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EDITORIAL

Cyclops syndrome following anterior cruciate ligament reconstruction: Can relapse occur after surgery?

Recep Öztürk

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Abstract

Symptomatic cyclops lesions are complications that can be seen at rates of up to approximately 10% after anterior cruciate ligament reconstruction. However, recurrent cyclops lesions have rarely been documented. There are case rare series in the literature regarding the treatment of recurrent cyclops lesion. Future large studies are needed to investigate factors contributing to the development of cyclops lesions and syndrome and treatment options.

Key Words: Cyclops lesion; Cyclops syndrome; Anterior cruciate ligament; Knee arthroscopy; Relaps

Core Tip: Although anterior cruciate ligament reconstruction is a surgery with low complication rates, it may sometimes require revision surgery. One of the reasons for this is cyclops syndrome, which can lead to knee extension limitation. However, recurrence after surgery is very rare. Discussion of this rare complication is important for the management of future complications.

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INTRODUCTION

Anterior cruciate ligament (ACL) reconstruction is a well-defined and common

operation with very low complication rates. However, loss of knee extension that can be seen in some patients may require revision surgery. In 1990, Jackson and Schaefer detected a fibrous nodule on the ligament in a patient with loss of extension after ACL surgery. In this entity, which they call Cyclops syndrome, the impact of the nodule on the notch during extension restricts extension. It is known that this nodule develops as a result of a fibrotic process after repeated traumas[1-3]. In fact, cases with similar mechanisms have also been reported in patients who did not undergo ACL reconstruction. There are also patients who are not actually symptomatic but have positive findings on magnetic resonance imaging (MRI). Some studies report rates of up to 50% of asymptomatic MRI findings[4].

The diagnosis of cyclops lesion can be made by evaluating the postoperative clinical examination findings and MRI findings. When a cyclops lesion is detected, early surgery is the recommended method to prevent degeneration and other knee pathologies that may develop. We also know that early surgery is effective in providing range of motion[2].

When the reports published over the years are systematically examined, it is reported that symptomatic cyclops lesions can actually be seen in 2% to 11%. It is known that the use of hamstring or patellar graft does not constitute a risk factor in the development of cyclops lesion. However, there are also studies reporting that bone-tendon-bone graft is a risk factor [2,5]. In fact, the list of risk factors is long and most of time it is difficult to say which factors caused it in a case report.

In fact, the best treatment is to take precautions to prevent it from occurring, but if revision is necessary, it is to be done as soon as possible. However, performing it at least within the first year after surgery may contribute to the results. Additionally, an effective rehabilitation program should be applied after the second surgery. Delcogliano *et al*[6] and Eckenrode[7] reported that the results were successful in 4 and 3 patients, respectively, who were operated on within the first 1 year due to cyclops lesions. However, the results can sometimes be disappointing after all[2,8].

Although recurrence of the cyclops lesion after surgery is very rare, Kelmer *et al*[9] reported a case that recurred after bone-tendon-bone ACL reconstruction and required revision surgery twice. This case is a good example that shows all surgeons and physiotherapy teams dealing with ACL reconstruction the importance of precautions that must be taken to prevent this lesion from developing. The fact that full recovery occurred after two surgeries still supports that the best treatment is surgical release.

When comparing interventions performed without anesthesia and with anesthesia after the cyclops lesion, the results after anesthesia are better. This may indicate that compression-related pain also contributes to the etiology[1,10]. While approximately 20% to 35% of cyclops lesions are seen in second-look arthroscopy after anterior cruciate ligament reconstruction, approximately 80% of them are asymptomatic. As a result, it is a fact that asymptomatic lesions do not require intervention, and authors agree that surgery is required for cyclops lesions. However, there is still a need for comparative studies.

CONCLUSION

In conclusion, recurrence may occur after cyclops lesion surgery, although very rarely. future larger studies are needed to better understand what factors contribute to the development of cyclops syndrome and the etiology of recurrent cases. In addition, comparison results of different treatment modalities may contribute to determining the gold standard management method.

