MediCAD, HECTEC GmbH, Landshut, Germany). The digital planning has been performed using a 17-inch LCD screen with a resolution of at least 1.024 × 768 pixels.

We used three groups for this comparative study: The first group included digital planning in 50 consecutive patients (who underwent surgery in 2015) using digital pelvic overview only (Figure 1). The second group also included digital planning in 50 consecutive patients (within the same year), but with an additional a.p. hip view for planning (Figure 2). All X-ray examinations (pelvic overview) were performed using a standardised technique with the patients in the supine position with a film-focus distance of 115 cm, a 10- to 15-degree internal rotation of the hip joint, and the central X-ray beam directed to the pubic symphysis.

A 25-mm external calibration marker (scaling sphere) was used for planning in both groups, and it was placed laterally from the hip joint requiring surgery or centred between the legs at the joint level at the height of the trochanter major. Moreover, surgeries in both groups were exclusively performed by the senior consultant surgeon who operated on the patients on the following day. Access to the hip was achieved exclusively in the lateral position using the minimally invasive technique according to Bertin and Röttinger[8]. The planning steps were performed according to the procedure described by Bono[3], Dastane *et al*[9], and Unnanuntana *et al*[10] (Figures 1 and 2).

Fifty consecutive patients with analogue planning (who underwent surgery the year before the digital software had become available) served as the control group (group zero). Here, the individual planning steps had been performed according to Eggli *et al*[11].

The indications for the 150 patients who received a cementless THA for both acetabular cup and femoral stem were primary osteoarthritis (n = 133), avascular femoral head necrosis (n = 11), and dysplasia (n = 6). The exclusion criteria were as follows: History of cemented or hybrid arthroplasty, additional osteotomies, and revision surgery for any reason.

Preoperative planning, surgical reports, and post-operative X-ray (within 6 wk) for the first and second group were performed prospectively, and group zero was evaluated retrospectively. The cup component was a Fitmore or an Allofit press-fit cup (Zimmer, Freiburg, Germany), and the stem was a CLS Spotorno (Zimmer), exclusively in all three of the groups. The study was approved by the local ethics committee.

Statistical analysis

SPSS version 23 (SPSS, Chicago, IL, United States) was

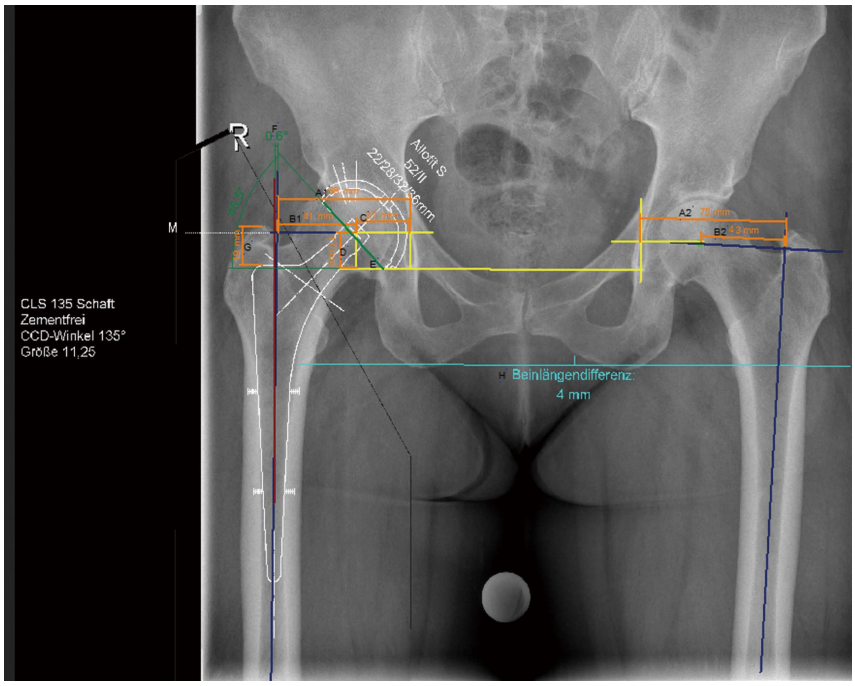


Figure 1 Digital planning of cup and stem for total hip arthroplasty of the right side (group 1). A1: Hip offset: Perpendicular line from the teardrops through the centre of rotation to the femoral shaft axis, *i.e.*, line B1 + C; A2: Contralateral hip offset; B1: Femoral offset: Perpendicular line from the centre of rotation to the axis of the femur; B2: Contralateral femoral offset; C: Horizontal position of the centre of rotation: Distance determined by the centre of rotation and one line perpendicular to the teardrops drawn through the centre of the teardrop; D: Vertical position of the centre of rotation: Line determined by the inter-teardrop line and the centre of rotation; E: Inclination angle: Angle determined by the inter-teardrop line and one axis extending through the cup opening; F: Stem orientation: Angle between femoral shaft axis and implant shaft axis; G: Implantation depth: Line between the upper edge of the prosthesis and the tip of the greater trochanter; H: Leg length difference: Quantified by subtracting the perpendicular distance from the biischial line to the proximal corner of the minor trochanters of both sides (measurements according to Bono, Dastane, Unnanuntana, Eggli[3,9-11]).

used for statistical analysis. Descriptive analysis was performed by determination of values, averages, and standard deviations. Differences were compared using the χ^2 test for nominal variables. The *t*-test was used for a comparison of continuous variables. A *P* value of < 0.05 was set as the significance threshold.

RESULTS

Among the 150 patients who underwent cementless THA, 63 were female, 87 were male, and the mean age was 63 years (30 to 83). No patient received bilateral THA. The descriptive data (sex, age, BMI, indications, and duration of surgery) within the three groups were not significantly different ($P > 0.05$).

For all 150 patients, no major postoperative complications, *e.g.*, periprosthetic fracture, fracture of the trochanter tip, or hip dislocation - were documented.

Acetabular cup size

The exact acetabular cup sizes within the three groups are shown in Table 1. The size increments within the two cups are 2 mm. Within the second group, including additional a.p. hip view, a total of 48 out of 50 (96%) were predicted within ± one size without a significant difference between both of the utilised components (Allofit or Fitmore). The results for exact size accuracy between the three groups were significantly different ($P = 0.02$).

Femoral stem size

The exact femoral stem sizes within the three groups are shown in Table 2. The increments of the femoral stems are between 1 and 1.25 mm. Within the second group that included an additional a.p. hip view, a total of 47 out of 50 (94%) were predicted within a one size deviation. The results for exact size accuracy between the first and the second group were significantly different ($P < 0.001$).

Centre of rotation

A distance of $\leqslant$ 5 mm between the vertical and horizontal centre of rotation after implantation when compared to the scheduled position was found in a total of 48% ($n = 24$) of patients in group zero and in a total of 72% ($n = 36$) of patients in the digital group. The planning accuracy difference between both groups was significantly different ($P = 0.014$).

Femoral and hip offset

A femoral offset of $\leqslant$ 5 mm when compared to the scheduled position was found in a total of 68% ($n = 34$) in the analogue planning group and in a total of 70% ($n = 35$) in the digital group. The hip offset was scheduled $\leqslant$ 5 mm in 50% of patients ($n = 25$) of both groups (both with analogue and digital planning).

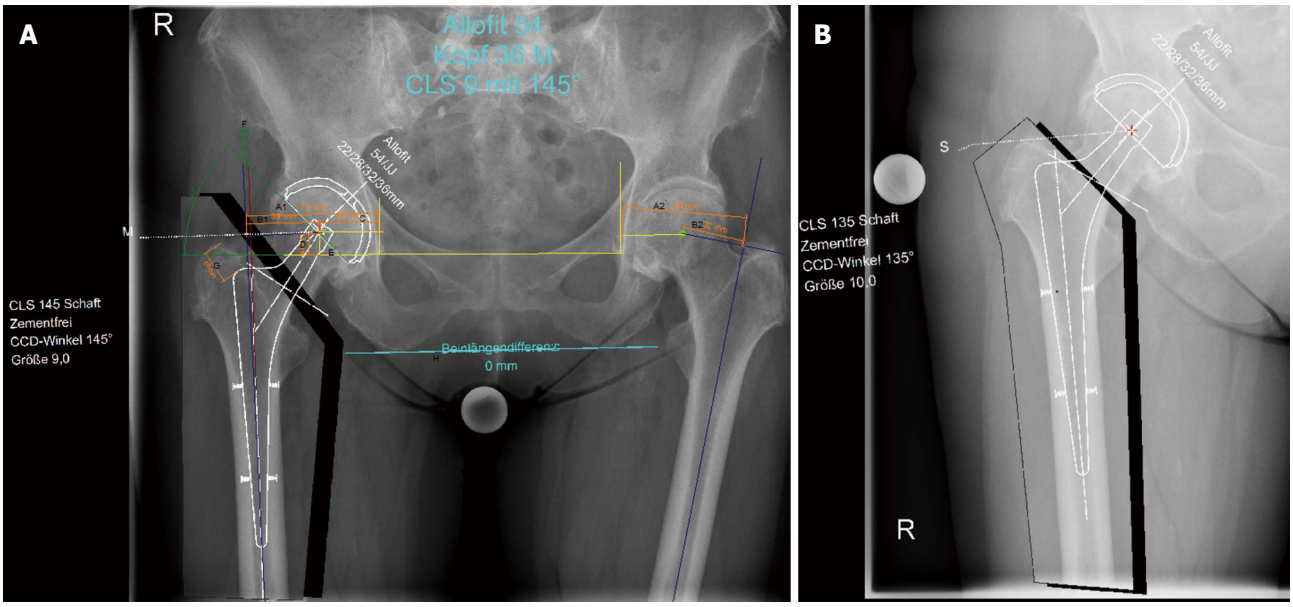


Figure 2 Pelvic overview plus antero-posterior hip view (group 2). A: Digital planning of cup and stem for total hip arthroplasty of the right side; B: Additional antero-posterior hip view for planning. With this true antero-posterior view of the hip, planning is more accurate.

Table 1 Accuracy of acetabular cup *n* (%)

Preoperative planning *vs* implant used	Group zero *n* = 50	First group *n* = 50	Second group *n* = 50
- 2 sizes smaller	-	-	-
- 1 size smaller	6 (12)	8 (16)	5 (10)
Exact size	17 (34)	27 (54)	38 (76)
+ 1 size larger	15 (30)	12 (24)	5 (10)
+ 2 sizes larger	9 (18)	2 (4)	2 (4)
+ 3 sizes larger	2 (4)	1 (2)	-
+ 4 sizes larger	1 (2)	-	-

Table 2 Accuracy of femoral stem *n* (%)

Preoperative planning *vs* implant used	Group zero *n* = 50	First group *n* = 50	Second group *n* = 50
- 2 sizes smaller	1 (2)	3 (6)	3 (6)
- 1 size smaller	11 (22)	20 (40)	9 (18)
Exact size	16 (32)	16 (32)	33 (66)
+ 1 size larger	17 (34)	10 (20)	5 (10)
+ 2 sizes larger	5 (10)	1 (2)	-

Acetabular cup inclination

The mean inclination angle of the acetabular cup was 44.5° (SD ± 4.2°) in group zero and 45° (SD ± 5.8°) in the digital planning group, and there was no significant difference between the two groups.

A total of 88% of the prostheses (*n* = 44) in the analogue planning group and 92% (*n* = 46) in the digital planning group were implanted at angles between 30° und 50°.

Leg length difference

The mean postoperative leg length difference (LLD) was 4.6 mm in the analogue planning group (SD ± 5.0 mm) and 2.7 mm in the digital planning group (SD ± 3.4 mm). A total of 80% of patients in group zero and 90% in the digital planning group had postoperative leg length differences of < 10 mm.

DISCUSSION

This study covers multiple aspects of preoperative planning: Although several studies of analogue planning have been previously reported[11,12], our study offers an additional direct comparison with digital planning. Few studies have compared analogue and digital planning procedures. Surprisingly, their results varied: González Della Valle *et al*[13] demonstrated that analogue planning resulted in a higher planning accuracy for both cup and femoral stem. However, The *et al*[1] concluded that digital planning was superior to analogue planning in regard to both components. In contrast, Gamble *et al*[6] found a significantly higher accuracy only for the acetabular cup when digital planning was used, whereas identical results were achieved with femoral stems. The results of the latter study are similar to ours: We also found an equally low exact precision (32%) for the femoral stem with both analogue and digital planning (when only a pelvic overview was used). However, in total, our data clearly showed that analogue planning offered the lowest levels of results for both exact precision and deviation by one size.

However, digital planning of the acetabular cup resulted in a clearly higher exact size determination (54%) in our study when compared to the results of other recent studies that reported an accuracy of only 34% to 42%[4,6,10]. Nevertheless, this result is still not satisfactory for several reasons: First, whether the scaling sphere was actually placed in the correct plane cannot be retrospectively evaluated[14]. Accordingly,

inaccurate positioning and an inappropriately rotated femur have detrimental effects on X-ray imaging quality and, thus, on planning precision. The femoral stem component is more prone to such effects than the cup[15]. This may explain the lower planning accuracy with regard to the stem component. In our study, it was more common that a smaller-than-needed size of the femoral stem component was selected (though the difference was only one size) when compared to a larger-than-needed size (40% *vs* 20%). Kniesel *et al*[16] reported similar results. In their evaluation of different calibration methods, Franken *et al*[17] also found that there was a tendency to underestimate the real dimensions when the reference sphere was placed in the centre between the patient's legs. Furthermore bone density is a crucial criterion when selecting the stem component: It is common that larger components are selected for patients with lower bone density[4].

Second, we were able to demonstrate for the first time that the exact correlation between planning and eventually implanted components (cup and stem) can be significantly increased to more than 2/3 of the cases with an additional a.p. hip view. When a size deviation of ± one size is also taken into account, an accuracy level of above 90% can be achieved for both the cup and the stem. Hip view with central X-ray beam targeting the proximal femur results in the minimisation of parallax shifts with reduction of rotational deviations[7], which may explain the higher planning precision. However, there are no data currently available with regard to an additional centred hip view for component planning.

In additional to component selection, it is clear that leg length difference is another very important preoperative planning parameter, even though a maximum clinical difference of 10 mm is generally considered to be acceptable[18]. The validation of different measurement methods for leg length differences has been the subject of multiple studies, with various results. Meermans *et al*[19] found that the horizontal line through the teardrops offers a more accurate reference marker when compared to the line between the two ischial tuberosities. However, Tripuraneni *et al*[20] concluded that the teardrop line is most commonly prone to measurement errors and that the obturator line would be the most accurate reference. In our study, the biischial line was used as an anatomical landmark for LLD assessment. We found a significant difference in planning accuracy in favour of the digital method: 90% of the patients showed a postoperative leg length difference of less than 10 mm, which is in line with the results reported in the studies of Unnanuntana *et al*[10] or González Della Valle *et al*[21]. However, it must be emphasised that complete compensation of leg length differences is not always practical and necessary, particularly in elderly patients with scoliotic deformities.

With regard to offset, analogue and digital procedures were found to be equivalent in terms of planning and correlation with implant positions. The digital method was significantly superior to the analogue method in terms of planning vertical and horizontal positions of the rotation centre. Good results were achieved for both cup planning and implantation when the inclination angle was within the "safe zone" (30°-50°) according to Lewinnek *et al*[22]. This was observed in both groups. Implantation outside of this range is known to promote abrasion and prosthesis loosening in the mid and long term[23].

Finally, it is necessary to address the weaknesses of the present study: Digital planning was performed by the senior surgeon who then also operated the patients. Hence, it is possible that the use of the initially scheduled component size was "enforced" during surgery. However, severe post-surgery complications, *e.g.*, hip dislocation, periprosthetic fractures or stem loosening were reported in none of the 100 patients with digital planning and implantation. Conversely, a common sentiment in the literature is that planning should be performed by the operating surgeon[1,18], and this procedure has been propagated by the authors in those studies.

Moreover, an advancement of the digital two-dimensional planning is already underway using a three-dimensional CT. However, this method can expose patients to high levels of radiation and is probably not necessary for most THA patients with osteoarthritis[24]. In contrast, the addition of the a.p hip view confers a negligible radiation exposure of only 0.05 mSv. Because our study exclusively investigated cementless total hip arthroplasties, the results cannot be completely transferred to cemented THA or to other components. To date, it also remains unclear if the commonly occurring minor differences between planning and surgery cause long-term clinical consequences. Studies on this aspect are not available yet and are needed.

In conclusion, the digital planning of cementless THA performed by the surgeon based on additional antero-posterior hip view significantly increases the correlation between preoperative planning and eventual implant sizes. Therefore, we recommend that it should be implemented as a standard in preoperative planning.

COMMENTS

Background

Digital preoperative planning is an essential practice in total hip arthroplasty (THA). However, the accuracy is variable and often insufficient.

Research frontiers

The current research hotspot is the analysis and the improvement of preoperative planning in THA.

Innovations and breakthroughs

This case-control study could represent that digital THA planning performed by the operating surgeon and based on additional antero-posterior hip view increases the accuracy of preoperative planning in THA.

Applications

An additional antero-posterior hip view should be implemented as a standard in preoperative planning.

Peer-review

The authors present a nice prospective study about accuracy in digital planning of cementless total hip replacement.

REFERENCES

1 **The B**, Verdonschot N, van Horn JR, van Ooijen PM, Diercks RL. Digital versus analogue preoperative planning of total hip arthroplasties: a randomized clinical trial of 210 total hip arthroplasties. *J Arthroplasty* 2007; **22**: 866-870 [PMID: 17826278 DOI: 10.1016/j.arth.2006.07.013]

2 **Knight JL**, Atwater RD. Preoperative planning for total hip arthroplasty. Quantitating its utility and precision. *J Arthroplasty* 1992; **7** Suppl: 403-409 [PMID: 1431923 DOI: 10.1016/s0883-5403(07)80031-3]

3 **Bono JV**. Digital templating in total hip arthroplasty. *J Bone Joint Surg Am* 2004; **86-A** Suppl 2: 118-122 [PMID: 15691116]

4 **Efe T**, El Zayat BF, Heyse TJ, Timmesfeld N, Fuchs-Winkelmann S, Schmitt J. Precision of preoperative digital templating in total hip arthroplasty. *Acta Orthop Belg* 2011; **77**: 616-621 [PMID: 22187836]

5 **The B**, Diercks RL, van Ooijen PM, van Horn JR. Comparison of analog and digital preoperative planning in total hip and knee arthroplasties. A prospective study of 173 hips and 65 total knees. *Acta Orthop* 2005; **76**: 78-84 [PMID: 15788312 DOI: 10.1080/00016470510030364]

6 **Gamble P**, de Beer J, Petruccelli D, Winemaker M. The accuracy of digital templating in uncemented total hip arthroplasty. *J Arthroplasty* 2010; **25**: 529-532 [PMID: 19493647 DOI: 10.1016/j.arth.2009.04.011]

7 **Bunke J**, Delorme S, Kamm KF, Kooijman H, Lorenz A. Physical-technical principles of image creation. In: Schmidt T, Aichinger H, editors. Manual of diagnostic radiology. Radiation physics, radiation biology, radiation protection. Heidelberg: Springer, 2003: 1-159 [DOI: 10.1007/978-3-642-55825-2_1]

8 **Bertin KC**, Röttinger H. Anterolateral mini-incision hip replacement surgery: a modified Watson-Jones approach. *Clin Orthop Relat Res* 2004; **(429)**: 248-255 [PMID: 15577495 DOI: 10.1097/01.blo.0000150294.81825.8c]

9 **Dastane M**, Dorr LD, Tarwala R, Wan Z. Hip offset in total hip arthroplasty: quantitative measurement with navigation. *Clin Orthop Relat Res* 2011; **469**: 429-436 [PMID: 20844997 DOI: 10.1007/s11999-010-1554-7]

10 **Unnanuntana A**, Wagner D, Goodman SB. The accuracy of preoperative templating in cementless total hip arthroplasty. *J Arthroplasty* 2009; **24**: 180-186 [PMID: 18534455 DOI: 10.1016/j.arth.2007.10.032]

11 **Eggli S**, Pisan M, Müller ME. The value of preoperative planning for total hip arthroplasty. *J Bone Joint Surg Br* 1998; **80**: 382-390 [PMID: 9619923 DOI: 10.1302/0301-620x.80b3.7764]

12 **Miashiro EH**, Fujiki EN, Yamaguchi EN, Chikude T, Rodrigues LH, Fontes GM, Rosa FB. Preoperative planning of primary total hip arthroplasty using conventional radiographs. *Rev Bras Ortop* 2004; **49**: 140-148 [PMID: 26229790 DOI: 10.1016/j.rboe.2014.03.019]

13 **González Della Valle A**, Comba F, Taveras N, Salvati EA. The utility and precision of analogue and digital preoperative planning for total hip arthroplasty. *Int Orthop* 2008; **32**: 289-294 [PMID: 17404731 DOI: 10.1007/s00264-006-0317-2]

14 **Kirschner S**, Hamann C, Handreka S, Günther KP, Hartmann A. [Templating and radiological outcome monitoring for elective total hip arthroplasty. Applied quality management principles for safe patient care]. *Unfallchirurg* 2011; **114**: 776-785 [PMID: 21870133 DOI: 10.1007/s00113-011-2029-3]

15 **White SP**, Bainbridge J, Smith EJ. Assessment of magnification of digital pelvic radiographs in total hip arthroplasty using templating software. *Ann R Coll Surg Engl* 2008; **90**: 592-596 [PMID: 18831869 DOI: 10.1308/003588408X318101]

16 **Kniesel B**, Konstantinidis L, Hirschmüller A, Südkamp N, Helwig P. Digital templating in total knee and hip replacement: an analysis of planning accuracy. *Int Orthop* 2014; **38**: 733-739 [PMID: 24162155 DOI: 10.1007/s00264-013-2157-1]

17 **Franken M**, Grimm B, Heyligers I. A comparison of four systems for calibration when templating for total hip replacement with digital radiography. *J Bone Joint Surg Br* 2010; **92**: 136-141 [PMID: 20044692 DOI: 10.1302/0301-620x.92b1.22257]

18 **Bertz A**, Indrekvam K, Ahmed M, Englund E, Sayed-Noor AS. Validity and reliability of preoperative templating in total hip arthroplasty using a digital templating system. *Skeletal Radiol* 2012; **41**: 1245-1249 [PMID: 22588597 DOI: 10.1007/s00256-012-1431-4]

19 **Meermans G**, Malik A, Witt J, Haddad F. Preoperative radiographic assessment of limb-length discrepancy in total hip arthroplasty. *Clin Orthop Relat Res* 2011; **469**: 1677-1682 [PMID: 20878559]

20 **Tripuraneni KR**, Archibeck MJ, Junick DW, Carothers JT, White RE. Common errors in the execution of preoperative templating for primary total hip arthroplasty. *J Arthroplasty* 2010; **25**: 1235-1239 [PMID: 20022456 DOI: 10.1016/j.arth.2009.10.004]

21 **González Della Valle A**, Slullitel G, Piccaluga F, Salvati EA. The precision and usefulness of preoperative planning for cemented and hybrid primary total hip arthroplasty. *J Arthroplasty* 2005; **20**: 51-58 [PMID: 15660060 DOI: 10.1016/j.arth.2004.04.016]

22 **Lewinnek GE**, Lewis JL, Tarr R, Compere CL, Zimmerman JR. Dislocations after total hip-replacement arthroplasties. *J Bone Joint Surg Am* 1978; **60**: 217-220 [PMID: 641088]

23 **Kennedy JG**, Rogers WB, Soffe KE, Sullivan RJ, Griffen DG, Sheehan LJ. Effect of acetabular component orientation on recurrent dislocation, pelvic osteolysis, polyethylene wear, and component migration. *J Arthroplasty* 1998; **13**: 530-534 [PMID: 9726318 DOI: 10.1016/s0883-5403(98)90052-3]

24 **Steinberg EL**, Shasha N, Menahem A, Dekel S. Preoperative planning of total hip replacement using the TraumaCad™ system. *Arch Orthop Trauma Surg* 2010; **130**: 1429-1432 [PMID: 20069428 DOI: 10.1007/s00402-010-1046-y]

P- Reviewer: Anand A, Zak L **S- Editor**: Gong XM **L- Editor**: A **E- Editor**: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.36

World J Orthop 2017 January 18; 8(1): 36-41
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Retrospective Study

Heterotopic ossification after the use of recombinant human bone morphogenetic protein-7

Marianthi Papanagiotou, Zoe H Dailiana, Theophilos Karachalios, Sokratis Varitimidis, Michael Hantes, Georgios Dimakopoulos, Marianna Vlychou, Konstantinos N Malizos

Marianthi Papanagiotou, Zoe H Dailiana, Theophilos Karachalios, Sokratis Varitimidis, Michael Hantes, Konstantinos N Malizos, Department of Orthopaedic Surgery, Faculty of Medicine, University of Thessalia, 41500 Larissa, Greece

Georgios Dimakopoulos, Medical Statistics, Epirus Science and Technology Park, University of Ioannina Campus, 45500 Ioannina, Greece

Marianna Vlychou, Department of Radiology and Medical Imaging, Faculty of Medicine, University of Thessalia, 41500 Larissa, Greece

Author contributions: All the authors contributed to the manuscript.

Supported by The European Union (European Social Fund - ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF)-Research Funding Program: Heracleitus II.

Institutional review board statement: This study was reviewed and approved by the Educational Board of the University Hospital of Larissa, Greece.

Informed consent statement: Patients provided informed consent to receive the specific treatment. In the present study the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data on this topic are available.

Manuscript source: Invited manuscript

Correspondence to: Zoe H Dailiana, MD, PhD, Associate Professor, Department of Orthopaedic Surgery, Faculty of Medicine, University of Thessalia, 3 Panepistimiou St, Biopolis, 41500 Larissa, Greece. dailiana@med.uth.gr
Telephone: +30-24-13502722
Fax: +30-24-13501011

Received: June 13, 2016
Peer-review started: June 20, 2016
First decision: July 29, 2016
Revised: August 29, 2016
Accepted: October 25, 2016
Article in press: October 27, 2016
Published online: January 18, 2017

Abstract

AIM

To present the incidence of heterotopic ossification after the use of recombinant human bone morphogenetic protein-7 (rhBMP-7) for the treatment of nonunions.

METHODS

Bone morphogenetic proteins (BMPs) promote bone formation by auto-induction. Recombinant human BMP-7 in combination with bone grafts was used in 84 patients for the treatment of long bone nonunions. All patients were evaluated radiographicaly for the development of heterotopic ossification during the standard assessment for the nonunion healing. In all patients (80.9%) with radiographic signs of heterotopic ossification, a CT scan was performed. Nonunion site palpation and ROM evaluation of the adjacent joints

were also carried out. Factors related to the patient (age, gender), the nonunion (location, size, chronicity, number of previous procedures, infection, surrounding tissues condition) and the surgical procedure (graft and fixation type, amount of rhBMP-7) were correlated with the development of heterotopic ossification and statistical analysis with Pearsons χ^2 test was performed.

RESULTS

Eighty point nine percent of the nonunions treated with rhBMP-7, healed with no need for further procedures. Heterotopic bone formation occurred in 15 of 84 patients (17.8%) and it was apparent in the routine radiological evaluation of the nonunion site, in a mean time of 5.5 mo after the rhBMP-7 application (range 3-12). The heterotopic ossification was located at the femur in 8 cases, at the tibia in 6, and at the humerus in one patient. In 4 patients a palpable mass was present and only in one patient, with a para-articular knee nonunion treated with rhBMP-7, the size of heterotopic ossification affected the knee range of motion. All the patients with heterotopic ossification were male. Statistical analysis proved that patient's gender was the only important factor for the development of heterotopic ossification (P = 0.007).

CONCLUSION

Heterotopic ossification after the use of rhBMP-7 in nonunions was common but it did not compromise the final clinical outcome in most cases, and affected only male patients.

Key words: Nonunion; Bone morphogenetic protein; Recombinant human bone morphogenetic protein-7; Heterotopic ossification; Long bone; Bone graft; Osteoinduction

Core tip: Bone morphogenetic proteins are identified as factors promoting osteogenesis. In this study an attempt was made to estimate the rate of heterotopic bone formation in patients with long bone nonunions treated with recombinant human bone morphogenetic protein-7 (rhBMP-7), and to identify predisposing factors, related to the patient, the nonunion characteristics, and the surgical procedure. Eighteen percent of the patients developed heterotopic ossification on the radiographs, without functional limitations. All patients that developed heterotopic ossification were male. This rate of heterotopic ossification after rhBMP-7 use for the treatment of long bone nonunions is higher than the rates reported in literature.

Papanagiotou M, Dailiana ZH, Karachalios T, Varitimidis S, Hantes M, Dimakopoulos G, Vlychou M, Malizos KN. Heterotopic ossification after the use of recombinant human bone morphogenetic protein-7. *World J Orthop* 2017; 8(1): 36-41 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/36.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.36

INTRODUCTION

Heterotopic ossification is commonly complicating orthopaedic procedures and trauma but its highest incidence occurs after brain injuries. The hip, the elbow, and the knee are the most commonly affected joints after muscle damage, intramuscular hematoma and brain trauma[1-7]. Depending on the site and the location of the heterotopic bone, it may interfere with muscle and tendon function and limit the range of joint motion[3,4]. In experimental models, heterotopic bone is induced after implantation of bone marrow cells in muscle or in the peritoneal cavity[7] and allo-transplatation of demineralized bone matrix[8]. The later is linked to the activity of Bone Morphogenetic Proteins (BMPs) as factors promoting osteogenesis by auto-induction in extra-skeletal sites, as described by Urist *et al*[8].

Since their identification BMPs have been isolated and experimentally applied in several preclinical models. Recombinant (rh) forms are available for two of the BMPs (rhBMP-2 and rhBMP-7), and have been licensed by the american food and drug administration for clinical use in tibia nonunions (rhBMP-7)[9-11], and acute tibia fractures (rhBMP-2)[12,13]. Although the formation of heterotopic bone after the rhBMPs application in experimental animal models is well known[14], only a few reports confirm these findings in the clinical practice.

The aim of our study is to describe the development of heterotopic ossification in a series of 84 patients with long bone nonunions treated with bone graft and rhBMP-7, and to identify risk factors related to the patient, the nonunion and the surgical procedure.

MATERIALS AND METHODS

Eighty-four patients (60 men and 24 women), with long bone nonunions treated with the combination of bone grafts and rhBMP-7 (Osigraft, Stryker Pharmaceutical) between 2004 and 2008[15] were evaluated for the development of heterotopic ossification. Nonunions were located in the upper (13) and lower (71) extremity and all patients had undergone at least one previous failed procedure for the treatment of the nonunion. The product used consisted of 3.3 mg of lyophilized rhBMP-7 combined with 6.7 mg of type I bovine collagen. The standard surgical procedure consisted of debridement of the nonunion site till normal viable bone margins. RhBMP-7 was applied mixed with bone grafts[15]. After rhBMP-7 implantation, irrigation was avoided, so as to prevent product leakage at the surrounding tissues.

Heterotopic ossification was diagnosed as a delayed postoperative complication, during the standard postoperative radiographic evaluation for the assessment of healing of the nonunion. The efficacy of rhBMP-7 on the treatment of long bone nonunions, in this series

Figure 1 Heterotopic ossification in a 28-year-old male patient treated for femoral nonunion (3D CT reconstruction).