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EDITORIAL

Update on the use of 45S5 bioactive glass in the treatment of bone defects in regenerative medicine

Dayane Maria Braz Nogueira, Marcelie Priscila de Oliveira Rosso, Daniela Vieira Buchaim, Mariana Schutzer Ragghianti Zangrando, Rogério Leone Buchaim

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Abstract

Bone regeneration is a critical area in regenerative medicine, particularly in orthopedics, demanding effective biomedical materials for treating bone defects. 45S5 bioactive glass (45S5 BG) is a promising material because of its osteoconductive and bioactive properties. As research in this field continues to advance, keeping up-to-date on the latest and most successful applications of this material is imperative. To achieve this, we conducted a comprehensive search on PubMed/MEDLINE, focusing on English articles published in the last decade. Our search used the keywords "bioglass 45S5 AND bone defect" in combination. We found 27 articles, and after applying the inclusion criteria, we selected 15 studies for detailed examination. Most of these studies compared 45S5 BG with other cement or scaffold materials. These comparisons demonstrate that the addition of various composites enhances cellular biocompatibility, as evidenced by the cells and their osteogenic potential. Moreover, the use of 45S5 BG is enhanced by its antimicrobial properties, opening avenues for additional investigations and applications of this biomaterial.

Key Words: Biocompatible materials; Bioglass; Bone regeneration

Core Tip: Regenerative medicine demands materials with effective osteoconductive and bioactive properties. Compared with other materials, 45S5 bioactive glass not only exhibits more biocompatibility but also enhances bone growth when combined with composites. Moreover, its antimicrobial properties offer many possibilities for future applications.

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INTRODUCTION

As human life expectancy increases, there is a corresponding rise in the prevalence of bone-related medical conditions, such as fractures, bone tumors, periodontal diseases, and degenerative cartilage disorders. These conditions can significantly affect individuals' daily activities, given the vital role bones play in providing mechanical support, facilitating hematopoiesis, and protecting internal organs. Bone regeneration is a complex biological process that involves a series of coordinated events to stimulate and regulate the formation of new bone. Considering the negative impact on the skeletal system, there is an increasing demand for tissue engineering approaches that specifically focus on promoting bone regeneration in humans[1-3].

Reconstructing critical bone defects resulting from trauma, accidents, and bone necrosis has historically posed a complex challenge for patients and surgeons worldwide. Although autologous bone grafts and allografts have shown potential in restoring lost structure and function, they face significant challenges such as size incompatibility, immunological rejection, donor shortage, extensive graft resorption, prolonged surgical time, and the risk of postoperative infection and pain. These challenges ultimately limit the application of autologous bone grafts and allografts. Accordingly, numerous studies have been conducted in recent decades to identify viable alternatives, resulting in the introduction of various substitute materials in the field of regenerative medicine. These materials are often made of metals such as aluminum, zirconium, and titanium, which are used in the manufacturing of prostheses, plates, pins, screws, and similar devices. However, these materials often lack the durability required for long-term human use, prompting the search for more enduring alternatives[4-7].

To overcome these challenges, the field of medical biomaterials has undergone substantial growth in recent years, offering innovative solutions to reduce fracture healing time and address other bone regeneration issues. Currently, biomaterials play a prominent role in promoting bone tissue regeneration in humans. Various synthetic materials have been developed, with bioactive glass (BG) ceramics emerging as a significant contributor. Categorized as second-generation biomaterials, BG interacts with the biological environment, enhancing tissue adhesion and progressively degrading as new tissue regenerates and heals, similar to hydroxyapatite[8].

We are currently in the era of third-generation biomaterials, which have the capability to trigger specific cellular responses at the molecular level. At the forefront of this field are bioactive glasses (BGs). These glasses consist of a group of calcium phosphate compounds that exhibit the remarkable capacity to rapidly form a strong bond with tissue, as exemplified by 45S5 bioactive glass (45S5 BG)[9-11].

In the late 1960s, researcher Larry L. Hench and his pioneering team at the University of Florida introduced 45S5 BG [12]. During their research, they made a remarkable discovery: this type of glass formed such a strong bond with bone that separation was impossible without causing a fracture. Subsequent *in vivo* studies showed that 45S5 BG exhibited osteoinductive and osteoconductive properties by forming carbonated hydroxyapatite (CHA) within the bone[13].

BGs are typically amorphous calcium-containing silicates that have osteoinductive capacity[14]. The most commonly used type of BG is 45S5 (Figure 1), composed of 45% SiO_2, 24.5% CaO, 24.5% Na_2O, and 6% P_2O_5[15,16]. This type of BG is osteoconductive, osteogenic, and biodegradable. Currently, BGs are produced using the sol-gel method, which uses a solvent at low temperatures. This method has the advantages of creating a porous and highly bioavailable structure and incorporating various additives to produce a range of glass-ceramics[15]. The unique combination of characteristics makes BG a potential substitute biomaterial because of its association with growth factors and biomolecules used in regenerative medicine[16,17].

BGs from various commercial brands have been successfully used, either alone or in combination with various metal ions, to reconstruct jawbone defects. BGs elicit a biocompatible response at the bone-tissue interface, thus enabling numerous medical applications[16]. Initially, the main goal of these materials was to enhance bone regeneration[14]. Applying a BG coating to a surface before it receives a metal prosthetic implant can provide stability by creating a bonding interface between the bioactive coating and the host tissue[18]. BG-coated surfaces can also protect the substrate (thus preventing corrosion) and even inhibit the release of potentially toxic metal ions[19].

More than 60 years after the discovery of BGs, the field of regenerative medicine continues to evolve, with many studies indicating vast opportunities for exploitation. BG shows remarkable efficacy in promoting bone regeneration, surpassing other bioactive ceramics. This particularity is related to BG's dissolution products, which act at the genetic level, stimulating the cells. This characteristic has fundamentally changed the way doctors, scientists, and regulatory agencies perceive the concept of bioactivity. 45S5 BG, a pioneer in this category, has only recently become widely used in orthopedics. To date, 45S5 BG has contributed to the bone regeneration of more than 1.5 million patients in the fields of

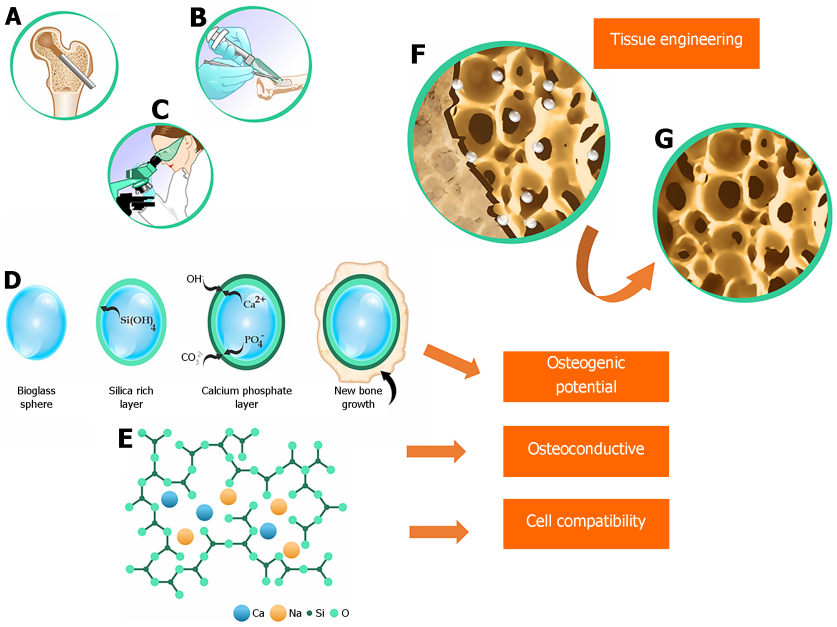

Figure 1 An example of the articles reviewed in this editorial. 45S5 bioactive glass (45S5 BG) stands out in regenerative medicine. 45S5 BG is biocompatible and has osteoinductive and osteoconductive properties by forming carbonated hydroxyapatite (CHA). These characteristics result from the creation of a highly bioavailable porous structure and the ability to incorporate various additives to produce a variety of glass-ceramics. A: Bone defect; B: Bone defect filling with 45S5 BG granules; C: Evaluation of histological sections of bone following experiments; D: Demonstration of the bioactive properties of 45S5 BG due to its ability to form a mineral surface layer of CHA similar to bone tissue. 45S5 BG particles are absorbed, and the released ions interact with local ions [$Si(OH)_4$, OH^-, CO_3^{2-}, PO_4, Ca^{2+}] to form hydroxycarbonate apatite (HCA), providing an ideal surface for the formation of new bone; E: Example of the composition of a 45S5 BG chain (in weight%): 45% SiO_2, 24.5% CaO, 24.5% Na_2O and 6% P_2O_5. The green arrows indicate the characteristics of 45S5 BG observed in the reviewed studies: osteogenic potential, osteoconductivity, and cell compatibility; F: Stimulation and cell adhesion of the 45S5 BG granules to the new bone surface; G: Absorption of the granules and formation of new tissue with bone repair.

orthopedics and dentistry[20,21].