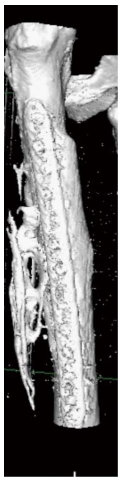


Figure 2 Heterotopic ossification in a 51-year-old male patient treated for femoral nonunion (3D CT reconstruction).

of patients, has already been published in a previous study[15]. In all patients with apparent signs of heterotopic bone formation on the radiographs, a quantitative computed tomography (Q-CT) and 3D-CT reconstruction (employing Osirix software) were obtained to confirm the diagnosis. The patients with heterotopic ossification were additionally evaluated clinically by palpation and examination of the range of motion of the adjacent joints.

Factors related to the patient (age, gender), the nonunion (location, size, chronicity, number of previous failed procedures, presence of infection, and condition of the surrounding soft tissues) and the type of the index surgical procedure (type of graft and amount of rhBMP-7 used), were also analyzed and correlated with the presence of heterotopic ossification.

Statistical analysis was performed with the Pearson χ^2 test and with a logistic regression model under Firth's correction (Stata version 10).

RESULTS

Heterotopic bone formation was diagnosed as a delayed complication within the first postoperative year in 15 patients (17.8%) (Figures 1-3). All patients were male (Figure 4) and the mean time to heterotopic ossification radiographic appearance was 5.5 mo (3 to 12 mo) after the index procedure. The heterotopic ossification was located at the lower extremity in 14 cases, 6 of them at the tibia and in 8 at the femur. In one case heterotopic ossification developed in a patient with a humeral nonunion. The ectopic bone was palpable in 4 patients, but only one had a limitation of the range of motion after the treatment of a para-articular distal femoral nonunion. This patient developed a significant restriction of flexion and extension of the knee joint (Figure 3).

The results were presented with the use of means and standard deviations or counts and percentages, where appropriate. The effect of categorical variables on the main outcome was examined with the use of the χ^2 test, while the effect of scale variables with the use of the *t* test for independent samples or the Mann-Whitney test where normality did not hold, after implementation of the Shapiro Wilk test. The variables were then used in a logistic regression model under Firth's correction. Significance was in all cases set at 0.05. The analysis was carried out with the use of the software Stata v.10.0.

Statistical analysis with the use of χ^2 test, proved that patient's gender was the only factor significantly correlating with the development of heterotopic ossification with statistical significance (P = 0.007) (Table 1 and Figure 4), while no other parameter had any effect on the development of this complication. The logistic regression model which was used, under Firth's correction, did not show any parameter significantly affecting heterotopic bone formation, probably due to the small number of patients who developed this complication (Table 1).

DISCUSSION

The incidence of heterotopic bone formation in this series is relatively high (17.8%), but in the majority of cases (14 of 15) it did not compromise the functional outcome of the limb. This high incidence may be attributed to the preexisting muscle trauma and extensive excision of the scar at the site of rhBMP-7 application, as these patients had undergone several operations prior to the index procedure. It has been demonstrated that repeated blunt trauma in the extremities, may induce degenerative changes in the muscle predisposing to ectopic bone formation[3,7,16].

The development of heterotopic ossification has been studied in several experimental models, however the exact pathophysiology of this process has not been completely elucidated. According to the rhBMP-7 commercial product's safety database, the rate of undesirable effects (erythema, tenderness swelling and

Table 1 Analysis of the parameters affecting the development of heterotopic ossification

Parameter		No. of patients	HO	HO rate (%)	*P* value (χ^2)	*P* value (logistic regression firth's correction)
Gender	Male	60	15	25		
	Female	24	0	0.0	0.007	0.081
	⩽ 30	20	6	30.0		
Age	31-55	39	8	20.5	0.067	0.205
	⩾ 56	25	1	4.0		
Extremity	Upper	13	1	7.7		
	Lower	71	14	19.7	0.298	0.733
Defect size	Critical	42	8	19.0		
	Non critical	42	7	16.0	0.776	0.997
Chronicity	> 1 yr	33	4	12.1		
	< 1 yr	51	11	20.3	0.229	0.731
Infection	Yes	30	4	13.3		
	No	54	11	20.3	0.420	0.451
Soft tissue defects	Yes	9	3	33.3		
	No	75	12	16.0	0.200	0.287
Previous procedures	1	56	8	14.3		
	2-3	28	7	25.0	0.227	0.315
Graft type	Autograft	67	13	19.4		
	Allograft	9	0	0	0.463	0.663
	No graft	8	2	25.0		
Amount of rhBMP-7	1 vial	75	14	18.6		
	2 vials	9	1	11.1	0.576	0.629

P values with the use of χ^2 test and with the use of logistic regression model under Firth's correction. HO: Heterotopic ossification; rhBMP-7: Recombinant human bone morphogenetic protein-7.

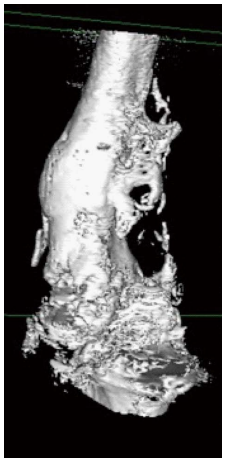


Figure 3 Heterotopic ossification in a para-articular femoral nonunion in a 44-year-old male patient, affecting knee joint range of motion (3D CT reconstruction).

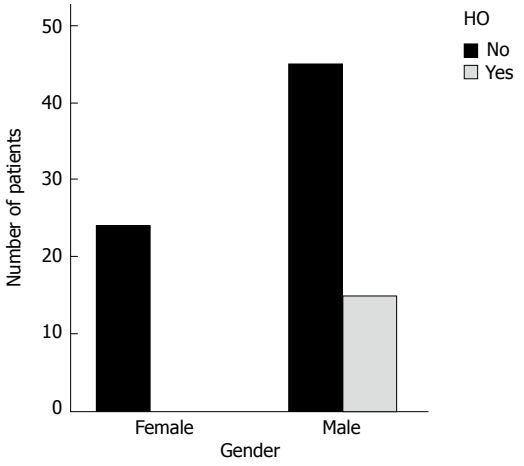


Figure 4 Gender effect on the development of heterotopic ossification after the use of recombinant human bone morphogenetic protein-7.

ectopic ossification) ranges from 1% to 10%[17].

Male gender significantly influenced the appearance of heterotopic bone. In a study evaluating the osteogenic capacity of mice skeletal muscle-derived stem cells (MDSCs), the male MDSCs revealed significantly greater ALP activity and expression of osteogenic genes when stimulated with rhBMP-4 *in vitro*. In addition, the implantation of these cells into intramuscular pockets in the mice led to more bone formation in the male mice compared to the female regardless of the implanted cells gender[18]. In a recent study in mice with cranial defect treated with MDSCs after transduction with a retrovirus encoding BMP-4, male mice demonstrated more rapid bone formation and larger volumes of ectopic bone than female[19]. These findings suggest a specific effect of the gender in the heterotopic ossification development.

The potential of mesenchymal progenitor cells to differentiate into osteoprogenitor cells in muscles, has been shown in animal models[20-22]. In a resent *in vitro* study human skeletal muscle-derived progenitor cells have been isolated and characterized for their osteogenic properties indicating a potential effect on heterotopic bone formatio[23]. These cells were identified as PDGFRα^+ cells, able to differentiate into

osteoprogenitor cells under the stimulation of bone morphogenetic proteins in mice[21]. The role of BMPs in the heterotopic bone formation has also been elucidated in the fibrodysplasia ossificans progressiva, where BMPs were found to promote muscle mesenchymal stem cells differentiation in preosteoblasts and osteoblasts[24].

Since 2001, when the use of rhBMP-7 was approved by the American Food and Drug Administration and the European Medicines Agency (European Marketing Authorization Number: EU/1/01/179/001) for the treatment of tibia nonunions, its use was extended to skeletal nonunions and spinal fusions with successful outcomes presented in several series[25-27]. Although rhBMP-7 has been widely used in the clinical practice, only few cases of heterotopic bone formation were reported in the literature after 2006. A case of myositis ossificans in a 49-year old woman, who underwent L4-L5 decompression and fusion with the use of rhBMP-7 was presented by Bennet *et al*[28]. The first case of heterotopic ossification in a long bone (distal humerus nonunion) after the use of rhBMP-7 was reported by Wysocki *et al*[29]. The patient gradually developed elbow stiffness from an extensive heterotopic ossification in the triceps muscle. Another small series of four patients that developed heterotopic ossification after the use of rhBMP-7 (3 patients) and rhBMP-2 (one patient) for the treatment of acute fractures or nonunions of the humerus was presented by Axelrad *et al*[30]. All patients had painful restriction of motion and underwent surgical excision of the heterotopic bone with good postoperative outcome. Heterotopic ossification after the use of rhBMP-7 for the treatment of femoral head osteonecrosis was also reported. In this case, it series the majority of patients developed heterotopic ossification at the lateral surface of the femur around the entry point of core decompression and fibula insertion, which, however, did not affect the range of motion[31].

The main limitation of this study is the lack of a control group of patients who did not received rhBMP-7. As all patients had several previous unsuccessful surgical procedures, the treating physicians decided to use all available means to treat the nonunions and considered unethical the deprivation of rhBMP-7 in the patients of a control group.

In conclusion, heterotopic ossification following the use of rhBMP-7 for the treatment of long bone non-unions was a relatively common complication. Also, a positive correlation between the male gender and the development of this side effect was found. Careful observation of postoperative radiographs may increase the reported heterotopic ossification rates in the literature as the majority of cases lack clinical relevance.

ACKNOWLEDGMENTS

Dr. Konstantinos Kokkinis: Chairman at the Department of Computed Tomography KAT Hospital Athens, Greece.

COMMENTS

Background

Bone morphogenetic proteins (BMPs) have been identified as factors promoting osteogenesis by auto-induction in extra-skeletal sites. In the recent years they have been used in the treatment of long bone nonunions in combination with bone grafts. In this study, the rate of heterotopic ossification occurring after the use of commercially available recombinant human bone morphogenetic protein-7 (rhBMP-7) for the treatment of long bone nonunions was estimated. In addition, the correlation between the development of heterotopic ossification and factors related to the patient (age, gender), the nonunion (location, size, chronicity, previous procedures, infection, surrounding tissues condition), and the surgical procedure (graft type, amount of rhBMP-7) was evaluated.

Research frontiers

BMPs and especially rhBMP-2 and rhBMP-7 have been used in several clinical studies but there are only few reported data related to the complications related to their use.

Innovations and breakthroughs

In this study, heterotopic ossification was a relatively common complication of the use of rhBMP-7, with higher rates than the ones reported in literature. In addition, a significant correlation between patient's gender and the development of this complication was found.

Applications

This study suggests that heterotopic ossification is a relatively common complication after the use of rhBMP-7 for the treatment on nonunions, related significantly with patient's gender. Although not clinically significant in the majority of cases, this complication should be acknowledged to the patients, especially the male, before rhBMP-7 use.

Terminology

rhBMP-7: Recombinant human bone morphogenetic protein-7; HO: Heterotopic ossification.

Peer-review

The rate of heterotopic ossification after the use of rhBMP-7 was higher in the present series than the rates reported in the literature and a significant correlation between male gender and the development of this complication was found. The lack of any clinical relevance of this complication in the vast majority of cases may be the reason of the low reported rates up to now. Thus, careful evaluation of postoperative radiographs may increase the reported rates.

REFERENCES

1 **Rath E**, Sherman H, Sampson TG, Ben Tov T, Maman E, Amar E. The incidence of heterotopic ossification in hip arthroscopy. *Arthroscopy* 2013; **29**: 427-433 [PMID: 23351728 DOI: 10.1016/j.arthro.2012.10.015]

2 **Neal B**, Gray H, MacMahon S, Dunn L. Incidence of heterotopic bone formation after major hip surgery. *ANZ J Surg* 2002; **72**: 808-821 [PMID: 12437693 DOI: 10.1046/j.1445-2197.2002.02549.x]

3 **Dailiana ZH**, Gunneson EE, Urbaniak JR. Heterotopic ossification after treatment of femoral head osteonecrosis with free vascularized fibular graft. *J Arthroplasty* 2003;**18**: 83-88 [PMID: 12555188 DOI: 10.1054/arth.2003.50000]

4 **Solomon L**, Warwick DJ, Nayagam S. Apley' system of orthopaedic and fractures, 8th edition

5 **Keschner MT**, Paksima N. The stiff elbow. *Bull NYU Hosp Jt Dis* 2007; **65**: 24-28 [PMID: 17539758]

6 **Ilahi OA**, Strausser DW, Gabel GT. Post-traumatic heterotopic ossification about the elbow. *Orthopedics* 1998; **21**: 265-268 [PMID: 9547811]

7 **Ekelund A**, Brosjö O, Nilsson OS. Experimental induction of heterotopic bone. *Clin Orthop Relat Res* 1991; **2**: 102-112 [PMID:

1899633 DOI: 10.1097/00003086-199102000-00011]
8 **Urist MR**. Bone: formation by autoinduction. *Science* 1965; **150**: 893-899 [PMID: 5319761 DOI: 10.1126/science.150.3698.893]
9 **Friedlaender GE**, Perry CR, Cole JD, Cook SD, Cierny G, Muschler GF, Zych GA, Calhoun JH, LaForte AJ, Yin S. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. *J Bone Joint Surg Am* 2001; **83-A** Suppl 1: S151-S158 [PMID: 11314793]
10 **Ristiniemi J**, Flinkkilä T, Hyvönen P, Lakovaara M, Pakarinen H, Jalovaara P. RhBMP-7 accelerates the healing in distal tibial fractures treated by external fixation. *J Bone Joint Surg Br* 2007; **89**: 265-272 [PMID: 17322450 DOI: 10.1302/0301-620X.89B2.18230]
11 **Kanakaris NK**, Calori GM, Verdonk R, Burssens P, De Biase P, Capanna R, Vangosa LB, Cherubino P, Baldo F, Ristiniemi J, Kontakis G, Giannoudis PV. Application of BMP-7 to tibial non-unions: a 3-year multicenter experience. *Injury* 2008; **39** Suppl 2: S83-S90 [PMID: 18804578 DOI: 10.1016/S0020-1383(08)70019-6]
12 **Govender S**, Csimma C, Genant HK, Valentin-Opran A, Amit Y, Arbel R, Aro H, Atar D, Bishay M, Börner MG, Chiron P, Choong P, Cinats J, Courtenay B, Feibel R, Geulette B, Gravel C, Haas N, Raschke M, Hammacher E, van der Velde D, Hardy P, Holt M, Josten C, Ketterl RL, Lindeque B, Lob G, Mathevon H, McCoy G, Marsh D, Miller R, Munting E, Oevre S, Nordsletten L, Patel A, Pohl A, Rennie W, Reynders P, Rommens PM, Rondia J, Rossouw WC, Daneel PJ, Ruff S, Rüter A, Santavirta S, Schildhauer TA, Gekle C, Schnettler R, Segal D, Seiler H, Snowdowne RB, Stapert J, Taglang G, Verdonk R, Vogels L, Weckbach A, Wentzensen A, Wisniewski T. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg Am* 2002; **84-A**: 2123-2134 [PMID: 12473698]
13 **Aro HT**, Govender S, Patel AD, Hernigou P, Perera de Gregorio A, Popescu GI, Golden JD, Christensen J, Valentin A. Recombinant human bone morphogenetic protein-2: a randomized trial in open tibial fractures treated with reamed nail fixation. *J Bone Joint Surg Am* 2011; **93**: 801-808 [PMID: 21454742 DOI: 10.2106/JBJS.I.01763]
14 **Love DA**, Lietman SA. The effect of osteogenic protein-1 dosing regimen on ectopic bone formation. *Clin Orthop Relat Res* 2004; **(423)**: 264-267 [PMID: 15232460 DOI: 10.1097/01.blo.0000129161.54751.8c]
15 **Papanagiotou M**, Dailiana ZH, Karachalios T, Varitimidis S, Vlychou M, Hantes M, Malizos KN. RhBMP-7 for the treatment of nonunion of fractures of long bones. *Bone Joint J* 2015; **97-B**: 997-1003 [PMID: 26130359 DOI: 10.1302/0301-620X.97B7.35089]
16 **Mavrogenis AF**, Soucacos PN, Papagelopoulos PJ. Heterotopic ossification revisited. *Orthopedics* 2011; **34**: 177 [PMID: 21410128 DOI: 10.3928/01477447-20110124-08]
17 **European Medicines Agency**. Osigraft summary of product Characteristics. Available from: URL: http//www.ema.europa.eu last updated 15/05/2014
18 **Zaccalini PS**, Urist MR. Traumatic periosteal proliferations in rabbits. the enigma of experimental myositis ossificans traumatica. *J Trauma*1964; **4**: 344-357 [PMID: 14170156]
19 **Corsi KA**, Pollett JB, Phillippi JA, Usas A, Li G, Huard J. Osteogenic potential of postnatal skeletal muscle-derived stem cells is influenced by donor sex. *J Bone Miner Res* 2007; **22**: 1592-1602 [PMID: 17605633 DOI: 10.1359/jbmr.070702]
20 **Meszaros LB**, Usas A, Cooper GM, Huard J. Effect of host sex and sex hormones on muscle-derived stem cell-mediated bone formation and defect healing. *Tissue Eng Part A* 2012; **18**: 1751-1759 [PMID: 22712541 DOI: 10.1089/ten.TEA.2011.0448]
21 **Uezumi A**, Fukada S, Yamamoto N, Takeda S, Tsuchida K. Mesenchymal progenitors distinct from satellite cells contribute to ectopic fat cell formation in skeletal muscle. *Nat Cell Biol* 2010; **12**: 143-152 [PMID: 20081842 DOI: 10.1038/ncb2014]
22 **Uezumi A**, Ito T, Morikawa D, Shimizu N, Yoneda T, Segawa M, Yamaguchi M, Ogawa R, Matev MM, Miyagoe-Suzuki Y, Takeda S, Tsujikawa K, Tsuchida K, Yamamoto H, Fukada S. Fibrosis and adipogenesis originate from a common mesenchymal progenitor in skeletal muscle. *J Cell Sci* 2011; **124**: 3654-3664 [PMID: 22045730 DOI: 10.1242/jcs.086629]
23 **Oishi T**, Uezumi A, Kanaji A, Yamamoto N, Yamaguchi A, Yamada H, Tsuchida K. Osteogenic differentiation capacity of human skeletal muscle-derived progenitor cells. *PLoS One* 2013; **8**: e56641 [PMID: 23457598 DOI: 10.1371/journal.pone.0056641]
24 **Billings PC**, Fiori JL, Bentwood JL, O'Connell MP, Jiao X, Nussbaum B, Caron RJ, Shore EM, Kaplan FS. Dysregulated BMP signaling and enhanced osteogenic differentiation of connective tissue progenitor cells from patients with fibrodysplasia ossificans progressiva (FOP). *J Bone Miner Res* 2008; **23**: 305-313 [PMID: 17967130 DOI: 10.1359/jbmr.071030]
25 **Dimitriou R**, Dahabreh Z, Katsoulis E, Matthews SJ, Branfoot T, Giannoudis PV. Application of recombinant BMP-7 on persistent upper and lower limb non-unions. *Injury* 2005; **36** Suppl 4: S51-S59 [PMID: 16291324 DOI: 10.1016/j.injury.2005.10.010]
26 **Bong MR**, Capla EL, Egol KA, Sorkin AT, Distefano M, Buckle R, Chandler RW, Koval KJ. Osteogenic protein-1 (bone morphogenic protein-7) combined with various adjuncts in the treatment of humeral diaphyseal nonunions. *Bull Hosp Jt Dis* 2005; **63**: 20-23 [PMID: 16536213]
27 **Leach J**, Bittar RG. BMP-7 (OP-1) safety in anterior cervical fusion surgery. *J Clin Neurosci* 2009; **16**: 1417-1420 [PMID: 19665382 DOI: 10.1016/j.jocn.2009.02.012]
28 **Bennett M**, Reynolds AS, Dickerman RD. Recent article by Shields et al titled "adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 use in anterior cervical spine fusion". *Spine* (Phila Pa 1976) 2006; **31**: 2029-2030 [PMID: 16924224 DOI: 10.1097/01.brs.0000229387.20297.b1]
29 **Wysocki RW**, Cohen MS. Ectopic ossification of the triceps muscle after application of bone morphogenetic protein-7 to the distal humerus for recalcitrant nonunion: a case report. *J Hand Surg Am* 2007; **32**: 647-650 [PMID: 17482003 DOI: 10.1016/j.jhsa.2007.03.001]
30 **Axelrad TW**, Steen B, Lowenberg DW, Creevy WR, Einhorn TA. Heterotopic ossification after the use of commercially available recombinant human bone morphogenetic proteins in four patients. *J Bone Joint Surg Br* 2008; **90**: 1617-1622 [PMID: 19043134 DOI: 10.1302/0301-620X.90B12.20975]
31 **Papanagiotou M**, Malizos KN, Vlychou M, Dailiana ZH. Autologous (non-vascularised) fibular grafting with recombinant bone morphogenetic protein-7 for the treatment of femoral head osteonecrosis: preliminary report. *Bone Joint J* 2014; **96-B**: 31-35 [PMID: 24395307 DOI: 10.1302/0301-620X.96B1.32773]

P- Reviewer: Emara KM, Frenkel B, Zhao JW **S- Editor**: Qiu S
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.42

World J Orthop 2017 January 18; 8(1): 42-48
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Retrospective Study

Unhappy triad in limb reconstruction: Management by Ilizarov method

Barakat Sayed El-Alfy

Barakat Sayed El-Alfy, Orthopedic Department, Mansoura University Hospital, Mansoura City 35516, Egypt

Author contributions: El-Alfy BS performed the surgery in all cases, designed the study and wrote the paper.

Institutional review board statement: The study was approved by the ethical committee in our institution.

Informed consent statement: All patients gave their informed consent before being included in the study.

Conflict-of-interest statement: The author has no conflict of interest.

Data sharing statement: No available data sharing.

Manuscript source: Invited manuscript

Correspondence to: Barakat Sayed El-Alfy, MD, Assistant Professor, Orthopedic Department, Mansoura University Hospital, Elgomhorya Street, Mansoura City 35516, Egypt. barakatelalfy@yahoo.com
Telephone: +20-50-233480

Received: April 25, 2016
Peer-review started: April 26, 2016
First decision: July 5, 2016
Revised: August 8, 2016
Accepted: August 27, 2016
Article in press: August 29, 2016
Published online: January 18, 2017

Abstract

AIM

To evaluate the results of the Ilizarov method in management of cases with bone loss, soft tissue loss and infection.

METHODS

Twenty eight patients with severe leg trauma complicated by bone loss, soft tissue loss and infection were managed by distraction osteogenesis in our institution. After radical debridement of all the infected and dead tissues the Ilizarov frame was applied, corticotomy was done and bone transport started. The wounds were left open to drain. Partial limb shortening was done in seven cases to reduce the size of both the skeletal and soft tissue defects. The average follow up period was 39 mo (range 27-56 mo).

RESULTS

The infection was eradicated in all cases. All the soft tissue defects healed during bone transport and plastic surgery was only required in 2 cases. Skeletal defects were treated in all cases. All patients required another surgery at the docking site to fashion the soft tissue and to cover the bone ends. The external fixation time ranged from 9 to 17 mo with an average of 13 mo. The complications included pin tract infection in 16 cases, wire breakage in 2 cases, unstable scar in 4 cases and chronic edema in 3 cases. According to the association for study and application of methods of Ilizarov score the bone results were excellent in 10, good in 16 and fair in 2 cases while the functional results were excellent in 8, good in 17 and fair in 3 cases.

CONCLUSION

Distraction osteogenesis is a good method that can treat the three problems of this triad simultaneously.

Key words: Ilizarov methods; Bone defect; Soft tissue

reconstruction; Open bone transport

Core tip: Bone and soft tissue loss represent a true challenge for both the orthopedic and plastic surgeons. The presence of bone and soft tissue infection further complicates limb reconstruction. In this study a series of 28 patients with severe lower limb trauma were managed by the Ilizarov method without the need for major plastic surgery. The results were encouraging.

El-Alfy BS. Unhappy triad in limb reconstruction: Management by Ilizarov method. *World J Orthop* 2017; 8(1): 42-48 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/42.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.42

INTRODUCTION

Bone loss represents a true challenge for orthopedic surgeons. Soft tissue loss may complicate the condition and makes reconstruction more difficult. Bone infection may further complicate the condition and makes reconstruction extremely difficult[1-4]. So, the triad of bone loss, soft tissue loss and infection is considered to be an unhappy triad in the field of limb reconstruction. In the presence of this triad the scope for reconstruction becomes very narrow and amputation may be the end result.

It is important to restore a healthy soft tissue envelope for proper treatment of this complex problem. This could be done by major plastic surgery in the form of local myocutaneous flaps, or free flaps. But, in the presence of infection the chance for success of these plastic surgeries becomes very limited[5,6]. During distraction osteogenesis all the tissues are lengthened including the bone, vessels, nerves, muscles and skin. This gradual lengthening may lead to spontaneous closure of the soft tissue defects without the need for plastic surgery[7-9].

The aim of this study is to evaluate the results of distraction osteogenesis in management of cases with severe leg trauma complicated by bone loss, soft tissue loss and infection.

MATERIALS AND METHODS

Between April 2007 and Jun 2014, twenty eight patients with bone loss, soft tissue loss and infection were treated by distraction osteogenesis in our institution. The average age of the patients was 37 years (range: 16-58 years). There were 23 males and 5 females. The etiology of this complex problem was trauma sequelae in all of the cases. Plastic surgery was performed in 12 cases but it failed because of infection. After radical debridement, the average size of the skeletal defects was 8 cm (range: 6 to 14 cm) and the soft tissue defects ranged from 3 cm × 4 cm to 6 cm × 11 cm, with an average of 5 cm × 7 cm. The defects were located in the proximal third of the leg in 6 patients, middle third in 13 patients and distal third in 9 patients. All cases were infected with an active discharge. The ethical committee in our institution approved this study. Informed consent was taken from the patients before being included in the study. Under general or spinal anesthesia, the infected and dense fibrous tissues were excised. The infected and necrotic bone ends were debrided down to a healthy bleeding surface. Further debridement of the exposed bone ends was done until they became well covered by the skin and soft tissue. The Ilizarov frame was applied and corticotomy was performed in a healthy bone segment. The wounds were left open to drain (Figure 1). Physiotherapy was started early in the postoperative period to avoid joint contracture. It involved isometric contraction of the quadriceps muscles, active and passive range of movement and stretching exercises for the hamstring and gastrocsoleous complex. Bone transport was started after a latent period of about one week. Patients were discharged after an average of 8 d and followed up regularly in the outpatient clinic. During bone transport the bone segment carries its surrounding soft tissues with it and the soft tissue defects gradually close. As transport is done without sufficient soft tissue coverage it is called open bone transport. At the time of docking the skin becomes incarcerated between the bone ends (Figure 1D). At this stage the patient is taken to theater again where the soft tissue is removed from the docking site and the skin is fashioned to cover the bone ends. Transverse skin incision is preferred in this step to facilitate skin closure. It was made along the bone ends of the proximal and distal fragments. The incision was deepened down to the bone and the soft tissues were removed from the docking site. The bone ends were freshened and compressed against each other by the frame. This compression approximates the skin edges together and facilitates their closure over the bone ends (Figure 2). Bone graft was done at this time to stimulate bone healing in 15 cases. Partial limb shortening was done in 7 cases to reduce the size of both the soft tissue and bone gaps. After docking, bone lengthening was continued to equalize the limb lengths in those cases.

The frame was removed after healing of the docking site and full maturation of the regenerated bone. The average follow up period was 39 mo (range: 27 to 56 mo). The results were evaluated according to the association for study and application of methods of Ilizarov (ASAMI) scoring system[10]. In this system the results are divided into bone results and functional results. The bone results are evaluated according to union, infection, deformity and limb length discrepancy while the functional results are evaluated according to daily activities, joint stiffness, limp, pain and presence of

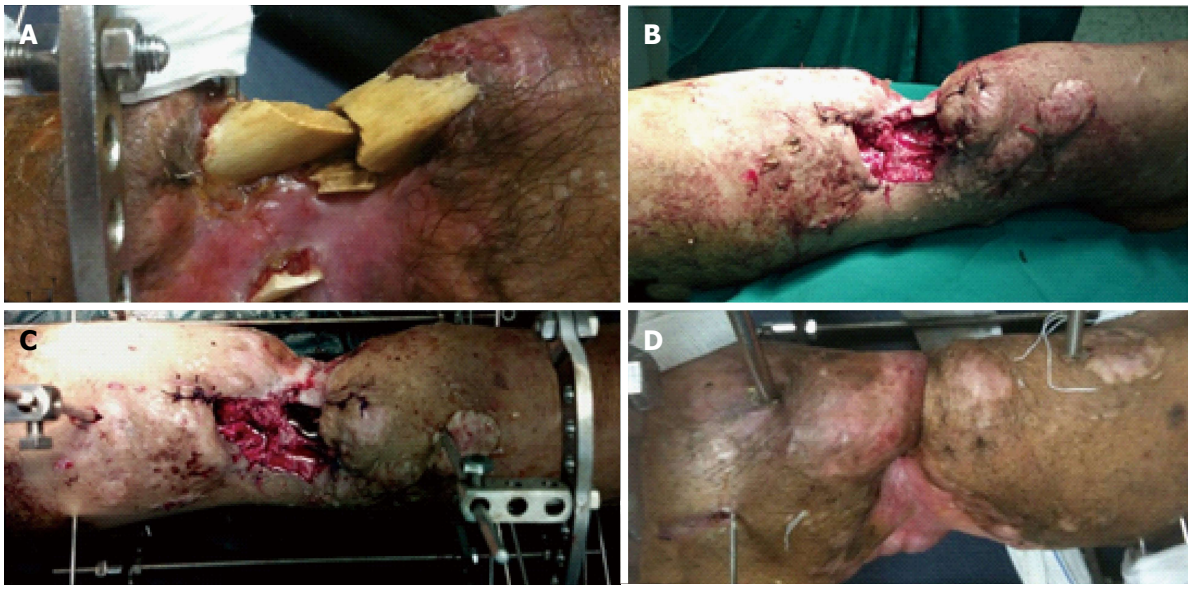


Figure 1 Surgical technique. The infected and necrotic bones are excised (A) and further debridement of the bone ends is done until they recessed under the skin and soft tissues (B); C: The Ilizarov frame is applied and bone transport started; D: At the time of docking the skin is invaginated between the bone ends.