45S5 BG was first used in medical practice to restore the bones of the middle ear and thus hearing. Subsequent research has advanced, presenting BG in the form of granules and modified compositions. This advancement enabled surgeons to manipulate it more precisely and customize it to meet the specific needs of each patient[20,22].

Under the name Perioglass®, 45S5 BG was initially used to treat jawbone defects. In 1999, 45S5 BG was launched as NovaBone® and used in clinical trials for the surgical treatment of adolescent idiopathic scoliosis. These trials demonstrated several advantages, including reduced infection and mechanical failure rates. Additionally, the use of 45S5 BG eliminates the need for a local donor. In 2015, the Food and Drug Administration (FDA) approved the term "osteostimulation" for 45S5 BG[23]. Another variation, BonAlive®, has received approval for use in orthopedic surgeries in more than 50 countries, being used for synthetic bone grafting in trauma, tumor removal, and the treatment of chronic osteomyelitis[20,24].

The application of 45S5 BG extends beyond orthopedics. Clinical and experimental tests of this biomaterial, molded with a borate glass structure, have successfully healed diabetic ulcers in humans that did not respond to conventional treatment[25]. Other potential applications of BG-containing composites include tissue engineering (*e.g.*, heart, lung, and nerve tissues), intervertebral disc structures, antibacterial activity, and dressing materials. However, *in vivo* tests are required to confirm their effectiveness before they can be recommended for clinical trials[17].

Bone regeneration is a critical aspect of regenerative medicine, and research in this field continues to advance. Therefore, it is crucial to stay up-to-date on the latest developments in biomaterials. The applications of 45S5 BG in the treatment of bone defects have progressed significantly. Therefore, this editorial aims to provide a comprehensive and up-to-date analysis of its applications. It will serve as a valuable resource for professionals and researchers in the field of regenerative medicine, helping to guide their clinical decisions and identify areas for future research.

CHARACTERIZATION OF THE MOST RECENT PUBLICATIONS ON 45S5 BG IN BONE DEFECTS

To develop this editorial and conduct a critical analysis, we searched the PubMed/MEDLINE database for articles published over the past 10 years using the search terms "bioglass 45S5 AND bone defect". The search returned 27 articles. We then analyzed the titles and abstracts to determine elegibility. Subsequently, we reviewed the articles to ascertain whether they met the eligibility criteria, which included application to both animals and humans, publication in English, full-text accessibility, and relevance to the topic. We included 15 articles as the basis for this editorial. Nine of these articles involved *in vitro* and *in vivo* experiments, five involved only *in vivo* experiments, and only one involved a human cohort study. Regarding the animal models used in the experiments, eight articles used rats, three used rabbits, two used

mice, and one used sheep. Regarding the experimental region of interest, six articles used the calvaria, four used the femur, two used the tibia, and two involved graft implantation in subcutaneous pouches in the hind and forelimbs.

The articles included in this editorial are listed in Table 1[3,10,26-38], along with the elements categorized according to the PICO strategy (P: Patient or problem; I: Intervention; C: Control or comparison; O: Outcome). Table 1 also provides details on the reference, objective, study type, bioactive glass composition, methods, and outcome measures for each article.

Most studies conducted in the last decade were designed to compare 45S5 BG with other cements or scaffolds, such as: (1) BGPN2.6; (2) Nb-substituted 45S5 BG; (3) Empty cavity; (4) CPC; (5) Magnesium- and strontium-doped BG; (6) BGNb; (7) A glass derived from the composition of 45S5 BG, Collapat® II, and Osteopure®; (8) Slow-resorbing ceramic granules, biphasic compounds of PEUR, and nHA; (9) Biosilicate® BioS-2P; (10) 45S5 BG scaffolds reinforced with BG-ZB; (11) Borosilicate glass 0106-B1; (12) Icariin-doped 45S5 BG seeded with ASCs; (13) 3D polymer-coated 45S5 BG scaffolds: gelatin-coated, cross-linked gelatin-coated, or PHBV-coated; and (14) LLLT in autogenous grafts.

We observed variation in the concentration of 45S5 BG in the reviewed studies. Research in regenerative medicine highlights the importance of determining and applying optimal concentrations[17]. This is essential to confirm the vascularization process in composites made of this biodegradable polymer, indicating a potential area for future research.

Only one study has assessed the interaction between alendronate and 45S5 BG[32]. As described in that study, the hybrid particles released alendronate and inorganic elements (Ca, Na, Si, and P) in a controlled manner. This controlled release exhibited a strong anti-osteoclastic effect *in vitro* and stimulated the regeneration of the osteoporotic femur in Wistar rats.