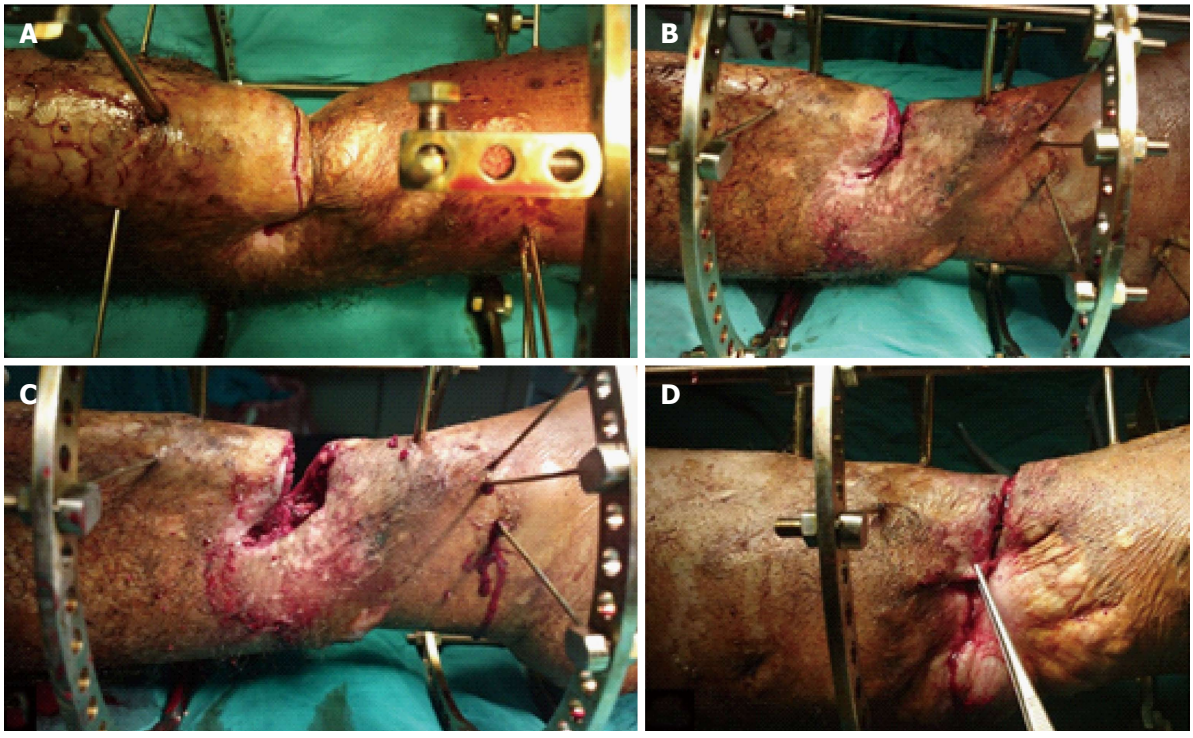


Figure 2 Management of the docking site. A: Transverse skin incision is made along the bone ends at the docking site; B: The incision is deepened down to the bone and the soft tissues are removed from the docking site; C: The bone ends are freshened and compressed against each other by the frame; D: This compression approximates the skin edges together and facilitates their closure over the bone ends.

reflex sympathetic dystrophy.

RESULTS

The infection was eradicated in all of the cases. All the soft tissue defects healed during the process of bone transport and plastic surgery was only required in two cases. Bone defects were bridged in all cases (Figure 3). All patients required another surgery at the time of docking to fashion the soft tissue and to cover the bone ends. The docking sites united without the need for bone graft in 13 cases and with bone graft in 15 cases. The average time of external fixation was 13 mo (range: 9 to 17 mo). The complications in this study were pin tract infection in 16 cases (treated by local care and oral antibiotics), wire breakage in 2 cases (treated by reinsertion of new wires), unstable scar in 4 cases and chronic edema in 3 cases. The limb length discrepancy

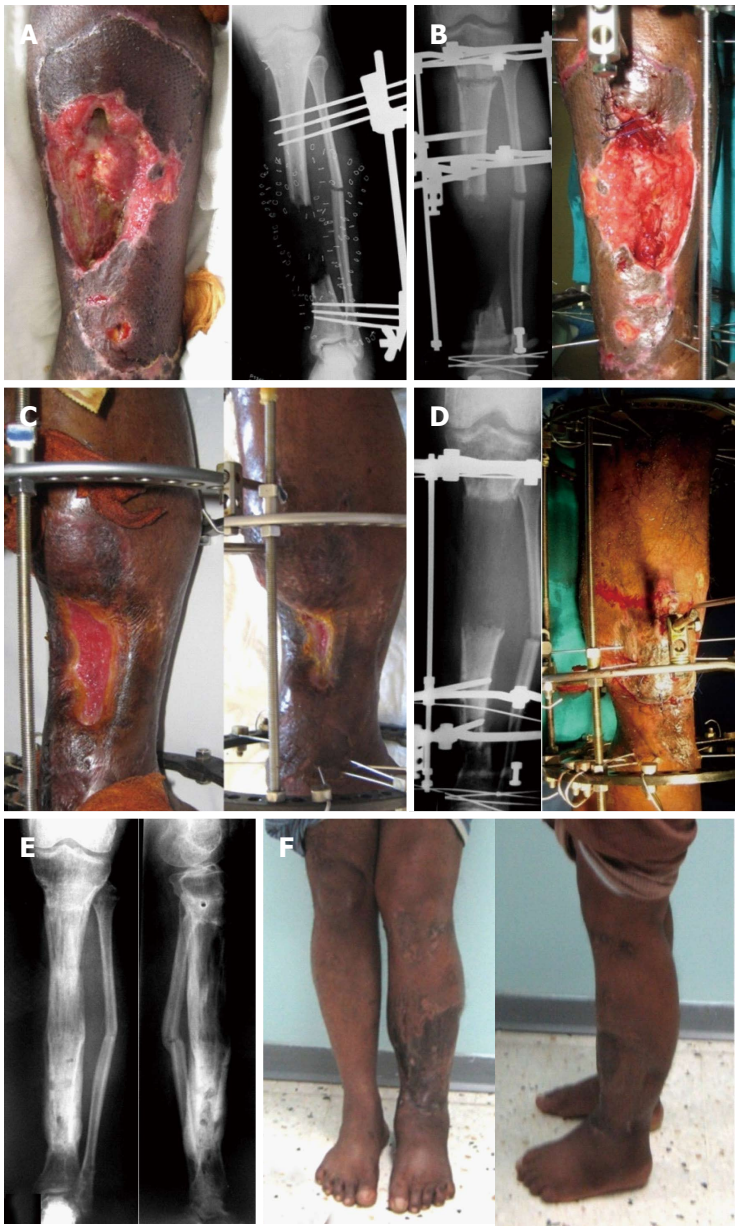


Figure 3 Middle third bone and soft tissue defects. A: Forty-seven year old male patient with combined bone loss, soft tissue loss and infection of his left leg as a complication of an open fracture of the tibia and fibula; B: Debridement of the bone ends was done, Ilizarov frame applied and bone transport started; C: During bone transport the soft tissue defect gradually closes; D: At the time of docking the skin was fashioned over the bone ends; E: After removal of the frame with good bone healing; F: The patient with good alignment and complete healing of the soft tissue.

did not exceed 2.5 cm except in one case. No cases were complicated by amputation or reflex sympathetic dystrophy. Using the ASAMI scoring system, the bone results were excellent in 10, good in 16 and fair in 2 cases while the functional results were excellent in 8, good in 17 and fair in 3 cases.

DISCUSSION

The tibia is the most common site for open fracture of the long bones due to its anatomic location and scanty soft tissue coverage. Also it is more liable for complications due to its poor blood supply. These complications include soft tissue necrosis, bone loss and infection[11-13]. Successful treatment of the soft tissue loss is vital for bone healing. This could be done by free or local myocutaneous flaps. But, in certain situations these major plastic surgeries may be not feasible or they may endanger the limb survival. These conditions include severe infection and local vascular problems. In the presence of infection the chance for success of plastic surgery is limited and additional surgery may be required to control infection prior to the major plastic surgery[5,14,15]. After severe trauma some limbs may be left with only one blood vessel and if it is used as a feeding artery for the graft this may threaten the limb life. In case of failure of these surgeries the choice between amputation and another modality of reconstruction should be made.

In this study, 28 patients with the complex problem of bone loss, soft tissue loss and infection were treated by the Ilizarov method with satisfactory results in most of them. All the wounds healed during bone transport and plastic surgery was only required in two cases. We found that it was not necessary to restore the soft tissue coverage before skeletal reconstruction. After thorough debridement the combined bone and soft tissue gaps could be treated simultaneously by the process of

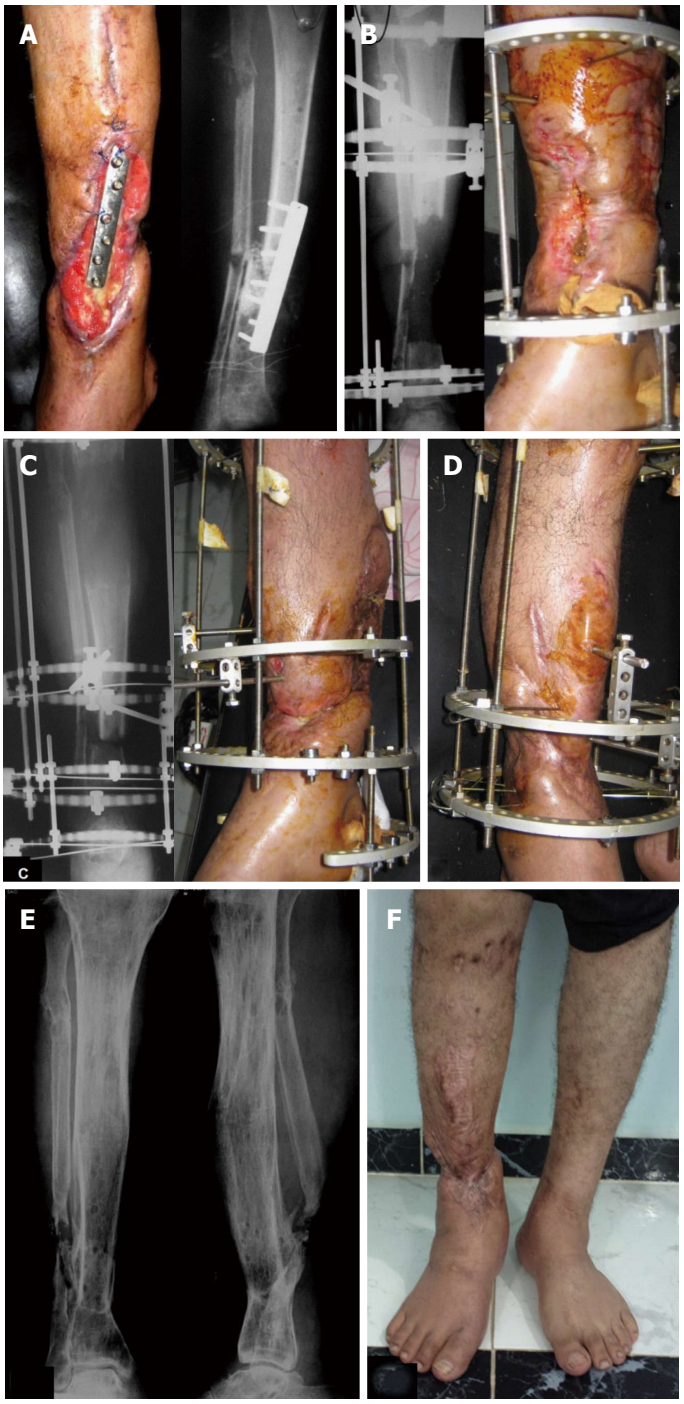


Figure 4 Lower third bone and soft tissue defects. A: Thirty-nine year old male patient with skin loss, infection and exposed plate in the lower third of his right leg; B: After radical debridement and application of the Ilizarov external fixator; At the time of docking the skin was fashioned to cover the bone ends (C) and it healed completely (D); After removal of the frame with good bone healing (E) and the patient with good alignment and complete healing of the soft tissue (F).

distraction osteogenesis. In the two cases that required plastic surgery, the soft tissue defects were big - 4 cm × 7 cm and 5 cm × 9 cm, respectively. During bone transport the defects decreased but did not close completely. The infection was eradicated in both of them and they were easily treated by local muscle flaps.

To avoid protrusion of the bone fragment from the wound during distraction the bone ends must be debrided until they become well covered by the skin. So, when distraction is started the bone fragment carries its surrounding soft tissue with it and the soft tissue creeps gradually until the defect heals spontaneously[9].

The soft tissue defects in the lower third of the leg are difficult to treat. Free-flaps is the best method for coverage of soft tissue defects in this area but the procedure is technically difficult, requires skilled surgeons and the recipient site should have suitable vessels which is a big problem in major tibial fractures[16-18]. Perforator-based flaps or a distally-based soleus flap may be suitable for the lower third of the leg but the results are controversial[19-21]. Karbalaeikhani *et al*[21] used a soleus flap to treat soft tissue defects in the middle and lower third of the leg and reported a high failure rate in the distal third. They recommend preoperative assessment by angiography before surgery.

In this study, the defects were present in the distal

third of the leg in 9 patients. All of them were treated by the Ilizarov method and none of them required plastic surgery (Figure 4). Partial shortening of the limb helps to reduce the size of the bone and soft tissue defects and decreases the time required for soft tissue healing. After docking the frame must be adjusted to allow for further lengthening to restore the limb length.

Bone graft was required in 15 cases to stimulate bone healing at the docking site. In such cases small amounts of cancellous bone graft were sufficient for this purpose. The unstable scar is an important problem with this technique. It happened in four of our patients early in the course of this study. It usually occurs at the docking site because the skin is thin and adherent in this area. This skin is liable to injury and chronic ulceration due to minor trauma. Prolonged protection of the skin is required to prevent it from injury. We could avoid this complication by resection of more bone at the time of docking until thick healthy skin meets each other over the bone at the docking site.

The method of Ilizarov is good for reconstruction of patients with bone loss, soft tissue loss and infection. The three problems could be treated simultaneously without the need for major plastic surgery. Infection is treated by radical debridement while the bone and soft tissue defects are managed by bone and soft tissue transport. Good experience with the Ilizarov frame, better understanding of the distraction process and proper handling of the soft tissues are required to get the best results.

COMMENTS

Background

Bone and soft tissue loss are common after major limb trauma. The presence of infection will further complicate limb reconstruction. The healthy soft tissue envelope is essential for bone healing. This could be achieved by either local or free myocutaneous flaps. Unfortunately these surgeries are technically demanding, time consuming and may be associated with major complications.

Research frontiers

During distraction osteogenesis both the bone and soft tissue are lengthened which may help in spontaneous closure of the soft tissue defect.

Innovations and breakthroughs

In this study the complex problem of combined bone loss, soft tissue loss and infection was treated by distraction osteogenesis without the need for major plastic surgery except in 2 cases.

Applications

This method could be used for treatment of cases with post traumatic bone and soft tissue loss with or without infection. It is not necessary to restore the soft tissue envelope before osseous reconstruction. During bone transport both the bone and soft tissue defects will heal spontaneously. It is highly indicated after failure of plastic surgeries and for cases with a poor vascular bed that does not allow major plastic surgery to be done.

Terminology

Distraction osteogenesis is the mechanical induction of new bone formation between two bony surfaces when they are gradually pulled apart. It was developed by Ilizarov in the fifties of the last century. A low grade cortical osteotomy is made in a healthy bone segment and the circular external fixator is usually used to apply the distraction force. It is also known as Ilizarov method; Bone transport: A condition in which a healthy bone segment is transported locally and gradually through the soft tissue to bridge a bone defect; The docking site is the site where the bone ends come to meet each other after bone transport.

Peer-review

The paper reports a good method for the treatment of lower limb tissue loss. It is interesting and well written. References are adequate.

REFERENCES

1 **Ilizarov GA**, Ledyaev VI. The replacement of long tubular bone defects by lengthening distraction osteotomy of one of the fragments. 1969. *Clin Orthop Relat Res* 1992; **(280)**: 7-10 [PMID: 1611766 DOI: 10.1097/00003086-199207000-00002]

2 **Green SA**. Skeletal defects. A comparison of bone grafting and bone transport for segmental skeletal defects. *Clin Orthop Relat Res* 1994; **(301)**: 111-117 [PMID: 8156661 DOI: 10.1097/00003086-199404000-00018]

3 **Yazar S**, Lin CH, Wei FC. One-stage reconstruction of composite bone and soft-tissue defects in traumatic lower extremities. *Plast Reconstr Surg* 2004; **114**: 1457-1466 [PMID: 15509933 DOI: 10.1097/01.PRS.0000138811.88807.65]

4 **Gordon L**, Chiu EJ. Treatment of infected non-unions and segmental defects of the tibia with staged microvascular muscle transplantation and bone-grafting. *J Bone Joint Surg Am* 1988; **70**: 377-386 [PMID: 3279039]

5 **Jordan DJ**, Malahias M, Hindocha S, Juma A. Flap decisions and options in soft tissue coverage of the lower limb. *Open Orthop J* 2014; **8**: 423-432 [PMID: 25408784 DOI: 10.2174/1874325001408010423]

6 **Jain AK**, Sinha S. Infected nonunion of the long bones. *Clin Orthop Relat Res* 2005; **(431)**: 57-65 [PMID: 15685056 DOI: 10.1097/01.blo.0000152868.29134.92]

7 **Paley D**, Maar DC. Ilizarov bone transport treatment for tibial defects. *J Orthop Trauma* 2000; **14**: 76-85 [PMID: 10716377 DOI: 10.1097/00005131-200002000-00002]

8 **Robert Rozbruch S**, Weitzman AM, Tracey Watson J, Freudigman P, Katz HV, Ilizarov S. Simultaneous treatment of tibial bone and soft-tissue defects with the Ilizarov method. *J Orthop Trauma* 2006; **20**: 197-205 [PMID: 16648701 DOI: 10.1097/00005131-200603000-00006]

9 **El-Alfy B**, El-Mowafi H, El-Moghazy N. Distraction osteogenesis in management of composite bone and soft tissue defects. *Int Orthop* 2010; **34**: 115-118 [PMID: 18493758 DOI: 10.1007/s00264-008-0574-3]

10 **Paley D**, Catagni MA, Argnani F, Villa A, Benedetti GB, Cattaneo R. Ilizarov treatment of tibial nonunions with bone loss. *Clin Orthop Relat Res* 1989; **(241)**: 146-165 [PMID: 2924458]

11 **Court-Brown CM**, Bugler KE, Clement ND, Duckworth AD, McQueen MM. The epidemiology of open fractures in adults. A 15-year review. *Injury* 2012; **43**: 891-897 [PMID: 22204774 DOI: 10.1016/j.injury.2011.12.007]

12 **Canale ST**, Beaty JH. Campbell's Operative Orthopaedics. 12th ed. Missouri: Mosby, 2012: 1405-1406

13 **Bucholz RW**, Heckman JD, Court-Brown CM. Rockwood and Green's Fractures in Adults. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2009: 376-377

14 **Olesen UK**, Juul R, Bonde CT, Moser C, McNally M, Jensen LT, Elberg JJ, Eckardt H. A review of forty five open tibial fractures covered with free flaps. Analysis of complications, microbiology and prognostic factors. *Int Orthop* 2015; **39**: 1159-1166 [PMID: 25750130 DOI: 10.1007/s00264-015-2712-z]

15 **Schöttle PB**, Werner CM, Dumont CE. Two-stage reconstruction with free vascularized soft tissue transfer and conventional bone graft for infected nonunions of the tibia: 6 patients followed for 1.5

to 5 years. *Acta Orthop* 2005; **76**: 878-883 [PMID: 16470446 DOI: 10.1080/17453670510045534]
16 **Heller L**, Levin LS. Lower extremity microsurgical reconstruction. *Plast Reconstr Surg* 2001; **108**: 1029-141; quiz 1042 [PMID: 11547168 DOI: 10.1097/00006534-200109150-00036]
17 **Pu LL**, Medalie DA, Rosenblum WJ, Lawrence SJ, Vasconez HC. Free tissue transfer to a difficult wound of the lower extremity. *Ann Plast Surg* 2004; **53**: 222-228 [PMID: 15480007]
18 **Abdelrahman I**, Moghazy A, Abbas A, Elmasry M, Adly O, Elbadawy M, Steinvall I, Sjoberg F. A prospective randomized cost billing comparison of local fasciocutaneous perforator versus free Gracilis flap reconstruction for lower limb in a developing economy. *J Plast Reconstr Aesthet Surg* 2016; **69**: 1121-1127 [PMID: 27289482 DOI: 10.1016/j.bjps.2016.04.013]
19 **Tajsic N**, Winkel R, Husum H. Distally based perforator flaps for reconstruction of post-traumatic defects of the lower leg and foot. A review of the anatomy and clinical outcomes. *Injury* 2014; **45**: 469-477 [PMID: 24075220 DOI: 10.1016/j.injury.2013.09.003]
20 **Pu LL**. Successful soft-tissue coverage of a tibial wound in the distal third of the leg with a medial hemisoleus muscle flap. *Plast Reconstr Surg* 2005; **115**: 245-251 [PMID: 15622258 DOI: 10.1093/icvts/ivv093]
21 **Karbalaeikhani A**, Saied A, Heshmati A. Effectiveness of the Gastrocsoleous Flap for Coverage of Soft Tissue Defects in Leg with Emphasis on the Distal Third. *Arch Bone Jt Surg* 2015; **3**: 193-197 [PMID: 26213703]

P- Reviewer: Lui PPY, Minana MD, Negosanti L **S- Editor**: Ji FF
L- Editor: O'Neill **E- Editor**: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.49

World J Orthop 2017 January 18; 8(1): 49-56
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Microvascular response to transfusion in elective spine surgery

J Matthias Walz, Ottokar Stundner, Federico P Girardi, Bruce A Barton, Aimee R Koll-Desrosiers, Stephen O Heard, Stavros G Memtsoudis

J Matthias Walz, Stephen O Heard, Department of Anesthesiology and Perioperative Medicine, UMass Memorial Healthcare, Worcester, MA 01655, United States

Ottokar Stundner, Department of Anesthesiology, Hospital for Special Surgery, Weill Cornell Medical Center, New York, NY 10021, United States

Ottokar Stundner, Department of Anesthesiology, Perioperative Medicine and Intensive Care Medicine, Paracelsus Medical University, 5020 Salzburg, Austria

Federico P Girardi, Department of Orthopedic Surgery, Hospital for Special Surgery, Weill Cornell Medical Center, New York, NY 10021, United States

Bruce A Barton, Aimee R Kroll-Desrosiers, Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA 01655, United States

Stavros G Memtsoudis, Department of Anesthesiology, Hospital for Special Surgery, Weill Cornell Medical Center, New York, NY 10021, United States

Author contributions: Walz JM, Heard SO and Memtsoudis SG designed the research; Girardi FP, Stundner O and Memtsoudis SG conducted the research; Barton BA and Kroll-Desrosiers AR developed the statistical model and performed all statistical analysis; all authors analyzed and interpreted the data; Walz JM wrote the first draft of the manuscript; all authors revised the manuscript, approved the final manuscript, and are accountable for all aspects of the work; Walz JM is the guarantor of the manuscript and takes full responsibility for the integrity of the work as a whole, from inception to published article.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board at the Hospital for Special Surgery, NY.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: None of the authors has any conflicts of interest relevant to this study.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: J Matthias Walz, MD, Department of Anesthesiology and Perioperative Medicine, UMass Memorial Healthcare, 55 Lake Avenue North, Worcester, MA 01655, United States. matthias.walz@umassmemorial.org
Telephone: +1-508-8563266

Received: June 12, 2016
Peer-review started: June 17, 2016
First decision: July 18, 2016
Revised: August 21, 2016
Accepted: October 25, 2016
Article in press: October 27, 2016
Published online: January 18, 2017

Abstract

AIM

To investigate the microvascular (skeletal muscle tissue oxygenation; SmO_2) response to transfusion in patients undergoing elective complex spine surgery.

METHODS

After IRB approval and written informed consent, 20 patients aged 18 to 85 years of age undergoing > 3

level anterior and posterior spine fusion surgery were enrolled in the study. Patients were followed throughout the operative procedure, and for 12 h postoperatively. In addition to standard American Society of Anesthesiologists monitors, invasive measurements including central venous pressure, continual analysis of stroke volume (SV), cardiac output (CO), cardiac index (CI), and stroke volume variability (SVV) was performed. To measure skeletal muscle oxygen saturation (SmO_2) during the study period, a non-invasive adhesive skin sensor based on Near Infrared Spectroscopy was placed over the deltoid muscle for continuous recording of optical spectra. All administration of fluids and blood products followed standard procedures at the Hospital for Special Surgery, without deviation from usual standards of care at the discretion of the Attending Anesthesiologist based on individual patient comorbidities, hemodynamic status, and laboratory data. Time stamps were collected for administration of colloids and blood products, to allow for analysis of SmO_2 immediately before, during, and after administration of these fluids, and to allow for analysis of hemodynamic data around the same time points. Hemodynamic and oxygenation variables were collected continuously throughout the surgery, including heart rate, blood pressure, mean arterial pressure, SV, CO, CI, SVV, and SmO_2. Bivariate analyses were conducted to examine the potential associations between the outcome of interest, SmO_2, and each hemodynamic parameter measured using Pearson's correlation coefficient, both for the overall cohort and within-patients individually. The association between receipt of packed red blood cells and SmO_2 was performed by running an interrupted time series model, with SmO_2 as our outcome, controlling for the amount of time spent in surgery before and after receipt of PRBC and for the inherent correlation between observations. Our model was fit using PROC AUTOREG in SAS version 9.2. All other analyses were also conducted in SAS version 9.2 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Pearson correlation coefficients varied widely between SmO_2 and each hemodynamic parameter examined. The strongest positive correlations existed between $ScvO_2$ (P = 0.41) and SV (P = 0.31) and SmO_2; the strongest negative correlations were seen between albumin (P = -0.43) and cell saver (P = -0.37) and SmO_2. Correlations for other laboratory parameters studied were weak and only based on a few observations. In the final model we found a small, but significant increase in SmO_2 at the time of PRBC administration by 1.29 units (P = 0.0002). SmO_2 values did not change over time prior to PRBC administration (P = 0.6658) but following PRBC administration, SmO_2 values declined significantly by 0.015 units (P < 0.0001).

CONCLUSION

Intra-operative measurement of SmO_2 during large volume, yet controlled hemorrhage, does not show a statistically significant correlation with either invasive hemodynamic, or laboratory parameters in patients undergoing elective complex spine surgery.

Key words: Transfusion; Complex spine surgery; Near infrared spectroscopy; Microvascular blood flow; Hemodynamic monitoring

Core tip: Tissue oxygenation determined by Near Infrared Spectroscopy has been used to assess the adequacy of end-organ perfusion in models of trauma and sepsis and has been shown to correlate with stroke volume in models of hemorrhagic shock. We sought to investigate muscle tissue oxygenation (SmO_2) during transfusion in patients undergoing complex spine surgery, and to study the association of SmO_2 with invasive hemodynamic parameters in the clinical setting. In our study, we were unable to demonstrate a statistically significant correlation between SmO_2 and either invasive hemodynamic, or laboratory parameters in patients undergoing elective complex spine surgery.

Walz JM, Stundner O, Girardi FP, Barton BA, Koll-Desrosiers AR, Heard SO, Memtsoudis SG. Microvascular response to transfusion in elective spine surgery. *World J Orthop* 2017; 8(1): 49-56 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/49.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.49

INTRODUCTION

Over 400000 elective spine fusion surgeries are performed annually in the United States[1]. Blood loss during complex spine surgery can be significant, and these patients frequently undergo either homologous or autologous blood transfusion, with the aim of preserving patient hemodynamics and adequate end-organ perfusion. While the transfusion of blood products is clearly indicated in situations of severe anemia associated with hemodynamic instability, the individual threshold at which a patient should undergo transfusion is less clear. Due to the properties of stored blood, unloading of oxygen may be impaired[2-4], and transfusion may thus not achieve the desired effect of optimizing oxygen supply to the tissues. Furthermore, liberal blood transfusions in patients undergoing elective orthopedic surgery are not associated with improved outcomes even in patients at high risk for cardiac complications, and may cause adverse side effects such as an increase in surgical side infections, pulmonary complications, and increased length of hospital stay in general patient populations undergoing non-cardiac surgery[5,6]. In addition, blood transfusions can cause a significant economic burden on the healthcare system if not clearly indicated[7].

Tissue oxygenation determined non-invasively by Near Infrared Spectroscopy (NIRS) has been suggested as one possible modality to determine the adequacy of end-organ perfusion in models of trauma and sepsis[8,9], and has been shown to correlate well with stroke volume in states of acute, untreated hypovolemia in models of hemorrhagic shock outside of the clinical arena[10]. We sought to investigate the microvascular (skeletal muscle tissue oxygenation; SmO_2) response to transfusion in patients undergoing elective complex spine surgery, and to study the association of muscle tissue oxygenation with invasive hemodynamic parameters obtained by pulse contour analysis in the clinical setting, thereby providing guidance as to when to transfuse a patient.

MATERIALS AND METHODS

Study design

After obtaining approval from the Institutional Review Board (Hospital for Special Surgery, New York, NY), potential participants were identified by review of the surgical schedule and approached on the day of surgery in the preoperative holding area. Twenty patients aged 18 to 85 years of age undergoing > 3 level anterior and posterior spine fusion surgery were enrolled. Exclusion criteria included minors, mentally disabled patients, pregnant women, employees, and prisoners. In addition, patients with skin lesions at the sensor placement site, and a history of allergies to skin adhesives were excluded from the study. Patients enrolled in the study were followed throughout the operative procedure, and for 12 h postoperatively.

Procedures and data collection

After informed consent was obtained, patients were taken to the operating room where general anesthesia was induced in standard fashion. In addition to standard American Society of Anesthesiologists (ASA) monitors, patients received an invasive arterial blood pressure catheter (Edwards Lifesciences, Irvine, CA) in the radial artery position, as well as a multi-lumen central venous catheter (Arrow International, Reading, PA) for administration of fluids, blood products, blood sampling, and measurement of central venous pressure. The arterial pressure transducer was connected to a pulse contour analysis module (FloTrac, Edwards Vigileo®, Edwards Lifesiences, Irvine, CA) for continual analysis of stroke volume (SV), cardiac output (CO), cardiac index (CI), and stroke volume variability (SVV). To measure skeletal muscle oxygen saturation (SmO_2) during the study period, a non-invasive adhesive skin sensor based on NIRS (CareGuide, Reflectance Medical, Westborough, MA) was placed over the deltoid muscle. After a 5-min period to obtain a stable baseline signal, continuous recording of optical spectra was performed throughout the operative procedure. Measurements were interrupted during prone positioning of the patient (anterior-posterior procedures), and during patient transport.

Central venous and mean arterial pressures were recorded with every routine lab draw during the procedure, and no less than every two hours intra-operatively. Lactate, hematocrit, base excess, arterial blood gases and central venous oxygen saturation were determined from blood samples that were drawn as part of routine care, and no less than every two hours intra-operatively.

Fluid administration and blood transfusion

No standardized protocol for administration of crystalloids, colloids, and blood products was used for the purpose of this study. Administration of fluids and blood products was performed at the discretion of the Attending Anesthesiologist based on individual patient comorbidities, hemodynamic status, and laboratory data. Crystalloid solutions were administered in the form of Lactated Ringer's. The colloid administered during the study period was human albumin 5% in 250 mL aliquots. Blood products transfused were either autologous blood from cell saver (Hemonetics, Braintree, MA) in 125 mL aliquots, or allogenic packed red blood cells (PRBC) from the blood bank. No specific transfusion triggers were used, and the healthcare team was blinded to the collection of NIRS spectra. All administration of fluids and blood products followed standard procedures at the Hospital for Special Surgery, without deviation from usual standards of care. Time stamps were collected for administration of colloids and blood products, to allow for analysis of SmO_2 immediately before, during, and after administration of these fluids, and to allow for analysis of hemodynamic data around the same time points. In general, PRBC were infused using pressure infusion bags (Vital Signs Inc, Totowa, NJ), whilst blood processed with the cell saver system was infused as a free flowing infusion.

Statistical analysis

Data on stroke volume, SmO_2, transfusion, and blood gas were collected on a total of 20 patients. Several variables were collected on a continuously throughout the surgery and included heart rate, blood pressure, mean arterial pressure, SV, CO, CI, SVV and SmO_2. These variables were identified at each time point with a time recording out to seconds. Patient data from the four sources was merged by a unique patient ID and timed at which the measurement occurred rounded to the nearest minute. Bivariate analyses were conducted to examine the potential associations between the outcome of interest, SmO_2, and each hemodynamic parameter measured using Pearson's correlation coefficient, both for the overall cohort and within-patients individually.

To examine the association between receipt of packed red blood cells and SmO_2, we created a dataset that included 11 patients who had received PRBC with documented administration times. After conducting an exploratory data analysis on SmO_2 using graphical techniques and percentile ranges, we excluded SmO_2

Table 1 Patient demographics

	Age (yr)	Height (cm)	Weight (kg)	BMI	Sex (m/f)
Mean (SD)	59.80 (10.96)	165.99 (9.83)	75.84 (15.75)	27.58 (5.45)	5/15

Table 2 Correlations with SmO_2

Variable	ρ (correlation)	No. of observations[1]
$ScvO_2$	0.40704	92
SV	0.30967	8490
PvO_2	0.20475	92
HCT	0.19402	89
CO	0.06498	8490
Lactate	0.0609	61
CI	0.05839	8490
pH A	0.0578	92
SVV	-0.10652	8490
RBC	-0.25085	18
Cell saver	-0.37471	37
Albumin	-0.42714	29

[1]Eight thousand four hundred and ninety total observations within 20 patients (not all hemodynamic parameters were examined at each observation).

values ⩽ 30 as well as values that jumped by > 10% from one time point to the next, unless the jump in values was typical for that specific patient. Due to the few occurrences of multiple PRBC administration during surgery in our data, we only focused on the first PRBC event.

A variable, "timecount", was created to standardize the time units, where the first minute of each patient surgery in our data was equal to one and subsequently increased by one unit for every minute until the end of the surgery. A second variable was created to flag the time at which PRBC was administered, where the variable was equal to 0 until the time at which PRBC were administered and 1 at every time point thereafter. Finally, an additional time variable, "postcount", was created to count the time after PRBC was administered, where postcount = 1 referred to the minute at which PRBC was given and increased by one unit per minute of time remaining in surgery for each subsequent measurement. These flagging variables allowed us to run an interrupted time series model, with SmO_2 as our outcome, controlling for the amount of time spent in surgery before and after receipt of PRBC and for the inherent correlation between observations. Our model was fit using PROC AUTOREG in SAS version 9.2. All other analyses were also conducted in SAS version 9.2 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Summative patient demographics are presented in Table 1. Pearson correlation coefficients varied widely between SmO_2 and each hemodynamic parameter examined. When examined for the overall cohort,

Table 3 SmO_2 statistics for individual patients and overall

Patient	No. of observations (time counts)	SmO_2 statistics			
		Mean	Std Dev	Minimum	Maximum
1	1609	47.30205	4.231185	39.24457	59.81775
2	261	54.48111	4.559080	41.36314	60.91571
3	110	58.08155	3.474810	49.92571	63.56974
4	1061	59.45269	5.814339	42.39521	67.48903
5	333	59.86487	6.765487	43.87553	70.40168
6	284	60.44015	2.490064	53.33939	68.04648
7	486	60.78656	13.90398	30.77515	75.79442
8	1440	60.95438	4.090378	48.86891	73.39652
9	420	61.17271	2.276567	54.89989	65.64407
10	1470	61.18899	2.880967	52.65419	69.78379
11	203	61.95770	3.067270	47.69575	71.06789
Total	7677	57.63074	7.677996	30.77515	75.79442

Sorted by mean SmO_2.

where each unit of time served as an observation, the maximum number of observations was 8490 among the 20 participants. Several parameters, including central venous oxygen saturation $ScvO_2$, lactate, venous blood oxygen tension (PvO_2), arterial pH (pH-A), hematocrit, PRBC, cell saver, and albumin had less than 100 observations among all participants. The strongest positive correlations existed between $ScvO_2$ (P = 0.41) and SV (P = 0.31) and SmO_2; the strongest negative correlations were seen between albumin (P = -0.43) and cell saver (P = -0.37) and SmO_2. Correlations for other laboratory parameters studied were weak and only based on a few observations (Table 2). When correlations were examined within individual patients, values varied widely; for example, correlations for SV varied from 0.40590 to -0.66903 for 18 patients with recorded SV values (data not shown).

Average SmO_2 for the 11 patients included in the final modeling was 57.63 (± SD 7.68), with a range of mean values from 47.30-61.92. The total number of observations analyzed was 7677, representing 7677 time counts, or minutes, of surgery over all patients included. Individual patient time counts ranged from 110 to 1609 (Table 3).

The final model showed a small, but significant increase in SmO_2 at the time of PRBC administration by 1.29 units (P = 0.0002). SmO_2 values did not change over time prior to PRBC administration (P = 0.6658) but following PRBC administration, SmO_2 values declined significantly by 0.015 units (P < 0.0001).

DISCUSSION

The key finding of our study is that when compared to experimental[11], and clinical settings of uncontrolled hemorrhagic shock[8], intra-operative measurement of SmO_2 during large volume, yet controlled hemorrhage does not show a statistically significant correlation with either invasive hemodynamic, or laboratory parameters in patients undergoing elective complex spine surgery.

The non-invasive assessment of tissue perfusion

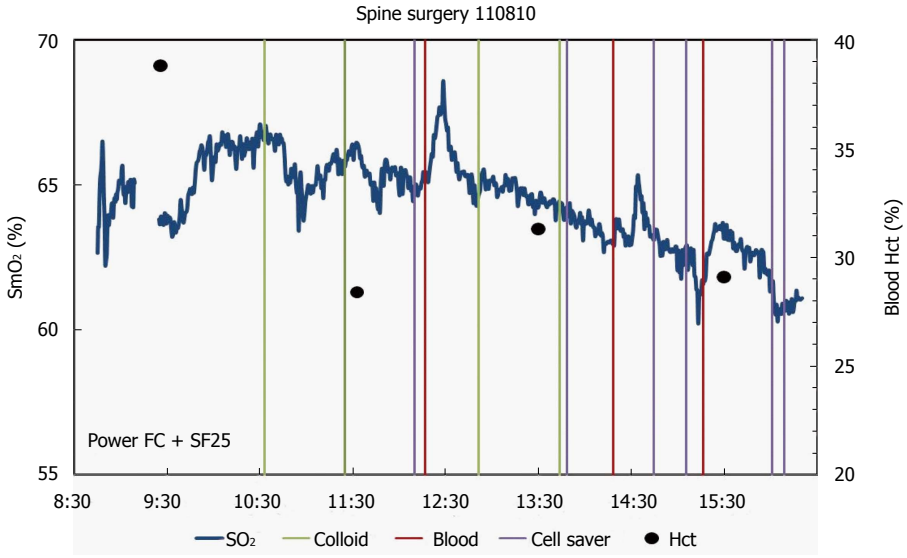


Figure 1 Representative SmO_2 response to infusion of colloid, cell saver, and homologous blood in one of the study patients. Notice the apparent lack of correlation between SmO_2 and HCT.

has garnered increasing interest in acute care medicine, based on the fact that traditional hemodynamic and oxygenation parameters such as blood pressure, central venous pressure, pulse oximetry, and central venous oxygen saturation are not necessarily reflective of the actual amount of blood loss, or the degree of shock a patient is experiencing. Furthermore, monitoring the macrocirculation with standard blood pressure, and heart rate monitors may not provide the clinician with relevant information about the adequacy of end-organ perfusion in certain disease states.

The ability of SmO_2 values derived by NIRS to track the adequacy of fluid resuscitation has been demonstrated in a model of swine hemorrhagic shock[12], and a NIRS-derived variable of tissue oxygenation (StO_2) has been used to guide closed-loop fluid resuscitation in animal models[13]. SmO_2 has also been shown to have a strong correlation with stroke volume in a human model of acute central hypovolemia[14]. Recently, Bohula May and coworkers were able to demonstrate correlation of SmO_2 with invasively-measured SvO_2, and cardiac index (CI) in patients hospitalized with heart failure and cardiogenic shock[15].

In disease states such as septic shock and traumatic hemorrhage, low tissue oxygen saturation determined by modalities such as NIRS, and persistent alterations in microcirculatory blood flow determined with OPS-imaging have been shown to correlate with severity of illness, and to be associated with organ failure, and death[9,16-18].

While we were able to demonstrate a positive correlation between SmO_2 and SV, no statistical significance was found in our study, despite significant blood loss experienced by some of the patients. It is important to note however that data generated in models of acute, un-resuscitated shock may not be comparable to the situation found during elective surgery, where patients undergo continuous administration of crystalloid, colloids, and blood products. The same is likely true for patients in cardiogenic shock on vasopressor therapy, where accumulation of significant oxygen debt is not uncommon, and is more likely to negatively affect tissue oxygenation.

No definitive transfusion triggers exist to guide clinicians during the intraoperative period, particularly during surgical procedures associated with substantial blood loss such as complex spine surgery. There is compelling retrospective data suggesting that intra-operative transfusion of blood in patients with anemia undergoing non-cardiac surgery, including orthopedic surgery is associated with an increase in morbidity and mortality[19]. The situation is different for post-operative patients, including those admitted to an intensive care unit with severe sepsis, as well as patients with active gastrointestinal hemorrhage outside the operating room. Several prospective, randomized controlled trials have shown that restrictive transfusion strategies are either superior, or non-inferior to liberal transfusion strategies with respect to outcomes such as in-hospital and 90-d mortality, infection, cardiac ischemia, and in-hospital acute myocardial infarction[5,6,20,21].

The most recent clinical practice guideline for perioperative blood management by ASA recommends that monitoring perfusion and oxygenation of vital organs should be continuous, and may include cerebral oximetry, and NIRS, in addition to standard hemodynamic monitors[22]. While conceptually attractive due to its non-invasive nature, and the ability to reliably monitor the microcirculation in a variety of tissue beds, data on the ability of NIRS to provide clinically relevant information in the intraoperative period during elective surgery is sparse, and is mostly restricted to the monitoring of cerebral oxygenation.

The microvascular response to red blood cell trans-

fusion has been studied in patients with severe sepsis and trauma, however to our knowledge, no such data has been collected in patients undergoing elective orthopedic surgery associated with significant blood loss to date. Sakr and coworkers analyzed the microvascular response to transfusion in patients with severe sepsis. The authors were unable to demonstrate an overall effect of transfusion on sublingual microvascular perfusion as assessed with OPS-imaging. However, baseline microvascular blood flow predicted the microvascular response to transfusion. Those patients who were shown to have reduced microvascular blood flow at baseline demonstrated improved perfusion with transfusion whereas those with normal perfusion suffered a decrease in microvascular blood flow after transfusion[23]. The same pattern has been demonstrated in trauma patients using Sidestream Dark Field imaging, with some decline in microvascular blood flow in response to transfusion of stored RBC in patients who had normal sublingual perfusion patterns at baseline[24]. More recent investigations using NIRS-based technology to analyze the microvascular response to transfusion in trauma patients suggest that increasing age of transfused RBC results in decreased StO_2 levels. This effect was demonstrated both in critically injured, as well as stable, but anemic patients[25,26]. These effects are likely attributable to "storage defects" of red blood cells, which decrease post-transfusion RBC survival. Changes that have been reported in the literature include depletion of adenosine triphosphate, and 2,3 diphosphoglycerate (2,3 DPG), a decrease in pH, release of potassium, reduced nitric oxide, increased cell volume, and reduced RBC deformability[27]. Further experimental evidence in support of a negative impact on physiologic properties of stored RBC comes from a recent analysis of the impact of exchange transfusion in a rat model using intravital microscopy among other techniques. Yalcin and coworkers were able to demonstrate that exchange transfusion with stored RBC's produced microcirculatory vasoconstriction resulting in decreased blood flow and oxygen delivery that was not found in anemia alone, or transfusion with fresh red blood cells. In addition, the authors showed that stored RBC's have a shorter circulating lifetime, and appear to be removed from circulating blood due to their impaired elastic, and hydrodynamic behavior[28].

In conclusion, while we detected a short-lived increase in SmO_2 in response to transfusion of PRBC, we were unable to detect a sustained, and relevant change in SmO_2 signal in a patient population subjected to significant intra-operative blood loss. The reasons for the short-lived increase (Figure 1) remain speculative, but might be explained by the aforementioned changes found in stored RBC's.

Study limitations

The limitations of our study are significant, and include the small number of subjects enrolled, and the fact that there were no specific treatment algorithms or outcomes studied in this proof-of-concept design. In addition, the age of transfused PRBC was not documented in our study protocol, which may limit the interpretability of our results. We were able however to evaluate a promising, non-invasive technology based on near-infrared spectroscopy in a "real-world" clinical setting, combined with a complex statistical analysis of continual oxygenation data. The results of this prospective, observational pilot study may provide a framework for future studies looking at specific patient outcomes associated with a hemodynamic management strategy incorporating real-time, microvascular blood flow data based on NIRS.

COMMENTS

Background

The assessment of the adequacy of end-organ perfusion in states of shock from sepsis or hemorrhage remain a challenge, as global hemodynamic measurements such as blood pressure, and cardiac filling pressures may not be reflective of perturbations of microcirculatory blood flow, and hence inadequate oxygen supply to critical end organs. Furthermore, standard physiologic parameters may not be sensitive to the early changes associated with hypovolemia from hemorrhage or anemia resulting in undetected tissue hypoxemia. Various technologies have been tested in both, exercise physiology laboratories as well as the clinical arena in an attempt to provide clinicians with more complete information regarding the state of the (micro) circulation, and oxygen supply to critical end organs. At the same time, individualized transfusion triggers based on objective data remain elusive, and there is ongoing research to determine rational, and safe transfusion patterns for hemodynamic impairment in states of shock from both, hemorrhagic, and non-hemorrhagic causes.

Research frontiers

One of the non-invasive technologies, which have shown promise in experimental settings both in the laboratory, as well as the clinical arena, is based on Near Infrared Spectroscopy (NIRS). The technology allows for accurate assessment of skeletal muscle oxygen saturation (SmO_2), which has been demonstrated to be a very early indicator of central hypovolemia in humans in a model of lower body negative pressure. It also shows excellent correlation with non-invasively measured stroke volume in the same model. A decrease in peripheral muscle NIR spectra is reflective of a decrease in tissue blood volume, and increased oxygen extraction by the peripheral tissues. NIRS has shown promise as an adjunct monitoring system for patients undergoing emergency surgery for trauma, or during treatment of patients in septic shock in addition to standard physiologic monitors for hemodynamic evaluation.

Innovations and breakthroughs

This study is the first to investigate tissue oxygenation based on NIRS in orthopedic patients undergoing elective complex spine surgery with anticipated high volumes of blood loss. While restrictive transfusion strategies appear safe in high-risk patients undergoing hip surgery, intra-operative blood loss during these procedures is usually much lower compared to estimated blood loss incurred during complex spine surgery. Optimal transfusion strategies during the latter type of surgery remain elusive, and largely based on experience and local practice patterns. The authors sought to determine in this observational pilot study if NIRS derived data on microcirculatory blood flow may provide useful objective information on the microcirculatory response to transfusion, which could guide subsequent prospective randomized controlled clinical trials on rational transfusion strategies in patients undergoing complex spine surgery. They also developed a complex statistical model for the analysis of continuous NIR spectra and their correlation with invasive hemodynamic and laboratory parameters, which can serve as a template for future trials in this area.

Application

As they were unable to detect a sustained, and relevant change in SmO_2 signal in a patient population subjected to significant intra-operative blood loss, the

role of NIRS during elective surgery associated with large volume blood loss will require further investigation.

Terminology

Light emitted in the near infrared spectrum from 700 to 100 nm near infrared spectroscopy can penetrate deep in to the muscle, and be reflected back to a sensor bundle providing information on the absorption spectra of hemoglobin, and de-oxyhemoglobin. This spectral information allows for the calculation of skeletal muscle tissue oxygenation with great accuracy. The sensor used in this clinical study also allows for correction of fat thickness and skin pigmentation, thus further increasing the accuracy of the spectral information derived from the tissues.

Peer-review

This manuscript is a well-written report of an original study, with good analysis and methodology, informative tables, and clear results.

REFERENCES

1 **Rajaee SS**, Bae HW, Kanim LE, Delamarter RB. Spinal fusion in the United States: analysis of trends from 1998 to 2008. *Spine* (Phila Pa 1976) 2012; **37**: 67-76 [PMID: 21311399 DOI: 10.1097/BRS.0b013e31820cccfb]

2 **Benesch RE**, Benesch R. The reaction between diphosphoglycerate and hemoglobin. *Fed Proc* 1970; **29**: 1101-1104 [PMID: 5443776]

3 **Sladen RN**. The oxyhemoglobin dissociation curve. *Int Anesthesiol Clin* 1981; **19**: 39-70 [PMID: 6793521]

4 **Marik PE**, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; **269**: 3024-3029 [PMID: 8501845]

5 **Glance LG**, Dick AW, Mukamel DB, Fleming FJ, Zollo RA, Wissler R, Salloum R, Meredith UW, Osler TM. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. *Anesthesiology* 2011; **114**: 283-292 [PMID: 21239971 DOI: 10.1097/ALN.0b013e3182054d06]

6 **Carson JL**, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, Macaulay W, Lewis C, Cook DR, Dobbin G, Zakriya KJ, Apple FS, Horney RA, Magaziner J. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011; **365**: 2453-2462 [PMID: 22168590 DOI: 10.1056/NEJMoa1012452]

7 **Shander A**, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion* 2010; **50**: 753-765 [PMID: 20003061 DOI: 10.1111/j.1537-2995.2009.02518.x]

8 **Cohn SM**, Nathens AB, Moore FA, Rhee P, Puyana JC, Moore EE, Beilman GJ. Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. *J Trauma* 2007; **62**: 44-54; discussion 54-55 [PMID: 17215732 DOI: 10.1097/TA.0b013e31802eb817]

9 **Creteur J**, Carollo T, Soldati G, Buchele G, De Backer D, Vincent JL. The prognostic value of muscle StO2 in septic patients. *Intensive Care Med* 2007; **33**: 1549-1556 [PMID: 17572876 DOI: 10.1007/s00134-007-0739-3]

10 **Soller BR**, Yang Y, Soyemi OO, Ryan KL, Rickards CA, Walz JM, Heard SO, Convertino VA. Noninvasively determined muscle oxygen saturation is an early indicator of central hypovolemia in humans. *J Appl Physiol* (1985) 2008; **104**: 475-481 [PMID: 18006869 DOI: 10.1152/japplphysiol.00600.2007]

11 **Soller BR**, Ryan KL, Rickards CA, Cooke WH, Yang Y, Soyemi OO, Crookes BA, Heard SO, Convertino VA. Oxygen saturation determined from deep muscle, not thenar tissue, is an early indicator of central hypovolemia in humans. *Crit Care Med* 2008; **36**: 176-182 [PMID: 18090350 DOI: 10.1097/01.CCM.0000295586.83787.7E]

12 **Soller BR**, Cingo N, Puyana JC, Khan T, Hsi C, Kim H, Favreau J, Heard SO. Simultaneous measurement of hepatic tissue pH, venous oxygen saturation and hemoglobin by near infrared spectroscopy. *Shock* 2001; **15**: 106-111 [PMID: 11220637]

13 **Chaisson NF**, Kirschner RA, Deyo DJ, Lopez JA, Prough DS, Kramer GC. Near-infrared spectroscopy-guided closed-loop resuscitation of hemorrhage. *J Trauma* 2003; **54**: S183-S192 [PMID: 12768123 DOI: 10.1097/01.TA.0000064508.11512.28]

14 **Cooke WH**, Ryan KL, Convertino VA. Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans. *J Appl Physiol* (1985) 2004; **96**: 1249-1261 [PMID: 15016789 DOI: 10.1152/japplphysiol.01155.2003]

15 **May EB**, Soller B, O'Brien M, Kidd S, Berg D, O'Malley R, Morrow D, Wiviott S. 173: Non-Invasive Measure of Tissue Perfusion, SMO2, Compared with Standard Invasive Assessements of Shock. *Crit Care Med* 2014; **42**: A1402 [DOI: 10.1097/01.ccm.0000457670.63893.fe]

16 **Sakr Y**, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med* 2004; **32**: 1825-1831 [PMID: 15343008 DOI: 10.1097/01.CCM.0000138558.16257.3F]

17 **De Backer D**, Donadello K, Sakr Y, Ospina-Tascon G, Salgado D, Scolletta S, Vincent JL. Microcirculatory alterations in patients with severe sepsis: impact of time of assessment and relationship with outcome. *Crit Care Med* 2013; **41**: 791-799 [PMID: 23318492 DOI: 10.1097/CCM.0b013e3182742e8b]

18 **De Backer D**, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002; **166**: 98-104 [PMID: 12091178 DOI: 10.1164/rccm.200109-016OC]

19 **Hébert PC**, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; **340**: 409-417 [PMID: 9971864 DOI: 10.1056/NEJM199902113400601]

20 **Villanueva C**, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñiz E, Guarner C. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; **368**: 11-21 [PMID: 23281973 DOI: 10.1056/NEJMoa1211801]

21 **Holst LB**, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, Johansson PI, Aneman A, Vang ML, Winding R, Nebrich L, Nibro HL, Rasmussen BS, Lauridsen JR, Nielsen JS, Oldner A, Pettilä V, Cronhjort MB, Andersen LH, Pedersen UG, Reiter N, Wiis J, White JO, Russell L, Thornberg KJ, Hjortrup PB, Müller RG, Møller MH, Steensen M, Tjäder I, Kilsand K, Odeberg-Wernerman S, Sjøbø B, Bundgaard H, Thyø MA, Lodahl D, Mærkedahl R, Albeck C, Illum D, Kruse M, Winkel P, Perner A. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med* 2014; **371**: 1381-1391 [PMID: 25270275 DOI: 10.1056/NEJMoa1406617]

22 **American Society of Anesthesiologists Task Force on Perioperative Blood Management.** Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. *Anesthesiology* 2015; **122**: 241-275 [PMID: 25545654 DOI: 10.1097/ALN.0000000000000463]

23 **Sakr Y**, Chierego M, Piagnerelli M, Verdant C, Dubois MJ, Koch M, Creteur J, Gullo A, Vincent JL, De Backer D. Microvascular response to red blood cell transfusion in patients with severe sepsis. *Crit Care Med* 2007; **35**: 1639-1644 [PMID: 17522571 DOI: 10.1097/01.CCM.0000269936.73788.32]

24 **Weinberg JA**, MacLennan PA, Vandromme-Cusick MJ, Angotti JM, Magnotti LJ, Kerby JD, Rue LW, Barnum SR, Patel RP. Microvascular response to red blood cell transfusion in trauma patients. *Shock* 2012; **37**: 276-281 [PMID: 22344313 DOI: 10.1097/SHK.0b013e318241b739]

25 **Weinberg JA**, MacLennan PA, Vandromme-Cusick MJ, Magnotti LJ, Kerby JD, Rue LW, Angotti JM, Garrett CA, Hendrick LE, Croce MA, Fabian TC, Barnum SR, Patel RP. The deleterious effect of red blood cell storage on microvascular response to transfusion. *J Trauma Acute Care Surg* 2013; **75**: 807-812 [PMID: 24158198 DOI: 10.1097/TA.0b013e3182a74a9b]

26 **Kiraly LN**, Underwood S, Differding JA, Schreiber MA. Transfusion

of aged packed red blood cells results in decreased tissue oxygenation in critically injured trauma patients. *J Trauma* 2009; **67**: 29-32 [PMID: 19590304 DOI: 10.1097/TA.0b013e3181af6a8c]

27 **Bennett-Guerrero E**, Veldman TH, Doctor A, Telen MJ, Ortel TL, Reid TS, Mulherin MA, Zhu H, Buck RD, Califf RM, McMahon TJ. Evolution of adverse changes in stored RBCs. *Proc Natl Acad Sci USA* 2007; **104**: 17063-17068 [PMID: 17940021 DOI: 10.1073/pnas.0708160104]

28 **Yalcin O**, Ortiz D, Tsai AG, Johnson PC, Cabrales P. Microhemodynamic aberrations created by transfusion of stored blood. *Transfusion* 2014; **54**: 1015-1027 [PMID: 23901933 DOI: 10.1111/trf.12361]

P- Reviewer: Alimehmeti R, Elgafy H, Kahveci R, Lakhdar F
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.57

World J Orthop 2017 January 18; 8(1): 57-61
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Observational Study

"Meniscal" scar as a landmark for the joint line in revision total knee replacement

Wasim Sardar Khan, Jagmeet Bhamra, Rhodri Williams, Rhidian Morgan-Jones

Wasim Sardar Khan, Jagmeet Bhamra, Rhodri Williams, Rhidian Morgan-Jones, Cardiff and Vale Orthopaedic Centre, Llandough University Hospital, Cardiff and Vale NHS Trust, Cardiff CF5 2LD, United Kingdom

Author contributions: Khan WS participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Bhamra J and Williams R participated in the drafting of the initial manuscript; Morgan-Jones R was the guarantor and designed the study; all authors reviewed and revised the article critically for important intellectual content; all authors approved the final submitted version.

Institutional review board statement: The study was reviewed and approved by the Cardiff and Vale Orthopaedic Centre.

Informed consent statement: All patients included in the study provided informed consent prior to undergoing surgery.

Conflict-of-interest statement: None.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository.

Manuscript source: Invited manuscript

Correspondence to: Wasim Sardar Khan, Knee Fellow, Cardiff and Vale Orthopaedic Centre, Llandough University Hospital, Cardiff and Vale NHS Trust, Longcross Street, Cardiff CF5 2LD, United Kingdom. wasimkhan@doctors.org.uk
Telephone: +44-79-71190720
Fax: +44-20-85703864

Received: April 23, 2016
Peer-review started: April 24, 2016
First decision: June 6, 2016
Revised: October 17, 2016
Accepted: November 16, 2016
Article in press: November 17, 2016
Published online: January 18, 2017

Abstract

AIM

To determine whether tissue identified at the joint line was actually remnant "meniscal" scar tissue or not.

METHODS

Nine patients undergoing revision knee surgery following informed consent had meniscal scar tissue sent to the histology department for analyses. All revisions were performed where joint line had been raised or lowered at earlier surgery. Although preoperative radiographic evaluations suggested that the joint line had been altered, intraoperatively there was scar tissue at the level of the recreated joint line. This scar tissue has traditionally been described as meniscal scar, and to identify the origins of this tissue, samples were sent for histological analyses. The tissue samples were stored in formalin, and embedded and sectioned before undergoing histochemical staining. All samples underwent macroscopic and microscopic examination by a histopathologist who was blind to the study aims. The specific features that were examined included tissue organisation, surface and central composition, cellular distribution including histiocytes, nuclear ratio and vasculature. Atypical and malignant features, inflammation and degeneration were specifically looked for. A statistical review of the study was performed by a biomedical statistician.

RESULTS

The histological findings for the nine patients showing

the macroscopic and microscopic findings, and the conclusion are outlined in a Table. The histological analyses were reviewed to determine whether the tissue samples were likely to be meniscal scar tissue. The response was yes (2, 22%), no (6, 67%) and maybe (1, 11%) based on the conclusions. The results were "yes" when on macroscopy, firm cream tissue was identified. In these two "yes" samples, microscopic analyses showed organised fibrous tissue with focal degenerative areas with laminated pattern associated with histiocytes peripherally but no inflammation. The "no" samples were assessed macroscopically and microscopically and were deemed to have appearances representing fibrous synovial tissue and features in keeping with degenerate scar tissue or connective tissue. One sample was indeterminate and microscopically contained fibro-collagenous tissue with synovial hyperplasia. It also contained some degenerate hyalinised tissue that may represent cartilage, but the appearances were not specific.

CONCLUSION

Based on our pilot study, we recommend reliance on a number of markers to identify the joint line as outlined above, and to exercise caution in using the "meniscal" scar.

Key words: Menical scar; Joint line; Revision surgery; Knee; Histology

Core tip: Our findings suggests that the structure identified as the "meniscal" scar may actually represent scar tissue that forms in the available space of the recreated joint line rather than actually represent the level of the native joint line where the meniscus once attached.

Khan WS, Bhamra J, Williams R, Morgan-Jones R. "Meniscal" scar as a landmark for the joint line in revision total knee replacement. *World J Orthop* 2017; 8(1): 57-61 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/57.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.57

INTRODUCTION

Revision total knee arthroplasty (TKA) is a complex procedure that generally does not achieve the same good results as primary knee replacement. There are a number of reasons for this and include the complexity of the revision procedure making it difficult to restore the joint line[1-3]. Restoring the joint line is associated with improved clinical outcomes, functional knee scores and range of motion as well as decreased anterior knee pain[4]. In revision surgery the joint line can more commonly become elevated due to distorted anatomical landmarks, excessive distal femoral bone resection and using an excessively thicker a tibial insert. Excessive distal femoral bone loss may be due to excessive bone resection at the primary joint replacement or as a result of deficient bone stock from infection, osteolysis, peri-prosthetic fracture, component migration or iatrogenic damage when attempting to remove implants and cement in revision surgery[1,3]. It is therefore proposed that distal femoral augments should be used rather than thicker polyethylene to avoid elevation of the joint line.

A number of landmarks have been described in the literature to facilitate the accurate reproduction of the joint line in revision TKA and include the (1) the "meniscal" scar; (2) 1.5-2 cm proximal to the fibular head; (3) 2 cm proximal to the tibial tubercle; (4) 2-2.5 cm distal to the lateral femoral epicondyle; and (5) 2.5-3 cm distal to the medial femoral epicondyle[5,6]. Other measurements used include two finger breadths above the tibial tubercle or 2 cm below the inferior patella pole in extension[7]. Less commonly used reference points include the adductor tubercle[7,8]. Some surgeons obtain historical radiographs of the ipsilateral, or up-to-date radiographs of the contralateral knee to help identify the location of the joint line relative to fixed bony landmarks[4,7]. Variations in technique exist when measuring from radiographs and other potential drawbacks include malrotation and magnification that can cause inaccurate measurements[5].

The bony and radiological methods described to identify the joint line can be unreliable and are not standardised or reproducible. The bony landmarks may not be easily accessible or identifiable intraoperatively and hence the greater reliance on the "meniscal" scar. We performed a histological study to determine whether tissue identified at the joint line was actually remnant "meniscal" scar tissue or fibrous tissue formed at the level of the recreated joint line from the previous surgery.

MATERIALS AND METHODS

Nine patients undergoing revision knee surgery following informed consent had "meniscal" scar tissue sent to the histology department for analyses. All revisions were performed where joint line had been raised or lowered at earlier surgery. Although preoperative radiographic evaluations suggested that the joint line had been altered, intraoperatively there was scar tissue at the level of the recreated joint line. This scar tissue has traditionally been described as meniscal scar but to identify the origins of this tissue, samples were sent for histological analyses.

The tissue samples were stored in formalin, embedded and sectioned before undergoing histochemical staining. All samples underwent macroscopic and microscopic examination by a histopathologist who was blind to the study aims. The specific features that were examined included tissue organisation, surface

Table 1 Histological reports for nine patients showing the macroscopic and microscopic findings, and the conclusion

Patient	Macroscopy	Microscopy	Conclusion	Is the tissue likely to be meniscal scar tissue?
1	Cream tissue	Organised fibrous tissue and synovial surface. No atypical features	Appearances likely represent fibrous synovial tissue	No
2	Yellow and white tissue	Fragments of fibrous tissue partly lined by synovium show focal areas of denuded surface with acellular fibrinoid exudate. No significant inflammation	Features in keeping with degenerate scar tissue	No
3	Firm cream tissue	Fibrous tissue with focal degenerate area. No inflammation seen	Meniscal tissue	Yes
4	Firm cream tissue	Sections showing organised fibrous tissue and laminated pattern associated with foamy histiocytes at the periphery under the synovial surface. In areas the fibrous tissue lack nuclei	Appearances likely represent meniscal remnants with degenerate features	Yes
5	Firm cream tissue	Fragments of connective tissue. No features of atypia, malignancy, or significant inflammation	Connective tissue	No
6	Cream tissue	Fragments of fibrous tissue with overlying synovium. There is a mild inflammatory infiltrate	Features in keeping with fibrous scar tissue	No
7	Firm cream tissue	Sections show fragments of connective tissue. No evidence of atypia or malignancy. No significant inflammation is identified. There is a small collection of blood vessels seen in one edge	Connective/scar tissue	No
8	Cream tissue	Fibro-collagenous tissue with synovial hyperplasia. Some degenerate hyalinised tissue that may represent cartilage, but the appearances are not specific	Features in keeping with non-specific articular tissue	Maybe
9	Yellow and white tissue	Fibrous tissue with no significant inflammation	Degenerate scar tissue	No

The histological analyses were reviewed to determine whether the tissue reported was likely to be meniscal scar tissue.

and central composition, cellular distribution including histiocytes, nuclear ratio and vasculature. Atypical and malignant features, inflammation and degeneration was specifically looked for. A statistical review of the study was performed by a biomedical statistician.

RESULTS

The histological findings for nine patients showing the macroscopic and microscopic findings as well as the conclusion are outlined in Table 1. The histological analyses were reviewed to determine whether the tissue samples were likely to be meniscal scar tissue. The response was yes (2, 22%), no (6, 67%) and maybe (1, 11%).

DISCUSSION

Restoring the joint line is important in knee surgery. Joint line elevation can cause patella baja, patella button impingement, accelerated wear and loosening, quadriceps weakness, anterior knee pain, laxity in knee mid-flexion, varus-valgus instability and hyperextension instability[1]. It also results in decreased knee range of motion caused by impingement of the patellar implant on the tibial component[9,10]. Mid-flexion instability is caused by tight posterior structures that provide stability in extension and at 90 degrees of flexion[6]. A recent review of studies demonstrated elevation of the joint line in 79% of revision TKAs by 3-13 mm[2,5,7]. Singerman *et al*[11] demonstrated that raising or lowering the joint line in revision TKA by more than 8 mm resulted in a decreased range of motion and lower modified Mayo Clinic knee scores. In another study, elevation greater than 8 mm was associated with reduced mean Knee Society scores of 141 *vs* 125[3]. Several studies have shown that elevation more than 5 mm significantly affects the functional outcome in revision TKA[1]. Mason *et al*[5] showed a significant difference in total Bristol knee scores and the functional component of the score when there was more than 5 mm elevation of the joint line. Proximal joint line displacement of more than 5 mm caused decreased knee flexion, increased patellofemoral forces that can cause pain, subluxation, dislocation, fracture and increased varus-valgus instability particularly in mid-flexion in cadaveric knees[12]. A less common occurrence of distal placement of the joint line, patella alta, can alter tracking of the extensor mechanism that can cause increased patellar strain[11]. Although Scuderi and Insall suggest that elevation of the joint line by 10 mm has no significant clinical effect[13], and Partington *et al*[3] demonstrated only a marginal statistical significance in clinical scores in a series of 99 revision TKA cases with more than 8 mm elevation of the joint line the overwhelming evidence points to the restoration of the joint line being important for a good clinical result.

The "meniscal" scar is increasingly being used to identify the level of the native joint line in revision knee surgery. The menisci are two fibrocartilagenous, semilunar concave shaped tissues that rest on the medial and lateral tibial plateau. Functions of the menisci include assistance in joint stability, to bear and transmit loads within the knee and to act as "shock

absorbers"[14]. The normal meniscus contains two cell populations, fibroblasts on the meniscal surface and fibrochondrocytes in the inner surface. Meniscus tissue has a complicated shape and anchoring network, but displays great regional variation in its extracellular matrix components. The menisci consist of water (75%), water (20%), type Ⅰ collagen and other substances (5%); including proteoglycans, elastin and type Ⅱ collagen. The majority of collagen fibres are arranged circumferentially with some running radially. The meniscal periphery is highly fibrous and abundant in cells and collagen type Ⅰ, with the inner portion of the tissue resembles hyaline cartilage with fewer cells, type Ⅱ collagen and higher proteoglycan content. The outer portion of the meniscal tissue is highly vascularized, in comparison to the inner menisci that is devoid of blood vessels[14]. There are several morphological variations in meniscal tissue with cells being classified as fibroblasts, fibrocytes, chondrocytes, fibro-chondrocytes and meniscus cells by researchers. However these morphologies have various cell profiles. Cells in the superficial meniscal layer are oval or fusiform in shape and represent fibroblast morphology. Cells in the deeper meniscal layer have a more spherical appearance similar to chondrocytes. The outer proportion of meniscus contains type Ⅰ collagen predominantly with fibrocartilaginous matrix. The inner meniscus is more hyaline-like consisting of predominantly type Ⅱ collagen and contains chondrocyte-like cells[14]. Meniscal tissue may contain few or no intrinsic viable cells[15].

These features suggest that it is reliable histologically to identify meniscal tissue. Our pilot study only identified 33% of samples as potentially being of meniscal origin. The remaining 67% were not likely to be of meniscal origin. This suggests that the structure identified as the "meniscal" scar may actually represent scar tissue that forms in the available space of the joint line rather than actually represent the level of the native joint line where the meniscus once attached. This has significant implications on restoring the joint line. We recommend reliance on a number of markers to identify the joint line as outlined above and to exercise caution in using the "meniscal" scar.

COMMENTS

Background

During primary and revision knee surgery, it is important to restore the joint line but this can be difficult especially where there has been previous trauma, surgery or infection. A number of landmarks have been described in the literature to facilitate the accurate reproduction of the joint line in revision total knee arthroplasty (TKA) and include the "meniscal" scar amongst others.

Research frontiers

A number of landmarks have been described in the literature to facilitate the accurate reproduction of the joint line in revision TKA but none of them are absolutely accurate. The bony and radiological methods to identify the joint line can be unreliable, and are not standardised or reproducible. The bony landmarks may not be easily accessible or identifiable intraoperatively and hence the greater reliance on the "meniscal" scar.

Innovations and breakthroughs

The authors' findings suggest that the structure identified as the "meniscal" scar may actually represent scar tissue that forms in the available space of the recreated joint line rather than actually represent the level of the native joint line where the meniscus once attached.

Applications

The research has significant implications on restoring the joint line. The authors recommend reliance on a number of markers to identify the joint line as outlined in this paper, and to exercise caution in using the "meniscal" scar.

Terminology

The "meniscal" scar is the remnant soft tissue on the peripheries of the knee joint after excision of the menisci during earlier knee arthroplasty surgery.

Peer-review

The present study described the "meniscal" scar as one of many landmarks used to identify the native joint line. It's a very well written paper.

REFERENCES

1 **Porteous AJ**, Hassaballa MA, Newman JH. Does the joint line matter in revision total knee replacement? *J Bone Joint Surg Br* 2008; **90**: 879-884 [PMID: 18591596 DOI: 10.1302/0301-620X.90B7.20566]

2 **Romero J**, Seifert B, Reinhardt O, Ziegler O, Kessler O. A useful radiologic method for preoperative joint-line determination in revision total knee arthroplasty. *Clin Orthop Relat Res* 2010; **468**: 1279-1283 [PMID: 19890683 DOI: 10.1007/s11999-009-1114-1]

3 **Partington PF**, Sawhney J, Rorabeck CH, Barrack RL, Moore J. Joint line restoration after revision total knee arthroplasty. *Clin Orthop Relat Res* 1999; **(367)**: 165-171 [PMID: 10546611 DOI: 10.1097/00003086-199910000-00020]

4 **Figgie HE**, Goldberg VM, Heiple KG, Moller HS, Gordon NH. The influence of tibial-patellofemoral location on function of the knee in patients with the posterior stabilized condylar knee prosthesis. *J Bone Joint Surg Am* 1986; **68**: 1035-1040 [PMID: 3745240]

5 **Mason M**, Belisle A, Bonutti P, Kolisek FR, Malkani A, Masini M. An accurate and reproducible method for locating the joint line during a revision total knee arthroplasty. *J Arthroplasty* 2006; **21**: 1147-1153 [PMID: 17162174 DOI: 10.1016/j.arth.2005.08.028]

6 **Hoeffel DP**, Rubash HE. Revision total knee arthroplasty: current rationale and techniques for femoral component revision. *Clin Orthop Relat Res* 2000; **(380)**: 116-132 [PMID: 11064981 DOI: 10.1097/00003086-200011000-00016]

7 **Hofmann AA**, Kurtin SM, Lyons S, Tanner AM, Bolognesi MP. Clinical and radiographic analysis of accurate restoration of the joint line in revision total knee arthroplasty. *J Arthroplasty* 2006; **21**: 1154-1162 [PMID: 17162175 DOI: 10.1016/j.arth.2005.10.026]

8 **Stiehl JB**, Abbott BD. Morphology of the transepicondylar axis and its application in primary and revision total knee arthroplasty. *J Arthroplasty* 1995; **10**: 785-789 [PMID: 8749761 DOI: 10.1016/S0883-5403(05)80075-0]

9 **Selvarajah E**, Hooper G. Restoration of the joint line in total knee arthroplasty. *J Arthroplasty* 2009; **24**: 1099-1102 [PMID: 18757171 DOI: 10.1016/j.arth.2008.06.030]

10 **Yoshii I**, Whiteside LA, White SE, Milliano MT. Influence of prosthetic joint line position on knee kinematics and patellar position. *J Arthroplasty* 1991; **6**: 169-177 [PMID: 1875209 DOI: 10.1016/S0883-5403(11)80013-6]

11 **Singerman R**, Heiple KG, Davy DT, Goldberg VM. Effect of tibial component position on patellar strain following total knee arthroplasty. *J Arthroplasty* 1995; **10**: 651-656 [PMID: 9273377 DOI: 10.1016/S0883-5403(05)80210-4]

12 **Martin JW**, Whiteside LA. The influence of joint line position on knee stability after condylar knee arthroplasty. *Clin Orthop Relat Res* 1990; **(259)**: 146-156 [PMID: 2208849 DOI: 10.1097/00003086-199010000-00021]

13 **Scuderi GR**, Insall JN. The posterior stabilized knee prosthesis.

Orthop Clin North Am 1989; **20**: 71-78 [PMID: 2919081]
14 **Sanchez-Adams J**, Athanasiou KA. The knee meniscus: A complex tissue of diverse cells. *Cell Mol Bioeng* 2009; **2**: 332-340 [DOI: 10.1007/s12195-009-0066-6]
15 **Mesiha M**, Zurakowski D, Soriano J, Nielson JH, Zarins B, Murray MM. Pathologic characteristics of the torn human meniscus. *Am J Sports Med* 2007; **35**: 103-112 [PMID: 17092929 DOI: 10.1177/0363546506293700]

P- Reviewer: Hasegawa M, Malik H, Pastides PS, Robertson GA
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.62

World J Orthop 2017 January 18; 8(1): 62-67
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Observational Study

Tourniquets do not increase the total blood loss or re-amputation risk in transtibial amputations

Christian Wied, Peter T Tengberg, Gitte Holm, Thomas Kallemose, Nicolai B Foss, Anders Troelsen, Morten T Kristensen

Christian Wied, Peter T Tengberg, Gitte Holm, Thomas Kallemose, Anders Troelsen, Morten T Kristensen, Department of Orthopedic Surgery, Copenhagen University Hospital Hvidovre, 2650 Hvidovre, Denmark

Thomas Kallemose, Clinical Research Centre, Copenhagen University Hospital Hvidovre, 2650 Hvidovre, Denmark

Nicolai B Foss, Department of Anesthesiology and Intensive Care, Copenhagen University Hospital Hvidovre, 2650 Hvidovre, Denmark

Morten T Kristensen, Physical Medicine and Rehabilitation Research-Copenhagen, Department of Physical Therapy, Copenhagen University Hospital Hvidovre, 2650 Hvidovre, Denmark

Author contributions: All the authors contributed to the manuscript.

Institutional review board statement: This retrospective study was undertaken using data from medical records only. The local ethics committee approved the protocol. Protocol: H-6-2014-FSP-026.

Informed consent statement: Our retrospective study contained data from medical records only. The study was registered at the regional data protection agency (04.12.2012) (j. no. 01975 HVH-2012-053).

Conflict-of-interest statement: The authors declare that they have no conflicts of interest. No benefits in any form have been received or will be received from any commercial party related directly or indirectly to the subject of this article.

Data sharing statement: The data from this study will be available on request.

Manuscript source: Unsolicited manuscript

Correspondence to: Christian Wied, MD, Department of Orthopedic Surgery, Copenhagen University Hospital Hvidovre, Kettegaard Alle 30, 2650 Hvidovre, Denmark. chr.wied@gmail.com
Telephone: +45-20-616831
Fax: +45-38-623782

Received: August 11, 2016
Peer-review started: August 11, 2016
First decision: September 28, 2016
Revised: October 28, 2016
Accepted: December 7, 2016
Article in press: December 9, 2016
Published online: January 18, 2017

Abstract

AIM

To investigate the total blood loss (TBL) and the safety with respect to the re-amputation rate after transtibial amputation (TTA) conducted with and without a tourniquet.

METHODS

The study was a single-centre retrospective cohort study of patients with a primary TTA admitted between January 2013 and April 2015. All patients with a primary TTA were assessed for inclusion if the amputation was performed because of arteriosclerosis or diabetic complications. All patients underwent a standardized TTA procedure that was performed approximately 10 cm below the knee joint and performed with sagittal

flaps. The pneumatic tourniquet, when used, was inflated around the femur to a pressure of 100 mmHg above the systolic blood pressure. The number of blood transfusions within the first four postoperative days was recorded. The intraoperative blood loss (OBL), which is defined as the volume of blood lost during surgery, was determined from the suction volume and by the weight difference of the surgical dressings. The trigger for a blood transfusion was set at a decrease in the Hgb level < 9.67 g/dL (6 mmol/L). Transfusions were performed with pooled red blood cells containing 245 mL per portion, which equals 55 g/L of haemoglobin. The TBL during the first four postoperative days was calculated based on the haemoglobin level and the estimated blood volume. The re-amputation rate was evaluated within 30 d.

RESULTS

Seventy-four out of 86 consecutive patients who underwent TTA within the two-year study period were included in the analysis. Of these, 38 were operated on using a tourniquet and 36 were operated on without using a tourniquet. There were no significant preoperative differences between the groups. The patients in both groups had a postoperative decrease in their Hgb level compared with preoperative baseline values. The patients operated on using a tourniquet received approximately three millilitres less blood transfusion per kilogram body weight compared with patients operated on without a tourniquet. The duration of surgery was shorter and the OBL was less for the tourniquet group than the non-tourniquet group, whereas no significant difference was observed for the TBL. The TBL median was 859 mL (IQR: 383-1315) in the non-tourniquet group *vs* 737 mL (IQR: 331-1218) in the tourniquet group (P = 0.754). Within the 30-d follow-up period, 9 patients in the tourniquet group and 11 in the non-tourniquet group underwent a re-amputation at the trans-femoral level. The use of a tourniquet showed no statistically significant association with the 30-d re-amputation at the femur level in the multiple logistic regression model (P = 0.78). The only variable with a significant association with re-amputation was age (OR = 1.07; P = 0.02).

CONCLUSION

The results indicate that tourniquets do not cause severe vascular damage with an increased postoperative bleeding or failure rate as the result.

Key words: Total blood loss; Intraoperative blood loss; Transtibial amputation; Lower extremity amputation; Pneumatic tourniquet; Re-amputation

Core tip: The authors performed a retrospective cohort study on the use of tourniquets during transtibial amputation with the primary aim of comparing various estimates of blood loss and re-operation between the groups with or without a tourniquet. The basis for investigating this subject is the theoretical risk of increased bleeding due to vascular damage in the tourniquet group, which may, in turn, lead to increased risk of re-amputation due to local oedema, among other factors. We found no significant difference in the total blood loss when calculated on day four after surgery or in the 30-d re-amputation rate between the tourniquet and the non-tourniquet group.

Wied C, Tengberg PT, Holm G, Kallemose T, Foss NB, Troelsen A, Kristensen MT. Tourniquets do not increase the total blood loss or re-amputation risk in transtibial amputations. *World J Orthop* 2017; 8(1): 62-67 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/62.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.62

INTRODUCTION

Recent studies have illuminated the challenges in lower extremity amputation surgery where a high short-term amputation failure rate is especially notable[1,2]. No clear explanation for this result has yet been established. With this retrospective cohort study, we aimed to investigate if the possible cause is related to the use of a pneumatic tourniquet during amputation. Studies have shown that the use of a tourniquet reduces the intraoperative blood loss (OBL) and facilitates the procedure (decreases the duration of surgery) during transtibial amputations (TTA)[3]. However, despite this advantage, the use of tourniquets remains a controversial topic in amputation surgery due to potential complications[4,5]. There is a theoretical risk that the tourniquet could aggravate the blood loss during the first postoperative days. When the tourniquet pressure is applied to arteriosclerotic vessels, there is a risk of causing minor lesions and, as a result, seepage of blood. This seepage could be unrecognized by the operating surgeons due to the late onset re-perfusion of the limb after the release of the tourniquet[6] and cause severe postoperative bleeding. Such "hidden blood loss" could potentially lead to oedema of the stump and maybe associated with an increased risk of early re-amputation.

The aims of this study were (1) to compare the total blood loss (TBL) evaluated on the fourth postoperative day in patients operated with or without the use of a tourniquet and (2) to evaluate if the use of tourniquet increases the risk of re-amputation within the first 30 d after TTA performed with sagittal flaps (ad modum Persson).

MATERIALS AND METHODS

The study was a single-centre retrospective cohort study of patients with a primary TTA admitted between January 2013 and April 2015. All patients with primary TTA were assessed for inclusion if amputated because

of arteriosclerosis or diabetic complications. Exclusion criteria were a bilateral amputation procedure, on-going gastrointestinal bleeding, amputation due to trauma or incomplete data or death before the final measurement of haemoglobin (Hgb).

All patients underwent a standardized TTA procedure[7] performed approximately 10 cm below the knee joint and performed with sagittal flaps. The pneumatic tourniquet, when used, was inflated around the femur to a pressure of 100 mmHg greater than the systolic blood pressure[8]. It was released again at the end of the procedure but before final closure to secure haemostasis. The decision to use a tourniquet relied on the surgeons. Standardized care was provided for all patients regarding bandages, pain management, rehabilitation, fluid replacement, pausation of antiplatelet drugs, treatment with blood transfusions and thromboprophylaxis[9]. Tranexamic acid was not administered.

Blood loss

The number of blood transfusions within the first four postoperative days was recorded where day 0 is the day of surgery (after the start of the surgical procedure). The OBL, which is defined as the volume of blood lost during surgery, was determined from the suction volume and by the weight difference of the surgical dressings. The trigger for a blood transfusion was set at a decrease in the Hgb level < 9.67 g/dL (6 mmol/L). Transfusions were performed with pooled red blood cells containing 245 mL/portion, which equals 55 g/L of haemoglobin. The TBL during the first four postoperative days was calculated based on the haemoglobin level and the estimated blood volume. The blood volume and loss was determined according to gender, weight, height and the Hgb of the patient using formulae described in previous studies[10,11]:

Blood volume (l) = height $(m)^3 \times 0.356$ + weight (kg) × 0.033 + 0.183 for women, and Blood volume (l) = height $(m)^3 \times 0.367$ + weight (kg) × 0.032 + 0.604 for men. Hgb_{loss} = blood volume × (Hgb_{adm} - Hgb_{fin}) + Hgb_{trans}, where Hgb loss is the calculated total haemoglobin loss (g), Hgb_{adm} is the haemoglobin value on admission, Hgb_{fin} is the final recorded haemoglobin value on day four and Hgb_{trans} is the total amount of haemoglobin (in grams) in the transfused red blood cells before the measurement of Hgb_{fin}. The calculated blood loss was estimated using the following formula:
Blood loss in millilitre = (Hgb_{loss}/Hgb_{adm}) × 1000.

Other variables

Eight predictor variables (age, gender, body mass index, ASA score, duration of surgery, the rank of surgeon, intraoperative blood loss, and anti-fibrinolytic medication) were included in the TBL analysis due to their previously established influence on patient outcome[10,12]. Re-amputations were included if performed within 30 d following the index amputation. Six patients died within the 30-d follow-up period, and of these six patients, all underwent re-amputation; these patients were still included in the re-amputation model.

Statistical analysis

Continuous data are presented as median values with interquartile ranges (IQRs) or mean values with standard deviations. Differences between the groups were tested using a *t* test or a Mann-Whitney *U* test based on the normal distribution assumption. Categorical data are presented as numbers and were compared using the χ^2 test or Fisher's exact test in cases with cell counts of five or less. The associations of TBL and OBL with tourniquets were analysed using univariable and multivariable linear regression. The models use either TBL or OBL as the dependent variable and all previously mentioned predictor variables along with tourniquets as independent variables. The residuals in the models were tested and found to be normally distributed. A logistic regression model with tourniquet as the dependent variable was performed to identify potential inherent selection bias. The association between the 30-d re-amputation and the use of tourniquet was analysed using a multiple logistic regression model. The fit of the model was evaluated using a Hosmer-Lemeshow goodness of fit test. A *P* value of 0.05 was considered statistically significant. All analyses were performed by a biostatistician working in R 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 74 out of 86 consecutive patients who underwent TTA within the two-year study period were included in the analysis. Of these, 38 were operated on using tourniquets and 36 without. Six patients died before the 30-d follow-up (n = 3 in the tourniquet group and n = 3 in the non-tourniquet group). Trained residents or senior consultants performed the surgical procedures. Reasons for exclusion were bilateral amputation (n = 8), trauma (n = 2), and death before the fourth postoperative day (n = 2). There were no significant preoperative differences between the groups (Table 1). The patients in both groups had a postoperative decrease in their Hgb level compared with the preoperative baseline values, as illustrated in Figure 1A. The patients operated on using tourniquets received approximately three millilitres less transfusion blood per kilogram body weight than the patients operated on without using a tourniquet (Figure 1B, $P \leqslant 0.03$ for all days). The duration of surgery was shorter, and the OBL was less for the tourniquet group compared with the non-tourniquet group, whereas no significant difference was observed for the TBL. When the median OBL was subtracted from the median TBL for all the patients in the two groups, no significant difference was found (Table 2, P = 0.241). Within the 30-d follow-up, 9 patients in the tourniquet group and 11 in the non-tourniquet group had a re-amputation at the transfemoral level.

The logistic regression analysis with tourniquet as

Table 1 Demographic of the included patients

Variables	All patients *n* = 74	Tourniquet group *n* = 38	Non-tourniquet *n* = 36	*P* value
Sex (female/male)	25/49	11/27	14/22	0.511
Age (yr)	72.3 ± 11.0	71.3 ± 9.8	73.4 ± 12.1	0.415
Height (cm)	172 ± 9	173 ± 9	171 ± 9	0.178
Weight (kg)	74.2 ± 18.8	78.2 ± 18.6	70.1 ± 18.4	0.065
Body mass index	25.0 ± 5.4	25.9 ± 5.5	23.9 ± 5.2	0.112
Cause of amputation (diabetes/arteriosclerosis)	39/35	19/19	20/16	0.806
ASA group 1-2/3-4	13/60	5/32	8/28	0.374
Rank of surgeon, (resident/consultant)	49/25	24/14	25/11	0.745
Preoperative hemoglobin (g/dL)	10.9 ± 1.6	11.2 ± 1.6	10.8 ± 1.4	0.246
Preoperative	368 ± 150	352 ± 121	380 ± 169	0.481
Thrombocyte (× 10^9/L)				
NSAID or acetylsalicylic acid (yes/no)	40/34	20/18	20/16	0.985
Clopidogrel (yes/no)	14/60	8/30	6/30	0.854

Data are presented as numbers or mean values with standard deviations. ASA: American Society of anesthesiologists; NSAID: Nonsteroidal anti-inflammatory drug.

Table 2 Perioperative data from included patients

All patients	*n* = 71[1]	Tourniquet *n* = 35	Non-tourniquet *n* = 36	*P* value
Duration of surgery (min)	82 (66-106)	78 (60-97)	88 (72-112)	0.041
Duration of Tourniquet (min)		30 (18-42)		
Intraoperative blood loss (mL)	250 (150-500)	200 (100-300)	300 (225-600)	< 0.001
Total blood loss from day 0-4 (mL)	773 (336-1218)	737 (331-1218)	859 (383-1315)	0.754
Delta TBL-OBL (mL)	479 (66-855)	495 (115-900)	296 (-30-803)	0.241

Data are presented as median values with interquartile range. [1]Three patients missing due to no registration of the intraoperative blood loss. TBL: Total blood loss; OBL: Intraoperative blood loss.

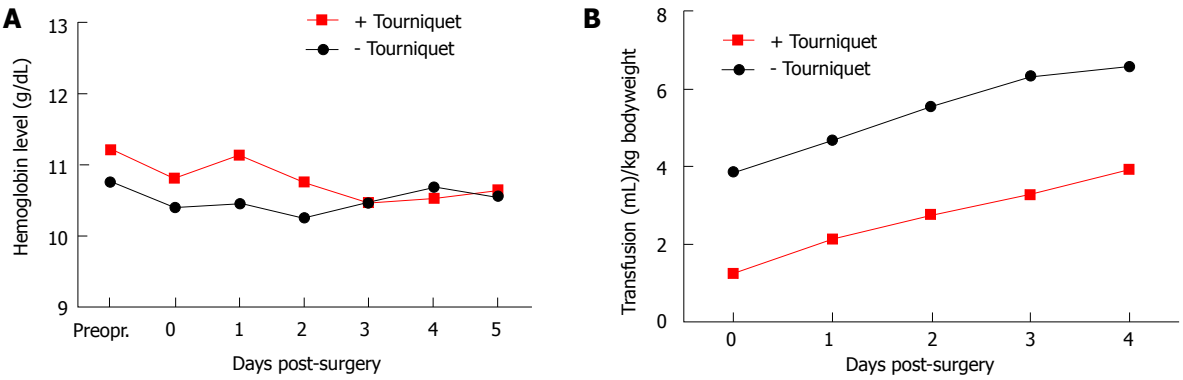


Figure 1 The patients in both groups had a postoperative decrease in their Hgb level compared with the preoperative baseline values. A: Development in Haemoglobin, Day 0 = day of surgery; B: Transfusion requirements.

the dependent variable identified no potential selection bias. However, there was a tendency that patients with a greater body mass index more often had a tourniquet installed during surgery (P = 0.059). The univariable linear regression analysis revealed no significant effect on the TBL from any of the selected variables. Still, the average TBL was lower for women and when consultants performed the procedures (Table 3). The multiple linear regression model of factors influencing the OBL showed that the non-tourniquet group, on average, experienced a greater OBL (mean of 243 mL, P = 0.004) compared with the tourniquet group. No other variables showed a significant association with OBL. There was no significant difference between the two groups regarding the TBL (Table 3). The use of a tourniquet showed no statistically significant association with a 30-d re-amputation at the femur level in the multiple logistic regression model (P = 0.78). The only variable with a significant association with re-amputation was age (OR = 1.07; P = 0.02). The Hosmer-Lemeshow goodness of fit test had a P-value of 0.06 in the re-amputation model.

DISCUSSION

We found that the use of a pneumatic tourniquet in

Table 3 Univariable and multivariate analysis with linear regression of association between risk factors for the total blood loss in the 74 patients

	Univariable estimate (95%CI)	*P* value	Multivariable estimate (95%CI)	*P* value
Tourniquet (used)	-39 (-370-293)	0.810	-78 (-431-275)	0.659
Age (per year older)	-10 (-25-5)	0.210	-7 (-23-9)	0.384
Women/men (men)	320 (-22-662)	0.066	221 (-149-590)	0.237
Specialist registrar/consultant (consultant)	-335 (-676-6)	0.054	-324 (-689-41)	0.081
Clopidogrel (in treatment)	33 (-390-456)	0.876	-86 (-520-349)	0.696
NSAID/acetylsalicylic acid (in treatment)	205 (-124-534)	0.218	223 (-126-572)	0.206
Duration of surgery (per minute)	1 (-5-7)	0.752	-3 (-10-5)	0.482
ASA-1-2/ASA 3-4 (ASA 3-4)	-1 (424-422)	0.995	-66 (-506-373)	0.764
Body mass index (per one unit)	21 (-9-52)	0.162	17 (-17-50)	0.322

Variables in parenthesis = reference; NSAID: Nonsteroidal anti-inflammatory drug; ASA: American society of anesthesiologists.

dysvascular TTA surgery ad modum Persson does reduce the duration of surgery, the blood transfusion rate (millilitres of blood transfusion per kilogram bodyweight) and the OBL, but there was no significant difference in the TBL when evaluated on the fourth postoperative day. We found no evidence that the tourniquet causes severe damage to vessels and, therefore, an increased postoperative blood loss. However, although not significant, we did find that patients who were operated by a consultant experienced a lower blood loss than those operated by surgeons with less experience. We found no difference between the groups regarding re-amputation at the femur level within 30-d follow-up. This finding is similar to studies on (ad modum Burgess) amputations with long posterior flaps and tourniquets[13,14].

Patients who require a TTA due to diabetes-related complications or severe arteriosclerosis are often old and have several co-morbidities[15]. Recent studies suggest that a more restrictive strategy towards blood transfusions in patients undergoing major amputations would be appropriate since blood transfusions appear to be associated with post-operative complications, such as acute renal failure and pneumonia[16,17]. The use of a pneumatic tourniquet around the femur can reduce the OBL and, therefore, the transfusion rate and risk of transfusion-related complications[13]. However, the effect of the tourniquet in TTA surgery is not thoroughly described, and the focus has primarily been towards the ability to reduce the OBL.

Our findings of a reduction in the OBL using a tourniquet are similar to the findings from a 2006 randomized controlled trial[13]. These findings are of no surprise since the major vessels are strangulated by the tourniquet and under-tied with sutures by the surgeons. It is reasonable to assume that the reduction in the OBL will reduce the transfusion rate[14]. Our concern was that the tourniquet could aggravate the seepage of blood from the wounds due to damage to the vessels during the time when the tourniquet is inflated. However, we found no statistically significant difference between the groups when the TBL was calculated on the fourth postoperative day indicating no radical change in blood loss.

The fact that the non-tourniquet group had a greater OBL and received more blood transfusions but had a similar TBL as the tourniquet group is a dilemma. This result could illustrate a late onset drop in Hgb level in the patients operated on using tourniquets, pointing at increased postoperative bleeding. Thus, it has been shown that an exsanguinated human limb will swell by approximately 10% of its original volume after the release of a pneumatic tourniquet and mainly due to the return of the exsanguinated blood volume[6]. This delayed reperfusion, which is associated with the duration of use of the tourniquet, creates a potential source of continuous minor bleeding if the surgeons overlook minor vessels not recognized during the time when the tourniquet is inflated[18]. Even if the surgical field is inspected for minutes after the release of the tourniquet, the possible delayed re-perfusion might still cause the non-under tied vessels to begin leaking when the patients are moved from the operating room. However, if serious seepage due to damaged vessels was the case, we would have expected a more dramatic drop in Hgb and a steeper development in the transfusion curve.

This study has some limitations. Although the formula used to calculate the TBL has been used widely in other orthopaedic sub-specialties[10,19], it has limitations in amputation surgery due to the changes in the body surface area after amputation. The patients will, because of this, have a different blood volume after surgery, which is difficult to correct in the equations. However, since we compared two groups with similar baseline values and our interests are the change in the values between the groups, we believe that the calculations are acceptable to illuminate the objectives of our study. Potential biases include the operating surgeons and the selection of patients for surgery with a tourniquet. However, the logistic regression model with respect to this matter showed no evidence that a specific patient's characteristics triggers the surgeons to use a tourniquet.

In conclusion, the use of a tourniquet reduces the duration of surgery, the OBL, and the transfusion rate in dysvascular TTA amputations. We found no significant

difference in the TBL when it is calculated on day four after surgery or in the 30-d re-amputation rate between the tourniquet and the non-tourniquet group. From a haemodynamics point of view, it appears to be advantageous and safe to use a tourniquet during ad modum Persson TTA amputations.

COMMENTS

Background

There is an increasing number of high-risk elderly and severely comorbid patients scheduled for dysvascular lower extremity amputations. Continuous optimization of current procedures is necessary. The use of a tourniquet in dysvascular amputees is considered controversial due to fear of vascular damage and potentially increased postoperative bleeding. The primary aim of this study was to compare the total blood loss after transtibial amputation conducted with and without tourniquets, and the secondary aim was to illuminate the safety aspect regarding the re-amputation rate following (ad modum Persson) transtibial amputations.

Research frontiers

The authors have reported the first series in the literature of patients with lower extremity amputations who were evaluated with the use of calculated total blood loss on day four after amputation. The approach provides valuable information regarding the blood loss when a tourniquet is applied during transtibial amputations.

Innovations and breakthroughs

The authors found that the use of a pneumatic tourniquet in dysvascular transtibial amputation surgery (ad modum Persson) does reduce the duration of surgery, the blood transfusion rate (millilitres of blood transfusion per kilogram bodyweight) and the intraoperative blood loss but without a significant difference in the total blood loss when evaluated on the fourth postoperative day. The authors found no evidence that the tourniquet causes severe damage to vessels and, therefore, an increased postoperative blood loss. The authors found no difference between the groups regarding re-amputation at the femur level within the 30-d follow-up. This finding is similar to studies on ad modum Burgess amputations with long posterior flaps and tourniquets.

Applications

The tourniquet can be considered during transtibial amputations to secure minimal blood loss and duration of surgery.

Peer-review

The study is valuable in showing that the total blood loss is not increased by either method.

REFERENCES

1 **Wied C**, Kristensen MT, Tengberg PT, Holm G, Krasheninnikoff M, Troelsen A. [Patients in need for major lower extremity amputations are a challenge]. *Ugeskr Laeger* 2015; **177**: pii: V10140540 [PMID: 26101134]

2 **Kristensen MT**, Holm G, Gebuhr P. Difficult to predict early failure after major lower-extremity amputations. *Dan Med J* 2015; **62**: A5172 [PMID: 26621398]

3 **Wakai A**, Winter DC, Street JT, Redmond PH. Pneumatic tourniquets in extremity surgery. *J Am Acad Orthop Surg* 2001; **9**: 345-351 [PMID: 11575914 DOI: 10.5435/00124635-200109000-00008]

4 **Smith DE**, McGraw RW, Taylor DC, Masri BA. Arterial complications and total knee arthroplasty. *J Am Acad Orthop Surg* 2001; **9**: 253-257 [PMID: 11476535 DOI: 10.5435/00124635-200107000-00005]

5 **Klenerman L**. The tourniquet in operations on the knee: a review. *J R Soc Med* 1982; **75**: 31-32 [PMID: 7057407]

6 **Silver R**, de la Garza J, Rang M, Koreska J. Limb swelling after release of a tourniquet. *Clin Orthop Relat Res* 1986; **(206)**: 86-89 [PMID: 3708997 DOI: 10.1097/00003086-198605000-00017]

7 **Persson BM**. Sagittal incision for below-knee amputation in ischaemic gangrene. *J Bone Joint Surg Br* 1974; **56**: 110-114 [PMID: 4818836]

8 **Ishii Y**, Matsuda Y. Effect of tourniquet pressure on perioperative blood loss associated with cementless total knee arthroplasty: a prospective, randomized study. *J Arthroplasty* 2005; **20**: 325-330 [PMID: 15809950 DOI: 10.1016/j.arth.2004.10.001]

9 **Kristensen MT**, Holm G, Krasheninnikoff M, Jensen PS, Gebuhr P. An enhanced treatment program with markedly reduced mortality after a transtibial or higher non traumatic lower extremity amputation. *Acta Orthop* 2016; **87**: 1-6 [DOI: 10.3109/17453674.2016.1167524]

10 **Foss NB**, Kehlet H. Hidden blood loss after surgery for hip fracture. *J Bone Joint Surg Br* 2006; **88**: 1053-1059 [PMID: 16877605 DOI: 10.1302/0301-620X.88B8.17534]

11 **Nadler SB**, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. *Surgery* 1962; **51**: 224-232 [PMID: 21936146]

12 **Taylor SM**, Kalbaugh CA, Blackhurst DW, Hamontree SE, Cull DL, Messich HS, Robertson RT, Langan EM, York JW, Carsten CG, Snyder BA, Jackson MR, Youkey JR. Preoperative clinical factors predict postoperative functional outcomes after major lower limb amputation: an analysis of 553 consecutive patients. *J Vasc Surg* 2005; **42**: 227-235 [PMID: 16102618 DOI: 10.1016/j.jvs.2005.04.015]

13 **Choksy SA**, Lee Chong P, Smith C, Ireland M, Beard J. A randomised controlled trial of the use of a tourniquet to reduce blood loss during transtibial amputation for peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2006; **31**: 646-650 [PMID: 16750790 DOI: 10.1016/j.ejvs.2006.03.008]

14 **Singh R**, Ghani A, Hakak A, Singh S, Singh B, Padha K, Muzafar K. Use of pneumatic tourniquet in transtibial amputation for peripheral vascular disease: A prospective randomized blinded controlled trail. *Int J Curr Res* 2015; **7**: 20086-20089

15 **Belmont PJ**, Davey S, Orr JD, Ochoa LM, Bader JO, Schoenfeld AJ. Risk factors for 30-day postoperative complications and mortality after below-knee amputation: a study of 2,911 patients from the national surgical quality improvement program. *J Am Coll Surg* 2011; **213**: 370-378 [PMID: 21723151 DOI: 10.1016/j.jamcollsurg.2011.05.019]

16 **D'Ayala M**, Huzar T, Briggs W, Fahoum B, Wong S, Wise L, Tortolani A. Blood transfusion and its effect on the clinical outcomes of patients undergoing major lower extremity amputation. *Ann Vasc Surg* 2010; **24**: 468-473 [PMID: 19900785 DOI: 10.1016/j.avsg.2009.07.021]

17 **Ponnusamy KE**, Kim TJ, Khanuja HS. Perioperative blood transfusions in orthopaedic surgery. *J Bone Joint Surg Am* 2014; **96**: 1836-1844 [PMID: 25378512 DOI: 10.2106/JBJS.N.00128]

18 **Klenerman L**, Crawley J, Lowe A. Hyperaemia and swelling of a limb upon release of a tourniquet. *Acta Orthop Scand* 1982; **53**: 209-213 [PMID: 7136565 DOI: 10.3109/17453678208992203]

19 **Sehat KR**, Evans RL, Newman JH. Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. *J Bone Joint Surg Br* 2004; **86**: 561-565 [PMID: 15174554 DOI: 10.1302/0301-620X.86B4.14508]

P- Reviewer: Bamberg SJM, Tuncer S **S- Editor**: Qiu S
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.68

World J Orthop 2017 January 18; 8(1): 68-76
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Observational Study

Reliability and concurrent validity of postural asymmetry measurement in adolescent idiopathic scoliosis

Ashleigh Prowse, Berit Aslaksen, Marie Kierkegaard, James Furness, Paul Gerdhem, Allan Abbott

Ashleigh Prowse, James Furness, Allan Abbott, Faculty of Health Science and Medicine, Bond University, Gold Coast, Queensland 4229, Australia

Berit Aslaksen, Marie Kierkegaard, Department of Physiotherapy, Karolinska University Hospital, SE-17177 Huddinge, Sweden

Marie Kierkegaard, Department of Neurobiology, Care Sciences and Society (NVS), Division of Physiotherapy, Karolinska Institutet, SE-17177 Huddinge, Sweden

Paul Gerdhem, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, SE-17177 Huddinge, Sweden

Allan Abbott, Department of Medical and Health Sciences, Division of Physiotherapy, Faculty of Health Sciences, Linköping University, SE-58183 Linköping, Sweden

Author contributions: Aslaksen B and Abbott A contributed to the study conception, design and data acquisition; Kierkegaard M and Abbott A contributed to data analysis; Prowse A, Furness J and Abbott A contributed to the interpretation of data; Prowse A, Aslaksen B, Kierkegaard M, Furness J, Gerdhem P and Abbott A contributed to the drafting, critical revision and final approval of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Swedish Research Council Regional Ethics Committee in Stockholm, Sweden (Dnr: 2012/172-31/4) and from Bond University Health Research Ethics Committee in 2014 (RO 1896).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

Conflict-of-interest statement: The authors have no conflict of interests. The authors have no financial or other interest in the product.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at allan.abbott@liu.se. Participants gave informed consent for data sharing of anonymized data.

Manuscript source: Invited manuscript

Correspondence to: Dr. Allan Abbott, PhD, Med, MSc, Physio, Grad, Cert, Clin, Ed, BExSci, Department of Medical and Health Sciences, Division of Physiotherapy, Faculty of Health Sciences, Linköping University, Lasarettsgatan, SE-58183 Linköping, Sweden. allan.abbott@liu.se
Telephone: +46-13-282495
Fax: +46-13-145004

Received: July 22, 2016
Peer-review started: July 27, 2016
First decision: September 6, 2016
Revised: September 17, 2016
Accepted: October 17, 2016
Article in press: October 18, 2016
Published online: January 18, 2017

Abstract

AIM

To investigate the reliability and concurrent validity of the Baseline® Body Level/Scoliosis meter for adolescent idiopathic scoliosis postural assessment in three anatomical planes.

METHODS

This is an observational reliability and concurrent validity study of adolescent referrals to the Orthopaedic department for scoliosis screening at Karolinska

University Hospital, Stockholm, Sweden between March-May 2012. A total of 31 adolescents with idiopathic scoliosis (13.6 ± 0.6 years old) of mild-moderate curvatures (25° ± 12°) were consecutively recruited. Measurement of cervical, thoracic and lumbar curvatures, pelvic and shoulder tilt, and axial thoracic rotation (ATR) were performed by two trained physiotherapists in one day. The intraclass correlation coefficient (ICC) was used to determine the inter-examiner reliability (ICC2,1) and the intra-rater reliability (ICC3,3) of the Baseline® Body Level/Scoliosis meter. Spearman's correlation analyses were used to estimate concurrent validity between the Baseline® Body Level/Scoliosis meter and Gold Standard Cobb angles from radiographs and the Orthopaedic Systems Inc. Scoliometer.

RESULTS

There was excellent reliability between examiners for thoracic kyphosis (ICC2,1 = 0.94), ATR (ICC2,1 = 0.92) and lumbar lordosis (ICC2,1 = 0.79). There was adequate reliability between examiners for cervical lordosis (ICC2,1 = 0.51), however poor reliability for pelvic and shoulder tilt. Both devices were reproducible in the measurement of ATR when repeated by one examiner (ICC3,3 0.98-1.00). The device had a good correlation with the Scoliometer (rho = 0.78). When compared with Cobb angle from radiographs, there was a moderate correlation for ATR (rho = 0.627).

CONCLUSION

The Baseline® Body Level/Scoliosis meter provides reliable transverse and sagittal cervical, thoracic and lumbar measurements and valid transverse plan measurements of mild-moderate scoliosis deformity.

Key words: Reliability; Validity; Scoliosis; Posture; Assessment

Core tip: The Baseline® Body Level/Scoliosis meter is inexpensive, easily administered and provides reliable transverse and sagittal cervical, thoracic and lumbar measurements as well as valid transverse plan measurements of mild-moderate scoliosis deformity.

Prowse A, Aslaksen B, Kierkegaard M, Furness J, Gerdhem P, Abbott A. Reliability and concurrent validity of postural asymmetry measurement in adolescent idiopathic scoliosis. *World J Orthop* 2017; 8(1): 68-76 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/68.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.68

INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is a three-dimensional (3D) structural deformation of the spine in otherwise normal adolescents during puberty[1]. AIS is characterized as: (1) a lateral spinal curvature in the frontal plane (Cobb angle > 10°); (2) a disturbance of spinal curvatures in the sagittal plane; and (3) an axial rotation of vertebrae in the transverse plane. In the majority of cases, spinal asymmetry is noted during primary health care screening[2], and the patients are referred to specialist orthopaedic clinics for assessment, longitudinal observation and treatment[3].

Methods for the clinical evaluation of trunk deformity that are reliable, valid, feasible and acceptable is of great importance for patients and clinicians to evaluate and monitor aspects of AIS[4]. Methods that are easy to administer and inexpensive could provide essential information replacing the need for repeated radiation from radiographs and also expensive surface topography equipment. An easy to administer and inexpensive test for scoliosis is measuring the axial thoracic rotation (ATR) using a Scoliometer[5]. The inter-observer and intra-observer reliability of Scoliometer assessments have in several studies ranged from very good to excellent, and the tool is reportedly useful as a screening device[6]. Further, the validity of the Scoliometer when correlated to the Gold Standard Cobb angle from radiographs has been found to be fair to very good[6,7]. A limitation with the Scoliometer ATR measurement and Cobb angle from radiographs is however that it only measures deformity in a single anatomical plane when scoliosis is a 3D deformity.

To obtain a better description of scoliosis related morphologic deformity in several anatomical planes and reduce the need of radiographic exposure, techniques such as 3D postural analysis systems have been developed[8]. However, these measurement systems are not accessible for most clinicians and require specialized training and complex data processing. Thus, a simpler, inexpensive 3D tool is needed to measure scoliosis morphology in a clinical setting. A thorough literature search[9] revealed no published research investigating the reliability and/or validity of simpler, inexpensive 3D tools. The Baseline® Body Level/Scoliosis meter is an inexpensive and easy to administer clinical tool that can be used to obtain quick measurements of scoliosis morphology in three anatomical planes.

The primary objective of this study was to investigate the inter-examiner reliability for the Baseline® Body Level/Scoliosis meter for the following parameters: Cervical, thoracic and lumbar curve in the sagittal plane; pelvic and shoulder tilt in the frontal plane as well as the inter-examiner and intra-examiner reliability for ATR in the transverse plane. A secondary objective was to investigate the concurrent validity of the Baseline® Body Level/Scoliosis meter compared to Orthopaedic Systems Inc. Scoliometer and Cobb angle from radiographs and discuss its clinical utility.

MATERIALS AND METHODS

Research design

This is an observational reliability and concurrent validity

Table 1 Patient demographic and descriptive data

	Mean (± SD)	*n* (%)
Age (yr)	13.6 (0.6)	
Sex		
Males		4 (13)
Females		27 (87)
Primary curve Cobbs angle (degrees)	25 (12)	
Scoliosis type (Lenke classification)		
Main thoracic (1AN)		22 (71)
Thoracolumbar/lumbar (5CN)		9 (29)

study. All study participants, or their legal guardian, provided informed written consent prior to study enrolment. The study received ethical approval from the Swedish Research Council Regional Ethics Committee in Stockholm, Sweden (Dnr: 2012/172-31/4) and from Bond University Health Research Ethics Committee in 2014 (RO 1896). The study followed Guidelines for Reporting Reliability and Agreement Studies, which contains issues to be addressed when reliability and agreement studies are reported[10].

Participants

Recruitment was achieved through consecutive adolescent referrals to the Orthopaedic department for scoliosis screening at Karolinska University Hospital, Stockholm, Sweden between March-May 2012. Informed consent was obtained from individuals that fulfilled the inclusion criteria to participate in the study. Inclusion criteria included: (1) diagnosis of idiopathic scoliosis; and (2) males and females aged 9-17 years. Exclusion criteria included: (1) scoliosis with a possible non-idiopathic aetiology (patients were excluded from the study if the pathogenesis of the scoliosis was due to a neuromuscular, neurological, congenital malformation or trauma related comorbidity); or (2) inability to understand Swedish. Thirty-one patients participated in the study, 27 females and 4 males with a mean age of 13.6 years and mean Cobb angle of 25°. The number of participants was deemed adequate to establish a practically useful clinically important change[11]. Patient characteristics and demographics are presented in Table 1.

Procedures and instrumentation

Two physiotherapists (10 and 15 years' experience) performed examination of all participants with AIS, using two devices. To standardize their method of assessment the examiners trained in the use of the devices for 5 h before the outset of the study and had clinical experience in the application of the devices. The Baseline® Body Level/Scoliosis meter (Figure 1), developed by Orthopaedics Systems Incorporation®, is a fluid filled inclinometer in which an enclosed ball shows the ATR on a scale of 1 degree increments that range from 0-30 degrees. To improve the conformity of measurements, the recorded value is the one corresponding to the highest value entirely crossed by the enclosed ball. Measurements of cervical, thoracic, lumbar curvatures and pelvic and shoulder tilt, as well as ATR were performed with the Baseline® Body Level/Scoliosis meter. Measurements of ATR were also performed using the original Orthopaedics Systems Incorporation "Scoliometer". In order to reduce the error associated with the measurement, both examiners used the same devices.

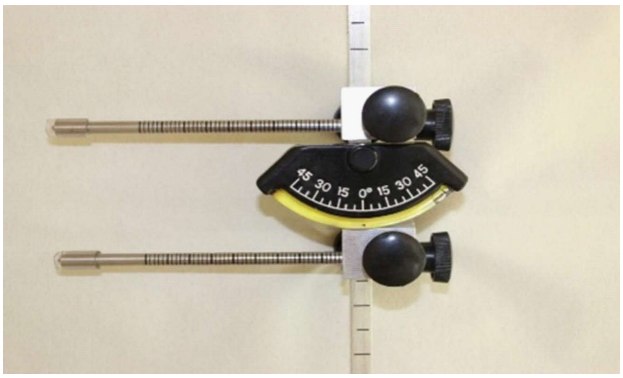


Figure 1 Baseline® Body Level/Scoliosis meter.

During the measurement, all subjects were barefoot and their back was exposed, which allowed palpation of the entire back. Trousers were lowered to the hip if there was difficulty in palpating the apex of the sacrum or L5. Measurements conducted by both raters were performed within 30 min and were executed in the same order. Examiners had no access to the results of the other measures to avoid recall of the previous values. A protocol that allowed as few manual changes as possible of the Baseline® Body Level/Scoliosis meter was chosen to obtain an efficient examination. The ATR measurements were repeated 3 times, as these measurements were associated with more sources of error. Other measurements were only executed once. Between each evaluation, the subject was instructed to leave the evaluation position to rest. The order of the therapist first taking measurements was randomized. Specific procedures regarding test positions, and device placement were performed according to the following protocol.

Measures using the Baseline® Body Level/Scoliosis meter

Cervical curve in centimetres: The subject was placed in standing position with feet together and asked to "stand straight". The spinous process of C4 was palpated by palpating the process of C2, and then C3 to C4. Then the spinous process of C7 was palpated, the most prominent process in the cervical area, and was distinguished from C6 by bending the head backwards, causing C6 to move anteriorly. After localizing C4 and C7 the rods of the Scoliometer was placed over these spinous processes. The lower rod was unlocked until the gauge indicated 0. Then the rod was locked and the

measurements were recorded in centimetres.

Thoracic curve in centimetres: The patient was placed in a standing position with feet together and asked to "stand straight". The spinous process of C7 was palpated to place the upper rod. The bottom rod was placed at the spinous process of the vertebrae at the apex of the thoracic kyphosis. If there was a deviation of curvature in the frontal plane, the position of the gauge had to be held vertically and therefore the rod could be placed lateral to the spinous process. The lower rod was unlocked until the gauge indicated 0. Then the rod was locked and the measurements were recorded in centimetres.

Anteroposterior angulation L5 and Sacrum in centimetres: The patient was placed in standing position with feet together and asked to "stand straight". The spinous process of L5 was palpated by placing the index fingers over the crest of the ilium and then palpating the spinous process at the same level, that usually is L4, and then the lower process should be L5. The next rod was placed over the most prominent tubercle of the sacral curvature. The lower rod was unlocked until the gauge indicated 0. Then the rod was locked and the measurements were recorded in centimetres.

ATR in degrees: The patient was placed in standing position with feet together and asked to "stand straight", the trunk was anteriorly flexed and almost parallel to the ground, with relaxed arms, hanging perpendicular to the trunk and hands folded. The distance between the rods was set individually for each patient, and placed in the middle of both right and left thorax sides in relation to the spinal column posteriorly level with the apex of the curvature. Both of the rods were locked in the same length and placed over the most prominent point of the curvature. In this position the gauge reading showed the degree of the curvature. Two point five degrees or more was listed.

Pelvic tilt in degrees: The patient was placed in standing position with feet together and asked to "stand straight". Both rods were loosened and placed firmly over each iliac crest and locked with the gauge in the middle. In this position the gauge reading showed the degree of the tilt with 2.5 degrees or more listed.

Shoulder tilt in degrees: The patient was sitting at a 43.5 cm high chair and asked to "sit straight". The sitting position was chosen to avoid the influence of leg length difference. Both rods were loosened and placed firmly over each acromioclavicular articulation and locked with the gauge in the middle. To palpate the acromioclavicular joint (AC joint), find the "soft spot" at the back of the clavicle, anterior to that is the AC joint. In this position the gauge reading showed the degree of the tilt, anything equal to or greater than 2.5 degrees was listed.

Measures using the Orthopaedics Systems Incorporation Scoliometer

ATR in degrees: The patient was placed in standing position with feet together and asked to "stand straight", with trunk anteriorly flexed and parallel to the ground, with relaxed arms, hanging perpendicular to the trunk and hands folded. The value indicated by the metal sphere after placing the Scoliometer over the spinous process is used to indicate the value of axial trunk rotation. Examiners drew the Scoliometer along the spinous processes to discover the level with the highest reading and measured the axial trunk rotation with 1 degree or more listed.

Measures of radiology Cobb angle in degrees

Standing scoliosis posteroanterior radiographs were performed and measured by a radiologist, and double-checked by the physiotherapist. For the lateral image the feet are together and parallel to the screen. The right side of the body faces the radiation source. The patient was to hold his/her hands on a bar in front of the body and above the shoulders, so that the shoulders and elbows were at 90 degrees flexion. In this position the arms did not obscure the vertebral column. The hands were placed adjacent to one another. If the patient was wearing a brace, it was not to be worn the night prior to the scoliosis radiographs being taken. The Cobb angle was formed by the inclination of the upper end plate of the upper end vertebra and the inclination of the lower end plate of the lower end vertebra measured on posteroanterior view X-ray radiographs[12].

Statistical analysis

Two independent researchers completed statistical analysis of the data utilizing SPSS software Version 22. The statistics were additionally reviewed by three of the authors who have specific biostatistical competency for reliability and validity studies. Descriptive statistics including means, standard deviations and ranges (minimum and maximum) were calculated for both raters and tabulated as a summary of measurements and patient demographic data. The intraclass correlation coefficient (ICC) is nowadays the preferred retest correlation coefficient and was the method used to determine reliability[11]. A two-way random analysis of variance and ICC2,1 was used to determine inter-observer reliability in small groups with two test occasions. The intra-observer reliability was determined for ATR with a two way mixed analysis of variance and ICC3,3 using the average of three measurements. The ICC was interpreted with values of < 0.39 as poor, 0.40-0.74 as adequate, and > 0.75 as excellent, as these are considered the minimum standards for reliability coefficients sufficient for research purposes[13]. A 95%CI for the mean difference between the two

Table 2 Summary of trunk measurements in 3 anatomical planes

	Examiner A						Examiner B					
	Mean	*n*	SD	Range	Min	Max	Mean	*n*	SD	Range	Min	Max
Cervical lordosis (cm)	2.5	31	0.8	3	1	4	3.0	31	0.8	4	2	6
Thoracic kyphosis (cm)	3.7	31	1.7	7	1.2	8.2	3.7	31	1.7	7.4	0.6	8
Lumbar lordosis (cm)	3.0	31	1.0	4.2	0.6	4.8	3.5	31	1.0	3.8	1.4	5.2
Pelvic tilt (degrees)	1.8	29	1.9	7.5	0	7.5	3.3	29	2.5	10	0	10
Shoulder tilt (degrees)	1.2	30	1.4	5	0	5	1.3	30	1.7	7.5	-2.5	5
ATR Scoliometer (degrees)	10.2	31	6.1	27.5	0	27.5	10.5	31	6.1	27.5	0	27.5
ATR Baseline Level/Scoliosis meter (degrees)	10.9	31	5.8	24.5	3	27.5	10.3	31	5.6	23.8	0	23.8

ATR: Axial thoracic rotation.

Table 3 Inter-examiner reliability of the Baseline® Body Level/Scoliosis meter measurements

Measures	ICC2,1	95%CI for ICC	Mean difference	95%CI for mean difference	SEM	SRD	95% SRD
Cervical Lordosis (cm)	0.51	0.02-0.76	-0.53	-0.84-0.21	0.82	2.28	-2.81-1.76
Thoracic Kyphosis (cm)	0.94	0.87-0.97	0.013	-0.29-0.31	1.66	4.60	-4.47-4.47
Lumbar Lordosis (cm)	0.79	0.47-0.91	-0.44	-0.71-0.17	0.99	2.74	-3.18-2.3
ATR Scoliometer (degrees)	0.94	0.88-0.97	-0.35	-1.39-0.70	6.07	16.81	-17.16-16.47
ATR Baseline Level/Scoliosis meter (degrees)	0.92	0.84-0.96	0.60	-0.51-1.72	5.67	15.72	-15.12-16.33
Shoulder tilt (degrees)	-0.30	-1.86-0.39	-0.17	-1.05-0.71	1.56	4.33	-4.49-4.49
Pelvic tilt (degrees)	-0.41	-0.89-0.47	-1.47	-0.267-0.26	2.32	6.42	-7.89-4.96

ICC: Intraclass correlation coefficient; ATR: Axial thoracic rotation; SEM: Standard error of measurement; SRD: Smallest real difference.

test occasions was formed with the formula 95%CI = mean diff - 2.05 × standard deviation (SD) to determine if a true systematic difference existed between the two raters[11]. The mean difference between raters was calculated to evaluate changes in the mean between two test occasions[11]. To interpret absolute reliability the standard error of measurement (SEM) was calculated using the formula SEM = $\sqrt{WMS}$[11,14], where WMS is the mean square error term from the analysis of variance[11]. The smallest real difference (SRD and 95% SRD) was also calculated to determine the magnitude of change that would exceed the threshold of measurement error at the 95% confidence level[11]. The formula used was SRD = 1.96 × SEM × $\sqrt{2}$. To calculate the 95% levels of agreement the formula mean difference - 2.05 × SD was applied, where *n* = 2.05 is a good approximation when the number of subjects is > 30[11]. The Spearman's correlation coefficient was used to analyse the concurrent validity between measurements from the Scoliometer devices and Cobb angles from radiographs, as Spearman's are not dependent on normality of test data. Correlation values smaller than 0.25 were considered poor, between 0.25 and 0.49 were low, between 0.50 and 0.69 were moderate, between 0.70 and 0.89 were good, and between 0.90 and 1.0 were excellent[15].

RESULTS

Descriptive results

Table 2 reports a descriptive summary of measurements taken by each of the raters.

Inter-examiner reliability of the Baseline® Body Level/Scoliosis meter and Scoliometer

Table 3 presents the inter-examiner reliability for the Baseline® Body Level/Scoliosis meter. In the measurement of thoracic kyphosis and ATR, there was excellent reliability between examiners with an ICC2,1 of 0.94 (95%CI: 0.87-0.97) and 0.92 (95%CI: 0.84-0.96) respectively. When taking into consideration excursions in the 95%CI, the method was adequate-to-excellent in the measurement of lumbar lordosis, with an ICC2,1 of 0.79 (95%CI: 0.47-0.91). Furthermore varying adequacy could be seen in the inter-observer reliability in the measurement of cervical lordosis (ICC2,1 = 0.51, 95%CI: 0.02-0.76), and poor inter-examiner reliability when used to measure secondary curves in the frontal plane; pelvic tilt (ICC2.1 = -0.41, 95%CI: -0.89-0.47) and shoulder tilt (ICC2,1 = -0.30, 95%CI: -1.86-0.39). When measurements from the Baseline® Body Level/Scoliosis meter were compared to measurements from the Scoliometer, which is the current Gold Standard to measure ATR, the reliability was similar, with an ICC2,1 of 0.92 (0.84-0.96), compared to the Scoliometer with an ICC2,1 of 0.94 (95%CI: 0.88-0.97).

Systematic error exists between raters in the mean measurements of lumbar lordosis and pelvic tilt when using the Baseline® Body Level/Scoliosis meter, as shown by the 95%CI for mean difference, suggesting non-random error exists. A large measurement error between examiners' measurements exists for pelvic

Table 4 Intra-examiner reliability of the Baseline® Body Level/Scoliosis meter and Orthopaedic Systems Inc. Scoliometer measurements

Measures	Examiner	ICC3,3	95%CI for ICC		Mean difference	95%CI for mean difference	SEM	SRD	95% SRD
ATR Scoliometer (degrees)	A	0.99	0.99-1.00	A1	0	0	1.35	3.74	-3.74-3.74
				A2	-0.24	-3.00-3.05	1.35	3.75	-4.00-3.51
				A3	-0.32	2.52-2.40	1.33	3.70	-3.37-3.37
	B	0.98	0.97-1.00	B1	0	0	1.39	3.90	-3.87-3.87
				B2	-0.23	-3.08-2.66	1.4	3.87	-3.65-3.65
				B3	0.34	2.63-3.34	1.47	4.07	-3.73-4.41
ATR baseline level scoliosis meter (degrees)	A	1.00	1.00-1.00	A1	0	0	1.37	3.79	-3.38-0.38
				A2	-0.32	-3.03-3.07	1.47	4.07	-4.04-4.04
				A3	-0.05	2.97	1.48	4.09	-4.14-4.14
	B	0.98	0.96-0.99	B1	0	0	1.23	3.40	-3.40-3.40
				B2	0.52	-2.24-2.54	1.35	3.75	-2.88-3.91
				B3	0.53	3.28-3.60	1.50	4.17	-3.63-4.70

ICC: Intraclass correlation coefficient; ATR: Axial thoracic rotation; SEM: Standard error of measurement; SRD: Smallest real difference.

tilt (SEM = 2.3°) and shoulder tilt (SEM = 1.6°). The small 95% SRD between measurements taken by two separate examiners for thoracic kyphosis (-4.5-4.5) and ATR with Baseline® Body Level/Scoliosis meter (-15.1-16.3), and ATR measured with Scoliometer (-17.2-16.5), suggests these measurements are more sensitive and can be considered highly reliable.

Intra-examiner reliability of the Baseline® Body Level/ Scoliosis meter and Scoliometer in measuring ATR

Table 4 presents the intra-examiner reliability for the ATR measures. Excellent intra-examiner reliability was seen in ATR measured by the Baseline® Body Level/ Scoliosis meter (Examiner A ICC3,3 = 1.00, Examiner B = 0.98) and by the Scoliometer (Examiner A ICC3,3 = 0.99, Examiner B = 0.98).

Concurrent validity of the Baseline® Body Level/ Scoliosis meter compared to Scoliometer and Cobb angle from radiographs

Table 5 presents the concurrent validity for the Baseline® Body Level/Scoliosis meter compared to the Scoliometer as well as Cobb angle as measured by radiographs. The correlation between measurements using the Baseline® Body Level/Scoliosis meter and measurements from the Scoliometer for ATR (degrees) was indicated by a Spearman's rho of 0.78 indicating a good, statistically significant correlation between these measures. When ATR measured with the Scoliometer and Baseline® Body Level/Scoliosis meter were each compared to Cobb angle measured from radiographs, there was a moderately significant correlation of rho = 0.58 and rho = 0.63, respectively. When Cobb angles measured from radiographs were compared with thoracic kyphosis in the sagittal plane, there was a low correlation (rho = 0.32).

DISCUSSION

In line with the study's objectives, the reliability and validity of the Baseline® Body Level/Scoliosis meter for measuring scoliosis morphology in three anatomical planes were studied. Results showed that the Baseline® Body Level/Scoliosis meter was as accurate as the Scoliometer when used repeatedly by the same examiner or by different examiners for the measurement of ATR in the transverse plane on patients with mild-moderate scoliosis. The Baseline® Body Level/Scoliosis meter had similar reliability in the measurement of ATR when compared to other high quality reliability studies assessing the Scoliometer[6,16,17] and smartphone applications such as the Scolioscreen with an acrylic sleeve[18].

Based on our results for assessment of the sagittal plane, the Baseline® Body Level/Scoliosis meter can be recommended based on excellent reliability for use by trained examiners for measuring thoracic kyphosis and lumbar lordosis on patients with mild-moderate scoliosis. Furthermore, in the measurement of cervical lordosis on patients with mild-moderate scoliosis, the instrument showed adequate reliability but larger variability in measurements between examiners. Previous research suggests that increased cervical kyphosis is often a secondary coupling effect of increased thoracic kyphosis and coronal plan deformation and that despite this, global spine-pelvis alignment remains well-balanced[19]. This suggests that for the purpose of screening mild-moderate scoliosis, measurement of thoracic and lumbar sagittal curvature may be suffice, leaving cervical curvature measures redundant in many cases. However the utility of cervical curvature measurement suggests that in may be relevant for some mild-moderate cases and may be of more importance when screening moderate-severe scoliosis.

When compared to the reliability of 3D computerized systems, the Baseline® Body Level/Scoliosis meter had similar reliability for thoracic measures but was less reliable for measuring lordotic sagittal curvatures[20]. Potential challenges in the accuracy of palpation of anatomical landmarks have been noted in reliability studies to cause observer variations especially in the sagittal and frontal planes[7,21,22].

A low inter-examiner reliability was found between trained examiners when measuring frontal plane

Table 5 Spearman's bivariate correlations (n = 31) of Baseline® Body Level/Scoliosis meter compared to gold standard Cobb angles from radiographs, and compared to Orthopaedic Systems Inc. Scoliometer

Baseline Level/Scoliosis meter	Cobb angle (degrees)
Cervical lordosis (cm)	-0.22
Thoracic kyphosis (cm)	-0.32
Lumbar lordosis (cm)	-0.03
ATR (degrees)	0.63
Pelvic tilt (degrees)	0.13
Shoulder tilt (degrees)	-0.00
ATR Scoliometer (degrees)	0.58
Baseline Level/Scoliosis meter ATR (degrees)	0.77

ATR: Axial thoracic rotation.

morphology in patients with mild-moderate scoliosis. The Baseline® Body Level/Scoliosis meter had similar reliability for shoulder and pelvic tilt measurements when compared to previous literature on aesthetic clinical tools, such as the Trunk Aesthetic Clinical Evaluation tool[21]. A potential source of the low reliability could be a low sensitivity for smaller measures in these frontal plane secondary measures of spinal curvature. For example, examiners in our study reported that when using the Baseline® Body Level/Scoliosis meter the fluid filled ball required 2.5 degrees of deformity in order for the ball to move. Therefore, the device was not sensitive for assessment of smaller secondary measures in the frontal plane for pelvic and shoulder tilt, and a digital recorder may be more precise. Based on our results, one can hypothesis that the Baseline® Body Level/Scoliosis meter may be reliable for larger secondary measures in the frontal plane for pelvic and shoulder tilt that are more common in moderate to severe cases of AIS. Future research should therefore assess the reliability and validity of the Baseline® Body Level/Scoliosis meter for patients with moderate to severe cases of AIS, with curvatures > 30-40 degrees to confirm this hypothesis.

In accordance with the secondary objectives of the study, measurements of ATR with the Baseline® Body Level/Scoliosis showed good correlation with measurements from the Scoliometer as well as the Gold Standard Cobb angles from radiographs. When examined in light of previous literature, the device had a similar correlation with Gold Standard Cobb angle from radiographs as the Scoliometer did[6,20], and better validity than 2D photography[23] and trunk surface examination[24] but lower validity than 3D computerized systems[20]. Therefore, the Baseline® Body Level/Scoliosis meter could be used for screening, and to monitor curve progression through measurement of ATR. However, ATR measures alone cannot replace Cobb angle measured from radiographs in the diagnosis of the condition, as it has been discussed in statistical literature that greater accuracy is required, with Spearman's correlation of > 0.9, for a measure to be considered accurate for diagnosis[15]. Furthermore, it is important to note that when screened, not all adolescents have an ATR of the spine, despite changes in the sagittal and frontal planes. When the apex of the Cobb angle is higher up the thoracic region, less rotation is seen in the spine due to coupled movement[25].

Additional frontal and sagittal plane measurements provided by the Baseline® Body Level/Scoliosis meter may add important information regarding clinical signs of progression to inform treatment and diagnostic decisions. Cervical and thoracic sagittal curves and frontal plane measures in our study had however low correlation with Cobb angle, perhaps because a Cobb angle of 25° may not have been severe enough and considering we had a larger group of patients with thoracic curves who often have less disturbed lordosis in the cervical and lumbar spine[25].

This study has its strengths and weaknesses one must consider when interpreting results. A methodological strength of the study was that two physiotherapists performed measurements in 3 anatomical planes for all subjects using the same Baseline® Body Level/Scoliosis meter with no knowledge of results between examiners. The therapists received 5 h training, and were considered proficient with application of the tool. Although there is no recommendation in the literature regarding the training time necessary, previous studies have trained up to 10 h of which the authors suggested contributed to the good to excellent reliability within the study[26]. The study method aimed to control potential variance in measures caused by fatigue from repeated measures by providing rest periods between measurements. Similarly the study method aimed to control variance due to patient flexibility, body mass index (BMI) or previous activity by re-testing within the same session. The methods lacked however intra-rater reliability measures for sagittal and frontal plan measures which could have provided more thorough information on reliability of the Baseline® Body Level/Scoliosis meter With regards to sample representativeness it can be considered a strength that our patient sample is consecutively recruited, has a female to male 6.8:1 ratio and main thoracic (1AN) to thoracolumbar/lumbar (5CN) 2:1 curve type ratio representative of the current prevalence of AIS in the population for a mean curvature of 20°-30°[27]. A possible limitation however is our sample size was not powered for gender or curve type subgroup analysis[27]. The size of our recruited sample was however adequate to establish group level clinically important change values and the sample was well above the minimum suggested sample size of 15-20 patients for reliability studies with continuous data[11].

Despite the discussed strengths and weaknesses of the study, the benefits of the Baseline® Body Level/Scoliosis meter outweigh the use of the Scoliometer and Cobb angle for initial screening of mild-moderate scoliosis. This mainly due to it providing reliable, valid, feasible and acceptable measures in several anatomical planes aiding decision making regarding the need for radiographic exposure and potential interventions to prevent AIS progression and dysfunction.

Within the study the authors were able to investigate the manual anthropometric measurement of 3D curvatures in AIS with a device that is inexpensive, easily administered and applicable in a clinical setting. The Baseline® Body Level/Scoliosis meter has the ability to provide reliable and valid measurements of mild-moderate scoliosis deformity in transverse and sagittal planes for the cervical, thoracic and lumbar spine, useful for screening scoliosis morphology.

COMMENTS

Background

Adolescent idiopathic scoliosis (AIS) is a structural deformation of the spine in the frontal, sagittal and transverse plans. Methods for the clinical evaluation of trunk deformity in all 3 planes that are reliable, valid, feasible and acceptable are of great importance for the prospecive measurement of severity and assessing the need of interventions to prevent deformity progression and dysfunction. Currently repeated radiological exposure or non-radiological methods requiring expensive equipment, specialized training and complex data processing are available.

Research frontiers

Current no published research has investigated the reliability and/or validity and discussed the feasibility and acceptability of simple, inexpensive clinical tools that assess trunk deformity in all 3 anatomical planes.

Innovations and breakthroughs

The Baseline® Body Level/Scoliosis meter is an inexpensive and easy to administer clinical tool that can be used to obtain quick measurements of scoliosis morphology in three anatomical planes. It provides reliable transverse and sagittal cervical, thoracic and lumbar measurements as well as valid transverse plane measurements of mild-moderate scoliosis deformity. Poor reliability in frontal plane measures is likely due to the Baseline® Body Level/Scoliosis meter not being sensitive in the first 0-2.5 degrees of pelvic and shoulder tilt which was common in mild-moderate AIS.

Applications

The Baseline® Body Level/Scoliosis meter is recommended for transverse and sagittal cervical, thoracic and lumbar measurements of mild-moderate scoliosis. It should be combined with a thorough history and physical assessment to aid decision making regarding the need for radiographs and interventions to prevent AIS progression and dysfunction. It is potentially reliable in measuring larger frontal plane deformity of pelvic and shoulder tilt which is more common in moderate-severe scoliosis but research is needed to confirm this.

Terminology

AIS is a three-dimensional structural deformation of the spine in otherwise normal adolescents during puberty. Axial thoracic rotation and Cobbs angle are common single pain measures of scoliosis morphology. Reliability refers to the reproducibility of measurements. Validity describes the extent to which a measure accurately represents the concept it claims to measure.

Peer-review

This is a well performed study with sound statistics and clear reliability tests. This is a non-invasive method for the evaluation of frontal and sagittal curvatures in mild AIS individuals.

REFERENCES

1 **Hawes MC**, O'brien JP. The transformation of spinal curvature into spinal deformity: pathological processes and implications for treatment. *Scoliosis* 2006; **1**: 3 [PMID: 16759413 DOI: 10.1186/1748-7161-1-3]

2 **Sabirin J**, Bakri R, Buang SN, Abdullah AT, Shapie A. School scoliosis screening programme-a systematic review. *Med J Malaysia* 2010; **65**: 261-267 [PMID: 21901941]

3 **Weinstein SL**, Dolan LA, Cheng JC, Danielsson A, Morcuende JA. Adolescent idiopathic scoliosis. *Lancet* 2008; **371**: 1527-1537 [PMID: 18456103 DOI: 10.1016/S0140-6736(08)60658-3]

4 **Zaina F**, Atanasio S, Negrini S. Clinical evaluation of scoliosis during growth: description and reliability. *Stud Health Technol Inform* 2008; **135**: 125-138 [PMID: 18401086]

5 **Bunnell WP**. An objective criterion for scoliosis screening. *J Bone Joint Surg Am* 1984; **66**: 1381-1387 [PMID: 6501335]

6 **Coelho DM**, Bonagamba GH, Oliveira AS. Scoliometer measurements of patients with idiopathic scoliosis. *Braz J Phys Ther* 2013; **17**: 179-184 [PMID: 23778766 DOI: 10.1590/S1413-35552012005000081]

7 **Korovessis PG**, Stamatakis MV. Prediction of scoliotic cobb angle with the use of the scoliometer. *Spine* (Phila Pa 1976) 1996; **21**: 1661-1666 [PMID: 8839469 DOI: 10.1097/00007632-199607150-00010]

8 **Fortin C**, Feldman DE, Cheriet F, Gravel D, Gauthier F, Labelle H. Reliability of a quantitative clinical posture assessment tool among persons with idiopathic scoliosis. *Physiotherapy* 2012; **98**: 64-75 [PMID: 22265387 DOI: 10.1016/j.physio.2010.12.006]

9 **Prowse A**, Pope R, Gerdhem P, Abbott A. Reliability and validity of inexpensive and easily administered anthropometric clinical evaluation methods of postural asymmetry measurement in adolescent idiopathic scoliosis: a systematic review. *Eur Spine J* 2016; **25**: 450-466 [PMID: 25917824 DOI: 10.1007/s00586-015-3961-7]

10 **Kottner J**, Audigé L, Brorson S, Donner A, Gajewski BJ, Hróbjartsson A, Roberts C, Shoukri M, Streiner DL. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. *J Clin Epidemiol* 2011; **64**: 96-106 [PMID: 21130355 DOI: 10.1016/j.jclinepi.2010.03.002]

11 **Lexell JE**, Downham DY. How to assess the reliability of measurements in rehabilitation. *Am J Phys Med Rehabil* 2005; **84**: 719-723 [PMID: 16141752 DOI: 10.1097/01.phm.0000176452.17771.20]

12 **Cobb JR**. The American Academy of Orthopedic Surgeons Instructional Course Lectures. Vol. 5. Ann Arbor, MI: Edwards, 1948

13 **Fleiss JL**. The Design and Analysis of Clinical Experiments. New York: John Wiley Sons, 1986: 1-432

14 **Hopkins WG**. Measures of reliability in sports medicine and science. *Sports Med* 2000; **30**: 1-15 [PMID: 10907753 DOI: 10.2165/00007256-200030010-00001]

15 **Munro BH**, Visintainer MA. Statistical methods for health care research. Vol 1, 5th ed. Philadelphia: Lippincott Williams and Wilkins, 2005: 1-494

16 **Bonagamba GH**, Coelho DM, Oliveira AS. Inter and intra-rater reliability of the scoliometer. *Rev Bras Fisioter* 2010; **14**: 432-438 [PMID: 21049239 DOI: 10.1590/S1413-35552010005000025]

17 **Murrell GA**, Coonrad RW, Moorman CT, Fitch RD. An assessment of the reliability of the Scoliometer. *Spine* (Phila Pa 1976) 1993; **18**: 709-712 [PMID: 8516699 DOI: 10.1097/00007632-199305000-00006]

18 **Driscoll M**, Fortier-Tougas C, Labelle H, Parent S, Mac-Thiong JM. Evaluation of an apparatus to be combined with a smartphone for the early detection of spinal deformities. *Scoliosis* 2014; **9**: 10 [PMID: 25075208 DOI: 10.1186/1748-7161-9-10]

19 **Yu M**, Silvestre C, Mouton T, Rachkidi R, Zeng L, Roussouly P. Analysis of the cervical spine sagittal alignment in young idiopathic scoliosis: a morphological classification of 120 cases. *Eur Spine J* 2013; **22**: 2372-2381 [PMID: 23580056 DOI: 10.1007/s00586-013-2753-1]

20 **Somoskeöy S**, Tunyogi-Csapó M, Bogyó C, Illés T. Accuracy and reliability of coronal and sagittal spinal curvature data based on patient-specific three-dimensional models created by the EOS 2D/3D imaging system. *Spine J* 2012; **12**: 1052-1059 [PMID: 23102842 DOI: 10.1016/j.spinee.2012.10.002]

21 **Zaina F**, Negrini S, Atanasio S. TRACE (Trunk Aesthetic Clinical Evaluation), a routine clinical tool to evaluate aesthetics in scoliosis patients: development from the Aesthetic Index (AI) and repeatability. *Scoliosis* 2009; **4**: 3 [PMID: 19154604 DOI: 10.1186/1748-7161-4-3]

22 **Pearsall DJ**, Reid JG, Hedden DM. Comparison of three noninvasive methods for measuring scoliosis. *Phys Ther* 1992; **72**: 648-657 [PMID: 1508972]
23 **Fortin C**, Feldman DE, Cheriet F, Labelle H. Validity of a quantitative clinical measurement tool of trunk posture in idiopathic scoliosis. *Spine* (Phila Pa 1976) 2010; **35**: E988-E994 [PMID: 20700086 DOI: 10.1097/BRS.0b013e3181cd2cd2]
24 **Grosso C**, Negrini S, Boniolo A, Negrini AA. The validity of clinical examination in adolescent spinal deformities. *Stud Health Technol Inform* 2002; **91**: 123-125 [PMID: 15462010]
25 **Schlösser TP**, Shah SA, Reichard SJ, Rogers K, Vincken KL, Castelein RM. Differences in early sagittal plane alignment between thoracic and lumbar adolescent idiopathic scoliosis. *Spine J* 2014; **14**: 282-290 [PMID: 24231781 DOI: 10.1016/j.spinee.2013.08.059]
26 **ROAF R**. Rotation movements of the spine with special reference to scoliosis. *J Bone Joint Surg Br* 1958; **40-B**: 312-332 [PMID: 13539116]
27 **Konieczny MR**, Senyurt H, Krauspe R. Epidemiology of adolescent idiopathic scoliosis. *J Child Orthop* 2013; **7**: 3-9 [PMID: 24432052 DOI: 10.1007/s11832-012-0457-4]

P- Reviewer: Erkan S, Korovessis P, Singh K **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.77

World J Orthop 2017 January 18; 8(1): 77-81
ISSN 2218-5836 (online)

CASE REPORT

Novel case of Trevor's disease: Adult onset and later recurrence

Amrit S Khalsa, Neil S Kumar, Matthew A Chin, Richard D Lackman

Amrit S Khalsa, Neil S Kumar, Matthew A Chin, the Department of Orthopaedic Surgery, Hahnemann University Hospital, Philadelphia, PA 19102, United States

Richard D Lackman, the Department of Orthopaedic Surgery, Cooper University Hospital, Camden, NJ 08103, United States

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

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at Cooper University Hospital in Camden.

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

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

Manuscript source: Invited manuscript

Correspondence to: Matthew A Chin, MD, the Department of Orthopaedic Surgery, Hahnemann University Hospital, 245 N. 15th Street, Philadelphia, PA 19102, United States. matthew.a.chin@gmail.com
Telephone: +1-215-7628168
Fax: +1-215-7623442

Received: February 2, 2016
Peer-review started: February 16, 2016
First decision: May 19, 2016
Revised: September 7, 2016
Accepted: October 17, 2016

Article in press: October 18, 2016
Published online: January 18, 2017

Abstract

Dysplasia epiphysealis hemimelica (DEH), or Trevor's disease, is an osteocartilaginous epiphyseal overgrowth typically occurring in children. The literature reports 6 adult cases and none describe recurrence requiring additional procedures. We present a new-onset proximal tibial DEH in an adult recurring approximately 3 years after open excision. A 39-year-old female presented with a history of right knee pain, swelling, and instability. Physical examination revealed a firm proximal tibial mass. Computed tomography (CT) imaging showed an exophytic, lobulated, sclerotic mass involving the anterolateral margin of the lateral tibial plateau. Magnetic resonance imaging was suggestive of an osteochondroma. The patient underwent curettage of the lesion due to its periarticular location. Histology revealed benign and reactive bone and cartilage consistent with periosteal chondroma. Two and a half years later, the patient presented with a firm, palpable mass larger than the initial lesion. CT revealed a lateral tibial plateau sclerotic mass consistent with recurrent intra-articular DEH. A complete excision was performed and histology showed sclerotic bone with overlying cartilage consistent with exostosis. DEH is a rare epiphyseal osteocartilaginous outgrowth frequently occurring in the long bones of children less than 8 years old. DEH resembles an osteochondroma due to its pediatric presentation and similar histologic appearance. Adult-onset cases comprise less than 1% of reported cases. Recurrence rate after surgical intervention is unknown. Only 1 such case, occurring in a child, has been described. Clinicians contemplating operative treatment for DEH should note the potential for recurrence and consider complete excision. A follow-up period of several years may be warranted to identify recurrent lesions.

Key words: Trevor's disease; Dysplasia epiphysealis hemimelica; Adult recurrence; Proximal tibia; Exostosis

Core tip: Dysplasia epiphysealis hemimelica (DEH), or Trevor's disease, is an osteocartilaginous epiphyseal overgrowth typically occurring in children. The literature reports 6 adult cases and none describe recurrence requiring additional procedures. We present a new-onset proximal tibial DEH in an adult recurring approximately 3 years after open curettage.

Khalsa AS, Kumar NS, Chin MA, Lackman RD. Novel case of Trevor's disease: Adult onset and later recurrence. *World J Orthop* 2017; 8(1): 77-81 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/77.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.77

INTRODUCTION

Dysplasia Epiphysealis Hemimelica (DEH), otherwise known as Trevor's Disease, is an exceedingly rare disorder of childhood[1,2]. Characterized by excessive cartilaginous growth from the epiphyseal region, DEH is grossly and histologically similar to osteochondromas found in the metadiaphyseal region[1]. Patients generally present with localized joint pain, tenderness, and dysfunction, most commonly affecting the foot and ankle but also reported in the knee, hip, and scapula. DEH has an incidence of approximately one in 1000000 with males affected up to three times more frequently than females[3]. Three types of clinical presentation have been described: Localized to one epiphysis; affecting more than one epiphysis in the same limb; and diffuse disease affecting the entire lower limb[2].

Though exceedingly rare, DEH usually presents in children before 8 years of age. Only six cases of DEH have ever been reported in individuals over 18 years of age; one in the proximal femur, one in the distal radius, one in the carpus, one in the distal tibia, one in the talus, and one in the proximal tibia[4-8]. Recurrence in an adult has never been reported nor has recurrence in any population requiring an additional open procedure. This often intra-articular lesion can lead to early degenerative changes if left undiagnosed or untreated and can cause functional debilitation[9].

We describe the novel case of a 39-year-old female with DEH of the proximal tibia in whom recurrence occurred three years after an initial open curettage and resection. The patient was eventually treated definitively with surgical excision.

CASE REPORT

A 39-year-old female initially presented to our outpatient office with a several month history of right knee pain, swelling, and instability, particularly with walking down stairs. Non-steroidal anti-inflammatory medications only mildly relieved her discomfort. She denied night pain, constitutional symptoms, or a recent history of trauma or injury. Medical history was significant for a history of congenital hip dysplasia and family history was negative for any inflammatory diseases, bone disorders, or dysplasia.

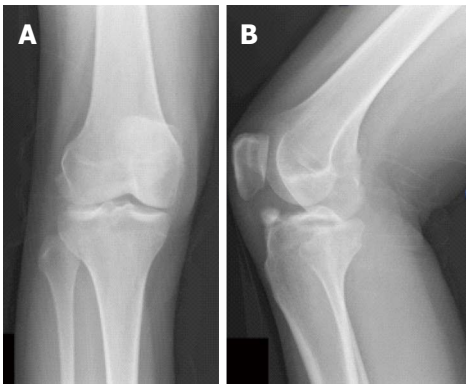


Figure 1 Initial radiographs of the right knee in the anteroposterior (A) and lateral (B) views.

On physical exam, a mild antalgic gait was noted. A right knee effusion was present as well as lateral joint line tenderness. A firm, palpable mass protruding from the anterolateral proximal tibia was easily appreciated. No erythema or skin ulceration was presented at the site of the mass. Her remaining physical exam was otherwise grossly normal.

Radiographs (Figure 1) of the right knee revealed an unusual calcific density measuring 2.0 cm × 1.0 cm above the anterolateral tibial plateau. Computed tomography (CT) (Figure 2) of the right knee revealed an exophytic, lobulated, sclerotic mass measuring 2.4 cm × 0.9 cm × 0.8 cm involving the anterolateral margin of the anterior lip of the lateral tibial plateau. An MRI showed a 1.2 cm well-marginated lesion abutting the anterolateral cortical surface of the lateral tibial plateau following bone marrow on all sequences, most likely due to an osteochondroma or loose body. Whole body bone scan also revealed mild to moderate uptake at the site of the lesion.

The patient underwent an open curettage and debulking of the right lateral proximal tibial lesion given its periarticular location, which prevented it from being amenable to marginal excision. Pathology revealed fragments of benign and reactive bone and cartilage consistent with a diagnosis of periosteal chondroma. The patient's symptoms fully resolved post-operatively with no signs of recurrence at 1-year and 2-year follow-up.

Two and a half years later, the patient presented with a two and a half month history of recurrent pain and swelling of her right knee. Furthermore, under her well-healed scar was a firm, palpable mass that was larger

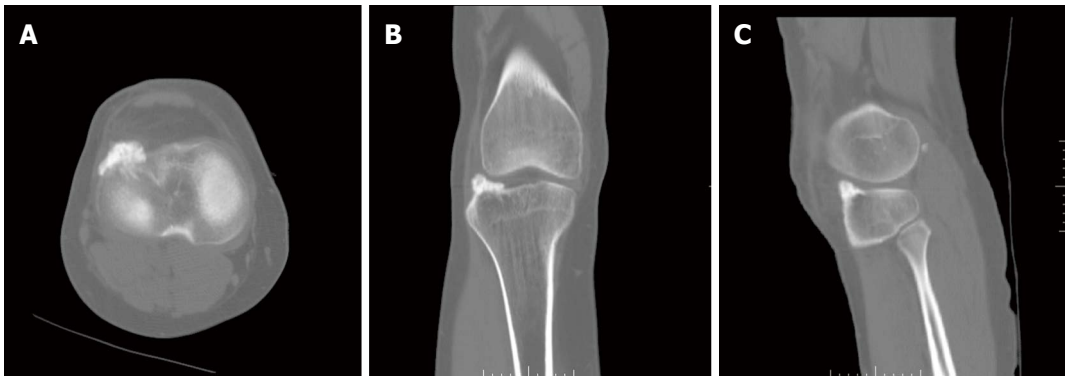


Figure 2 Initial computed tomography images of the right knee in the axial (A), coronal (B), and sagittal (C) planes.

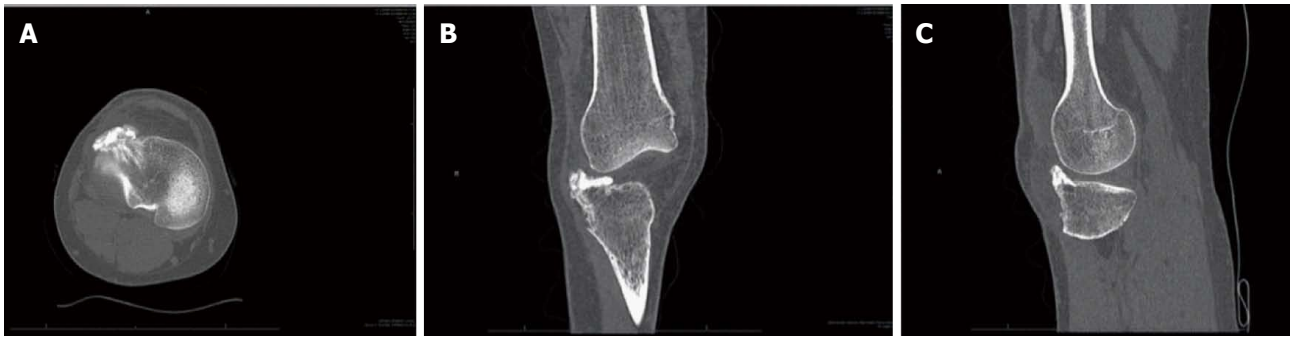


Figure 3 Computed tomography images of the right knee after lesion recurrence in the axial (A), coronal (B), and sagittal (C) planes.

than her original mass. CT (Figure 3) scan revealed a recurrent, sclerotic mass measuring 0.8 cm × 2.3 cm × 1.6 cm arising from the lateral tibial plateau consistent with recurrent intra-articular dysplasia epiphysealis hemimelica. A complete excision was performed and pathology showed sclerotic bone with overlying cartilage consistent with exostosis. At her one-year and two-year follow-up, the patient remains symptom-free with no appreciable mass recurrence.

DISCUSSION

Dysplasia Epiphysealis Hemimelica is a rare, oftentimes aggressive outgrowth of bone and cartilage occurring most frequently in the epiphyseal region of long bones. Mouchet first described the lesion in 1926, referring to the entity as *tarsomegalie* to describe the pathology as a lesion about the ankle[10]. In 1950, Trevor described 8 cases involving epiphyseal lesions about the knee and ankle, terming them tarso-epiphysial aclasis[11]. He postulated that a congenital error in lower limb bud formation ultimately resulted in cartilaginous hyperplasia. Fairbank eventually coined the term dysplasia epiphysialis hemimelica in 1956 after publishing a case series on 14 children with the lesion[12]. DEH can resemble an osteochondroma due to its predilection towards children and developing bones and similar histologic appearance. However, osteochondromas are generally found in the meta-diaphyseal region, unlike DEH, which is typically an epiphyseal lesion[13].

Most lesions are discovered before 8 years of age[14]. The most common location for DEH is the talus, where it was originally described, followed by the distal femur and the distal tibia[14,15]. To our knowledge, only six reported adult-onset cases have been previously described in the literature, comprising less than 1% of known cases. As of a recent systematic review by Gökkuş *et al*[7], six adult cases have been described in the proximal femur, distal radius, carpus, distal tibia, proximal tibia, and talus[4-8,11]. The re-appearance of an adult lesion in the proximal tibia is a novel finding.

The recurrence rate of this osteocartilaginous overgrowth is unknown after surgical intervention. It is agreed upon that the gold standard for treatment of extra-articular lesions is surgical excision in the setting of pain or decreased range of motion, yielding more favorable outcomes[13,16]. The treatment for intra-articular lesions is less clear and determined on a case-by-case basis, with excision only indicated in the presence of symptomatic loose bodies, because of the detrimental effects of excision to the articular cartilage. Currently, only 1 recurrent case has been described in the literature; this patient was a child and had 3 operations all before the age of 5 years. In this case, a new-onset proximal tibial DEH in an adult patient recurred approximately 3 years after initial open excision. There were no known factors affecting recurrence in this one case. However, the presence of pain two a half months prior to the patient's subsequent presentation may be explained by inadequate initial management, despite

debulking and curettage that was deemed sufficient at the first attempt. We recommend that clinicians considering operative treatment for these lesions should note the potential for recurrence and should contemplate a more aggressive excision as a preventative measure. We also recommend that a post-operative follow-up period of several years may be warranted to identify lesions in the initial stages of recurrence.

In conclusion, DEH, although rare, does often require surgical resection once diagnosed based on symptoms and relevant imaging. Although more commonly occurring in children, it should remain in the differential diagnosis for adults with bony lesions in the epiphyseal region. Surgical resection is a viable option in the setting of pain and decreasing range of motion and must be balanced with the sequelae of destroying articular cartilage, however adequate follow-up is advised for potential recurrent lesions.

ACKNOWLEDGMENTS

We thank Maureen Kaden and Francis Jennings for their assistance in gathering and organizing patient records. We also thank Cooper University Hospital (Camden, NJ, United States) for supporting to this work.

COMMENTS

Case characteristics

A 39-year-old female presented with a history of right knee pain, swelling, and instability.

Clinical diagnosis

A right knee effusion was present as well as lateral joint line tenderness, and a firm, palpable mass protruding from the anterolateral proximal tibia was easily appreciated.

Differential diagnosis

Dysplasia epiphysealis hemimelica, osteochondroma, periosteal chondroma, osteofibrous dysplasia, adamantinoma, osteosarcoma, synovial chondromatosis.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

CT scan revealed a recurrent, sclerotic mass measuring 0.8 cm × 2.3 cm × 1.6 cm arising from the lateral tibial plateau.

Pathological diagnosis

Intra-articular dysplasia epiphysealis hemimelica.

Treatment

Complete surgical excision of lesion.

Related reports

Dysplasia epiphysealis hemimelica (DEH) is a rare, oftentimes aggressive outgrowth of bone and cartilage occurring most frequently in the epiphyseal region of long bones. DEH can resemble an osteochondroma due to its predilection towards children and developing bones and similar histologic appearance.

Term explanation

DEH is a rare, frequently aggressive outgrowth of bone and cartilage occurring most frequently in the epiphyseal region of long bones. The most common location for DEH is the talus, where it was originally described, followed by the distal femur and the distal tibia.

Experiences and lessons

This entity is commonly mistaken for a neoplastic process due to its location and behavior. Clinicians considering operative treatment for these lesions should note the potential for recurrence and should contemplate a more aggressive excision as a preventative measure.

Peer-review

This paper is well written.

REFERENCES

1 **Perl M**, Brenner RE, Lippacher S, Nelitz M. Dysplasia epiphysealis hemimelica: a case report with novel pathophysiologic aspects. *Clin Orthop Relat Res* 2009; **467**: 2472-2478 [PMID: 19526273 DOI: 10.1007/s11999-009-0925-4]
2 **Azouz EM**, Slomic AM, Marton D, Rigault P, Finidori G. The variable manifestations of dysplasia epiphysealis hemimelica. *Pediatr Radiol* 1985; **15**: 44-49 [PMID: 3969295 DOI: 10.1007/BF02387852]
3 **Peduto AJ**, Frawley KJ, Bellemore MC, Kuo RS, Foster SL, Onikul E. MR imaging of dysplasia epiphysealis hemimelica: bony and soft-tissue abnormalities. *AJR Am J Roentgenol* 1999; **172**: 819-823 [PMID: 10063889 DOI: 10.2214/ajr.172.3.10063889]
4 **Levi N**, Ostgaard SE, Lund B. Dysplasia epiphysealis hemimelica (Trevor's disease) of the distal radius. *Acta Orthop Belg* 1998; **64**: 104-106 [PMID: 9586260]
5 **Sherlock DA**, Benson MK. Dysplasia epiphysialis hemimelica of the hip. A case report. *Acta Orthop Scand* 1986; **57**: 173-175 [PMID: 3705946 DOI: 10.3109/17453678609000896]
6 **Gölles A**, Stolz P, Freyschmidt J, Schmitt R. Trevor's disease (dysplasia epiphysealis hemimelica) located at the hand: case report and review of the literature. *Eur J Radiol* 2011; **77**: 245-248 [PMID: 21236611 DOI: 10.1016/j.ejrad.2010.11.034]
7 **Gökkuş K**, Atmaca H, Sagtas E, Saylik M, Aydin AT. Trevor's disease: up-to-date review of the literature with case series. *J Pediatr Orthop B* 2016 Apr 14; Epub ahead of print [PMID: 27082230]
8 **Sadeghifar AR**, Heshmati AA. Dysplasia epiphysealis hemimelica (trevor syndrome) of talus in a 21-year old woman; case report. *Arch Bone Jt Surg* 2014; **2**: 66-68 [PMID 25207317]
9 **Ouyang Z**, Xu M, Li X, Peng D. Dysplasia epiphysealis hemimelica with involvement of the distal tibial epiphysis and talus: recurrence of a case and literature review. *J Foot Ankle Surg* 2014; **53**: 199-202 [PMID: 24412001 DOI: 10.1053/j.jfas.2013.10.005]
10 **Mouchet A**, Berlot J. La tarsomegalie. *J Radiol Electrol* 1926; **10**: 289-293
11 **Trevor D**. Tarso-epiphysial aclasis; a congenital error of epiphysial development. *J Bone Joint Surg Br* 1950; **32-B**: 204-213 [PMID: 15422019]
12 **Fairbank TJ**. Dysplasia epiphysialis hemimelica (tarso-ephiphysial aclasis). *J Bone Joint Surg Br* 1956; **38-B**: 237-257 [PMID: 13295331]
13 **Rosero VM**, Kiss S, Terebessy T, Köllö K, Szöke G. Dysplasia epiphysealis hemimelica (Trevor's disease): 7 of our own cases and a review of the literature. *Acta Orthop* 2007; **78**: 856-861 [PMID: 18236195 DOI: 10.1080/17453670710014662]
14 **Struijs PA**, Kerkhoffs GM, Besselaar PP. Treatment of dysplasia epiphysealis hemimelica: a systematic review of published reports and a report of seven patients. *J Foot Ankle Surg* 2012; **51**: 620-626 [PMID: 22819617 DOI: 10.1053/j.jfas.2012.05.008]
15 **Skaggs DL**, Moon CN, Kay RM, Peterson HA. Dysplasia epiphysealis hemimelica of the acetabulum. A report of two cases. *J Bone Joint Surg Am* 2000; **82**: 409-414 [PMID: 10724233]

16 **Douira-Khomsi W**, Louati H, Mormech Y, Saied W, Bouchoucha S, Smida M, Ben Ghachem M, Hammou A, Bellagha I. Dysplasia epiphysealis hemimelica: a report of four cases. *Foot Ankle Surg* 2011; **17**: 37-43 [PMID: 21276564 DOI: 10.1016/j.fas.2009.02.003]

P- Reviewer: de Campos GC, Paschos NK, Spiro AS
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Wu HL

World Journal of Orthopedics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v8.i1.82

World J Orthop 2017 January 18; 8(1): 82-86
ISSN 2218-5836 (online)

CASE REPORT

Teriparatide anabolic therapy as potential treatment of type II dens non-union fractures

Enrico Pola, Virginia Pambianco, Debora Colangelo, Virginia M Formica, Giovanni Autore, Luigi A Nasto

Enrico Pola, Virginia Pambianco, Debora Colangelo, Virginia M Formica, Giovanni Autore, Spinal Unit, Department of Orthopaedics and Traumatology, "A. Gemelli" University Hospital, Catholic University of Rome, 00168 Rome, Italy

Luigi A Nasto, Centre for Spine Studies and Surgery, Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH, United Kingdom

Author contributions: Pola E and Pambianco V contributed equally to this work; Pola E, Pambianco V and Nasto LA designed the research and analysed the data; Pola E, Formica VM, Autore G and Nasto LA conceived the study and participated in its coordination; Pola E, Pambianco V, Colangelo D and Nasto LA wrote the paper; all authors had read and approved the final manuscript.

Institutional review board statement: This case report was exempt from the Institutional Review Board approval as per Catholic University of Rome guidelines.

Informed consent statement: The patient involved in this study gave her oral informed consent to be included in this study.

Conflict-of-interest statement: The authors have no conflicts of interests to disclose about this study.

Manuscript source: Unsolicited manuscript

Correspondence to: Enrico Pola, MD, PhD, Assistant Professor, Spinal Unit, Department of Orthopaedic and Traumatology, "A. Gemelli" University Hospital, Catholic University of Rome, L.go Agostino Gemelli 8, 00168 Rome, Italy. enrico.pola@rm.unicatt.it
Telephone: +39-340-2636062
Fax: +39-06-3051161

Received: March 31, 2016
Peer-review started: April 1, 2016
First decision: May 17, 2016
Revised: June 15, 2016
Accepted: July 14, 2016
Article in press: July 18, 2016
Published online: January 18, 2017

Abstract

Odontoid fractures account for 5% to 15% of all cervical spine injuries and 1% to 2% of all spine fractures. Type II fractures are the most common fracture pattern in elderly patients. Treatment (rigid and non-rigid immobilization, anterior screw fixation of the odontoid and posterior C1-C2 fusion) remains controversial and represents a unique challenge for the treating surgeon. The aims of treatment in the elderly is to quickly restore pre-injury function while decreasing morbidity and mortality associated with inactivity, immobilization with rigid collar and prolonged hospitalization. Conservative treatment of type II odontoid fractures is associated with relatively high rates of non-union and in a few cases delayed instability. Options for treatment of symptomatic non-unions include surgical fixation or prolonged rigid immobilization. In this report we present the case of a 73-year-old woman with post-traumatic odontoid non-union successfully treated with Teriparatide systemic anabolic therapy. Complete fusion and resolution of the symptoms was achieved 12 wk after the onset of the treatment. Several animal and clinical studies have confirmed the potential role of Teriparatide in enhancing fracture healing. Our case suggests that Teriparatide may have a role in improving fusion rates of C2 fractures in elderly patients.

Key words: Type II odontoid fractures; Non-union; Anabolic therapy; Teriparatide; Fracture healing

Core tip: Odontoid fractures are common in elderly patients and treatment of these injuries remains challenging. Conservative management consists of rigid immobilization with collar or Halo vest. Delayed union or non-union is a common outcome in patients treated conservatively. For a symptomatic non-union, surgery may be the only option. In this case report we discuss the case of a patient with an odontoid fracture non-union successfully treated with systemic anabolic Teriparatide therapy. A complete fusion was achieved after 12 wk of treatment. Teriparatide therapy may have a role in fostering fusion of C2 fractures in elderly patients.

Pola E, Pambianco V, Colangelo D, Formica VM, Autore G, Nasto LA. Teriparatide anabolic therapy as potential treatment of type II dens non-union fractures. *World J Orthop* 2017; 8(1): 82-86 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i1/82.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i1.82

INTRODUCTION

Odontoid fractures comprise 5% to 15% of all cervical spine fractures and represent the most common cervical spine injury in elderly patients (> 65-year-old)[1,2]. Type Ⅱ fractures (*i.e.,* a fracture through the base of the dens, below the transverse ligament) account for the majority of cases (67%). Odontoid fractures in the elderly are a potentially life threatening injury. Acute respiratory arrest and spinal cord injury have been described following fracture displacement. More commonly, patients present with acute neck pain and occasional occipital neuropathic pain. Reduced mobility, chronic pain, and the presence of multiple medical comorbidities often lead to a progressive decline of the health status and excess mortality in elderly patients. In a retrospective review, mortality risk at 1 year following a cervical fracture in patients > 65 years of age was 28%[3].

There is a lack of agreement regarding the optimal treatment of odontoid fractures in the elderly. The aim of treatment is to stabilize the fracture to prevent neurological damage and allow early and safe mobilization. Treatment options include conservative management (*i.e.,* hard collar and Halo vest immobilization) or surgical fixation. Surgery provides the advantage of early mobilization and higher fusion rates. However, it is also associated with high complication rates and perioperative morbidity[4]. Conservative management is a safer option but is associated with higher risk of delayed union or non-union (77%) and increased morbidity due to prolonged immobilization[5].

Factors determining the poor healing potential of odontoid fractures in the elderly are poorly understood.

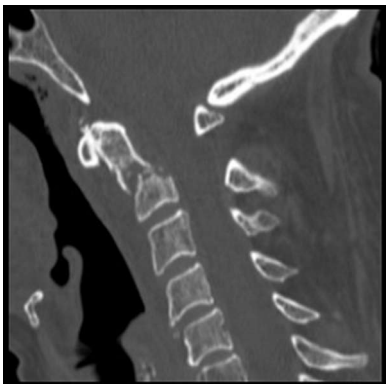


Figure 1 Computed tomography-scan at admission to the hospital showing a transverse fracture line above C2 vertebral body and below transverse ligament of the odontoid process (type Ⅱ fracture).

Known factors associated with higher risk of nonunion include age > 50, displacement greater than 6 mm, posterior displacement, angulation of the fragments, and smoking[6,7]. The role of segmental osteoporosis and poor osteoblastic response is less clearly defined but is commonly perceived as a potentially important factor in determining facture healing potential. Teriparatide (*i.e.,* rhPTH1-34) is the recombinant form of the biologically active component of the human parathyroid hormone. It is a novel anabolic drug therapy for osteoporosis which has also been shown to stimulate osteoblasts and enhance fracture healing *in vivo*. The aim of this study is to report our experience with the use of rhPTH1-34 in the treatment of a non-union type Ⅱ dens fracture in an elderly patient.

CASE REPORT

A 73-year-old woman was transferred to our emergency department following a road traffic accident. The patient was a restrained passenger of a car, the driver lost the control of the vehicle and the car fell into a ditch at the side of the road. The patient lost consciousness at the impact but was found alert and oriented at the time of the arrival of the ambulance. Patient observations were stable and there were no signs of other bone injuries. Patient had no neurological deficits and cranial nerves were intact. Past medical history of the patient included acute glaucoma and visual impairment.

A routine trauma series CT-scan was performed and showed a type Ⅱ odontoid fracture with anterior displacement (Figure 1). Patient was referred to our spinal unit and, after appropriate counselling, elected a non-operative treatment. Cervical spine was stabilized with a Philadelphia collar and patient was discharged home 3 d after the injury. The first outpatient clinic appointment was booked at 2 wk after discharge and patient was seen at regular intervals thereafter. Six months following the injury the patient was still complaining of significant axial neck pain requiring regular pain killer. An interval computed tomography

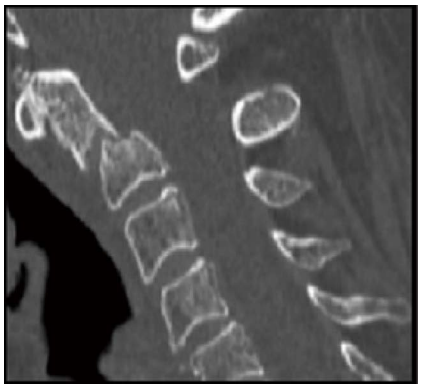


Figure 2 Interval computed tomography-scan 6 mo after the index injury. No healing is demonstrated, sclerotic bone margins are demonstrated at the fracture fragments.

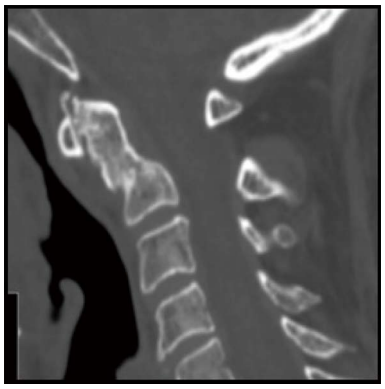


Figure 3 Computed tomography-scan performed at the end of 3 mo of anabolic therapy with Teriparatide confirming a complete fusion of the fracture with acceptable alignment.

(CT) scan at 6 mo after the injury revealed a non-union at the fracture site, distance between fracture fragments was 4 mm and there was evidence of sclerotic bone margins at the level of the fracture (Figure 2). Surgical options were discussed with the patient at this stage, but she again refused any surgical intervention.

Patient was maintained in rigid collar and was offered off-label therapy with daily subcutaneous injections of Teriparatide (rhPTH1-34) 20 μg/d which she accepted. This is the same regime used for treatment of osteoporosis in post-menopausal women. The anabolic treatment with Teraparatide was monitored through periodic examinations and regular measurements of serum levels of calcium, phosphorus, vitamin D, parathyroid hormone and alkaline phosphatase.

Forty-five days after starting Teriparatide treatment, an interval CT scan showed an initial phase of callus formation at the fracture site with partial closure of the fracture gap. Anabolic therapy was continued for 3 mo, at the end of the treatment a final CT scan confirmed a complete consolidation of the fracture (Figure 3). Flexion/extension X-rays of the cervical spine showed no residual instability, and axial neck pain had resolved as well. Mean Visual Analogic Scale score at the end of the treatment was 3 (from a baseline value of 8), whilst SF-12P score was 45.1 and the SF-12M score was 58 (from baseline values of 29.4 for SF-12P and 28.7 for SF-12M). The Neck Disability Index decreased from 70% to 15% at the time of last follow-up. No side effects related to the use of Teriparatide were noted in our patient.

DISCUSSION

The number of elderly patients is growing rapidly in western countries and worldwide. By 2025, one fifth of the world population will be over the age of 65 and the number of osteoporotic and fragility fractures are expected to rise accordingly. Odontoid fractures are common in elderly patients, and treatment remains controversial. Although modern surgical techniques (*i.e.*, C1-C2 transarticular and C1-C2 polyaxial screw fixation) allow significantly higher fusion rates (83%-100%) than traditional techniques, they remain technically demanding and are associated with a sizable perioperative complication rate[8-10]. Reported fusion rate for conservative management varies from 23% to 46%[7,11]. It is safer than surgery in the short term, but associated with prolonged immobilization and reduced mobility. Cranial, pulmonary and cardiac complications have all been reported in patients treated with rigid immobilization. Furthermore, the development of a fibrous non-union is a common finding in patients treated conservatively. Although achievement of a stable fibrous non-union is regarded as an acceptable outcome in elderly patients by some authors, there are cases described of late onset cervical myelopathy in patients with non-union of the odontoid process[12].

Teriparatide (rhPTH1-34) is a novel Food and Drug Administration (FDA) approved drug for treatment of post-menopausal osteoporosis. Teriparatide is a recombinant form of the N-terminal 1-34 fragment of the human parathyroid hormone (PTH). In humans, PTH regulates blood calcium levels by controlling renal calcium reabsorption and release of calcium from the skeleton. As such, continuous high levels of PTH determine progressive bone demineralization and systemic osteoporosis. Interestingly, the intermittent administration of PTH has opposite effects on bone metabolism and stimulates new bone formation (*i.e.,* anabolic action)[13]. Teriparatide is the only currently available drug with anabolic effect on bone metabolisms. It is FDA approved for use in patients with severe post-menopausal osteoporosis (*i.e.,* in women with a history of osteoporotic fractures or who are not responsive to other osteoporosis therapies) and can be administered for a maximum of 24 mo.

Several studies have investigated the role of Teriparatide in accelerating fracture healing and non-unions. In 1999 and 2001, Andreassen *et al*[14,15] reported the effects of systemic intermitted PTH treatment in a rat model of fracture healing. Treated animals showed increased fracture strength and callus volume at 8 wk after treatment. In 2010, similar findings were

published by Mognetti *et al*[16] in a mouse model of tibial fracture. The authors noted a stimulation of callus formation with Teriparatide dosage of 40 μg/kg per day; 15 d after treatment callus mechanical strength approximated normal bone. The anabolic effect of Teriparatide administration is not limited to the period of treatment as shown by Alkhiary *et al*[17] in a rat model. The authors showed that 49 d after discontinuing anabolic treatment, treated animals were still showing a continuous increase of bone mineral density and torsional strength[17]. The anabolic effect of Teraparatide administration has also been confirmed in animal models of delayed bone healing[18].

The effects of Teriparatide on human fracture healing have been investigated by several authors with contrasting results. In the only Level I study on this topic, Aspenberg *et al*[19] have studied a cohort of 102 post-menopausal patients with distal radius fractures treated conservatively. Median time to radiographic healing was 9.1 wk in the control group, and 7.4 and 8.8 wk in the groups treated with 20 μg and 40 μg of Teriparatide, respectively. The differences between the groups were not statistically significant[19]. Opposite results have been reported by Peichl *et al*[20] in a series of 65 post-menopausal women with pubic bone fracture treated with the 1-84 form of PTH. The median healing time was 7.8 wk for the treatment group *vs* 12.6 wk for the control group[20]. The only available data on the effects of anabolic treatment on spinal fractures healing have been reported by Bukata *et al*[21] in 2010. The authors studied a cohort of 145 patients with spinal or appendicular skeleton fractures. Fracture healing rate was 93% at 12 wk after treatment with Teriparatide.

To the best of our knowledge, no study has systematically investigated the role of Teriparatide in cervical spine fractures. The only available study on this topic is a case report by Rubery *et al*[22] published in 2010. The authors reported on 3 patients with painful delayed unions of type III odontoid fractures. All 3 patients were started on therapeutic doses of Teriparatide and experienced complete resolution of their symptoms and complete union[22]. In this study, we report the case of a painful delayed union of a type II odontoid fracture. Our patient presented with persistent pain and failed conservative treatment of the fracture. Teriparatide treatment was started 6 mo after the index injury and a complete fusion with resolution of the symptoms was observed 12 wk after the onset of the therapy.

The nature of our study does not allow a generalization of our results. It is impossible to know whether our patient would have developed a non-painful fibrous non-union at a later follow-up. Also, complete bone union can be observed as long as 9-12 mo after the index injury. Nevertheless, we think our case report raises an important point in the management of this very common injury in elderly patients. Teriparatide may represent a useful adjunct to the armamentarium of the clinician for treatment of painful cervical non-unions in frail elderly patients. We believe that a prospective study on the effects of anabolic therapy in type II odontoid fractures could have a profound impact on the management and outcomes of frail elderly patients.

We described a case of a painful non-union of type II odontoid fracture in an elderly patient treated conservatively. Due to no improvement in her symptoms and no progress of radiological union we offered our patient systemic treatment with rhPTH1-34 (Teriparatide) for 3 mo. At the end of the treatment a stable union of the fracture was achieved with complete resolution of the pain. Our report suggests that Teriparatide may have a role in enhancement of fracture healing in elderly patients with odontoid fractures.

ACKNOWLEDGMENTS

There was no external funding source and no funding source that played a role in the investigation. The work was undertaken at the Spinal Unit, Department of Orthopaedic Surgery, of the Catholic University of Rome, Italy.

COMMENTS

Case characteristics

A 73-year-old woman with type II odontoid fracture. Treated conservatively with Philadelphia collar. Patient presented at 6 mo with ongoing mechanical neck pain with no neurological deficits.

Clinical diagnosis

Painful non-union of type II odontoid fracture.

Differential diagnosis

Delayed union of type II odontoid fracture can present with similar symptoms. Displacement of the fragments can also determine delayed compression on the spinal cord with myelopathy symptoms.

Imaging diagnosis

Cervical CT-scan showing a transverse fracture line of the odontoid process below the transverse ligament. There was minimal fracture displacement with fragments osteoporosis and sclerotic bony margins (non-union).

Treatment

Rigid external immobilization with cervical collar (Philadelphia) and systemic anabolic therapy with Teriparatide (20 μg/die) for 12 wk.

Related reports

Painful non-union is common after conservative treatment of type II odontoid fractures in elderly patients. Treatment options involve delayed surgical stabilization and fusion or conservative treatment with analgesia and external rigid immobilization. Stability must be assessed with flexion/extension X-rays to prevent delayed cervical myelopathy.

Experiences and lessons

Systemic Teriparatide therapy can be a valuable alternative approach to surgical fixation and fusion in symptomatic non-unions of the odontoid process. Teriparatide use for fracture healing enhancement is non Food and Drug Administration approved and must be considered "off label".

Peer-review

Authors report the treatment of a relatively common disease (a type II odontoid

fracture) with a widely used therapeutic approach in enhancing fracture healing (teriparatide), that has not been specifically reported as a therapeutic agent in this precise condition.

REFERENCES

1 **Denaro V**, Papalia R, Di Martino A, Denaro L, Maffulli N. The best surgical treatment for type II fractures of the dens is still controversial. *Clin Orthop Relat Res* 2011; **469**: 742-750 [PMID: 21161745 DOI: 10.1007/s11999-010-1677-x]

2 **Ryan MD**, Henderson JJ. The epidemiology of fractures and fracture-dislocations of the cervical spine. *Injury* 1992; **23**: 38-40 [PMID: 1541497 DOI: 10.1016/0020-1383(92)90123-A]

3 **Spivak JM**, Weiss MA, Cotler JM, Call M. Cervical spine injuries in patients 65 and older. *Spine* (Phila Pa 1976) 1994; **19**: 2302-2306 [PMID: 7846575 DOI: 10.1097/00007632-199410150-00009]

4 **Vaccaro AR**, Kepler CK, Kopjar B, Chapman J, Shaffrey C, Arnold P, Gokaslan Z, Brodke D, France J, Dekutoski M, Sasso R, Yoon ST, Bono C, Harrop J, Fehlings MG. Functional and quality-of-life outcomes in geriatric patients with type-II dens fracture. *J Bone Joint Surg Am* 2013; **95**: 729-735 [PMID: 23595072 DOI: 10.2106/JBJS.K.01636]

5 **Ryan MD**, Taylor TK. Odontoid fractures in the elderly. *J Spinal Disord* 1993; **6**: 397-401 [PMID: 8274807 DOI: 10.1097/00002517-199306050-00005]

6 **Hadley MN**, Dickman CA, Browner CM, Sonntag VK. Acute axis fractures: a review of 229 cases. *J Neurosurg* 1989; **71**: 642-647 [PMID: 2809718 DOI: 10.3171/jns.1989.71.5.0642]

7 **Clark CR**, White AA. Fractures of the dens. A multicenter study. *J Bone Joint Surg Am* 1985; **67**: 1340-1348 [PMID: 4077905]

8 **Apfelbaum RI**, Lonser RR, Veres R, Casey A. Direct anterior screw fixation for recent and remote odontoid fractures. *J Neurosurg* 2000; **93**: 227-236 [PMID: 11012053]

9 **Jeanneret B**, Magerl F. Primary posterior fusion C1/2 in odontoid fractures: indications, technique, and results of transarticular screw fixation. *J Spinal Disord* 1992; **5**: 464-475 [PMID: 1490045 DOI: 10.1097/00002517-199212000-00012]

10 **Harms J**, Melcher RP. Posterior C1-C2 fusion with polyaxial screw and rod fixation. *Spine (Phila Pa 1976)* 2001; **26**: 2467-2471 [PMID: 11707712 DOI: 10.1097/00007632-200111150-00014]

11 **Koivikko MP**, Kiuru MJ, Koskinen SK, Myllynen P, Santavirta S, Kivisaari L. Factors associated with nonunion in conservatively-treated type-II fractures of the odontoid process. *J Bone Joint Surg Br* 2004; **86**: 1146-1151 [PMID: 15568528 DOI: 10.1302/0301-620X.86B8.14839]

12 **Crockard HA**, Heilman AE, Stevens JM. Progressive myelopathy secondary to odontoid fractures: clinical, radiological, and surgical features. *J Neurosurg* 1993; **78**: 579-586 [PMID: 8450331 DOI: 10.3171/jns.1993.78.4.0579]

13 **Campbell EJ**, Campbell GM, Hanley DA. The effect of parathyroid hormone and teriparatide on fracture healing. *Expert Opin Biol Ther* 2015; **15**: 119-129 [PMID: 25363308 DOI: 10.1517/14712598.2015.977249]

14 **Andreassen TT**, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. *J Bone Miner Res* 1999; **14**: 960-968 [PMID: 10352105 DOI: 10.1359/jbmr.1999.14.6.960]

15 **Andreassen TT**, Fledelius C, Ejersted C, Oxlund H. Increases in callus formation and mechanical strength of healing fractures in old rats treated with parathyroid hormone. *Acta Orthop Scand* 2001; **72**: 304-307 [PMID: 11480610 DOI: 10.1080/00016470152846673]

16 **Mognetti B**, Marino S, Barberis A, Martin AS, Bala Y, Di Carlo F, Boivin G, Barbos MP. Experimental stimulation of bone healing with teriparatide: histomorphometric and microhardness analysis in a mouse model of closed fracture. *Calcif Tissue Int* 2011; **89**: 163-171 [PMID: 21701938 DOI: 10.1007/s00223-011-9503-3]

17 **Alkhiary YM**, Gerstenfeld LC, Krall E, Westmore M, Sato M, Mitlak BH, Einhorn TA. Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). *J Bone Joint Surg Am* 2005; **87**: 731-741 [PMID: 15805200 DOI: 10.1359/jbmr.2002.17.11.2038]

18 **Roche B**, Vanden-Bossche A, Malaval L, Normand M, Jannot M, Chaux R, Vico L, Lafage-Proust MH. Parathyroid hormone 1-84 targets bone vascular structure and perfusion in mice: impacts of its administration regimen and of ovariectomy. *J Bone Miner Res* 2014; **29**: 1608-1618 [PMID: 24496950 DOI: 10.1002/jbmr.2191]

19 **Aspenberg P**, Genant HK, Johansson T, Nino AJ, See K, Krohn K, García-Hernández PA, Recknor CP, Einhorn TA, Dalsky GP, Mitlak BH, Fierlinger A, Lakshmanan MC. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. *J Bone Miner Res* 2010; **25**: 404-414 [PMID: 19594305 DOI: 10.1359/jbmr.090731]

20 **Peichl P**, Holzer LA, Maier R, Holzer G. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. *J Bone Joint Surg Am* 2011; **93**: 1583-1587 [PMID: 21915572 DOI: 10.2106/JBJS.J.01379]

21 **Bukata SV**, Puzas JE. Orthopedic uses of teriparatide. *Curr Osteoporos Rep* 2010; **8**: 28-33 [PMID: 20425088 DOI: 10.1007/s11914-010-0006-3]

22 **Rubery PT**, Bukata SV. Teriparatide may accelerate healing in delayed unions of type III odontoid fractures: a report of 3 cases. *J Spinal Disord Tech* 2010; **23**: 151-155 [PMID: 20051918 DOI: 10.1097/BSD.0b013e31819a8b7a]

P- Reviewer: Elgafy H, Gonzalez-Reimers E, Ma DY **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com