Only one study, Fares *et al*[30], investigated the outcomes in patients who underwent ACL reconstruction with patellar tendon autograft and various materials. Patients who received Glassbone® or Collapat® II grafts reported experiencing less pain and greater kneeling comfort than those who received the Osteopure® graft. No significant differences were observed among the three groups in knee function scores (International Knee Documentation Committee - IKDC and Lysholm) and anterior knee pain. The authors reported no wound healing complications. At the end of the 2-year follow-up, the type of material used had no effect on functionality.

Souza *et al*[26] compared the performance of BGPN2.6 with that of 45S5 BG for repairing CSD calvarial defects in rats. They comprehensively assessed biocompatibility, cell adhesion, and osteoblast cell proliferation in the presence of BGPN2.6. In animal models, micro-CT scans revealed that the application of BGPN2.6 almost completely regenerated the CSD within 8 wk, achieving over 90% coverage. In comparison, standard 45S5 BG achieved only 66% coverage. These results clearly demonstrate that Nb-containing BG is a safe and effective biomaterial for bone replacement in the treatment of CSD, with significant implications for regenerative medicine and orthopedics. This research provides encouraging evidence for the applicability of 45S5 BG in the treatment of CSD.

Continuing their research on the addition of Nb to 45S5 BG, Souza *et al*[3] tested rods made of different types of glass (BGPN1.3, BGPN2.6, and 45S5 BG) in rat tibiae. Their findings made important contributions, such as demonstrating the non-toxicity of Nb to hESCs and a significant increase in osteogenic capacity when adding up to 1.3 mol% of Nb_2O_5 to 45S5 BG. The substitution of an equivalent amount of Nb_2O_5 for phosphorus enhanced the osteostimulation of 45S5 BG.

The use of Nb combined with 45S5 BG has attracted the interest of researchers. Lopes *et al*[10] demonstrated that 45S5 BG with Nb at concentrations of 1 and 2.5 mol% stimulated osteogenic differentiation of BMMSCs after 21 d of treatment. BGNb is osteoconductive and osteostimulative. These results indicate that the bioglass (BGNb) is suitable for biomedical applications.

In another experiment investigating the effects of adding components to 45S5 BG, Esfahanizadeh *et al*[29] compared the elements strontium and magnesium to standard 45S5 BG. At 4 wk, the group treated with magnesium-doped 45S5 BG showed greater bone formation. At 8 wk, the group treated with strontium-doped 45S5 BG showed better results. The addition of strontium and magnesium into the composition of 45S5 BG improved bone regeneration compared to standard 45S5 BG. It should be noted that the rate of bone regeneration was higher than that of 45S5 BG, but without statistically significant differences. This finding may be attributed to the effect of magnesium and strontium ions in inhibiting osteoclastic activity, as well as the inherent ability of 45S5 BG to enhance angiogenesis and stimulate the secretion of growth and osteogenic factors.

Thomas; Anbarasu[27], who also focused on CSD in rat calvaria, demonstrate the growing research interest in this type of injury. They found that 45S5 BG achieved a cell viability rate of over 70%, confirming its cell compatibility. Furthermore, CBCT revealed a significant increase in VGi ($P < 0.001$) and a reduction in ROI ($P < 0.001$) from the fourth to the eighth week, indicating the potential of 45S5 BG for bone regeneration in CSD.

Zhang *et al*[34] addressed CSD in rabbit femurs and found that the strongest scaffolds, containing 4% low-melting ZB in 45S5 BG and 500 μm pores, were particularly beneficial for osteogenic capacity. This was accompanied by accelerated bone growth (6-18 wk), with the material itself showing mild resorption. In contrast, scaffolds with smaller pore sizes showed lower bone growth (< 32% after 6-12 wk). These results suggest a promising application of 45S5 BG in clinical settings, particularly in mechanically loaded bone defects.

Regenerative medicine depends on ongoing advancements to improve its principles and applications, including the development of complementary approaches to address bone defects. One example is the use of LLLT in bone lesions, which has shown promising results[39-41]. In this editorial, we highlight the study by Moreira *et al*[38], who used LLLT to heal CSDs filled with a blood clot, autogenous bone, or 45S5 BG. With the protocol used, LLLT did not increase ANFB when associated with autogenous bone or 45S5 BG. This underscores the need for further research and improvement of complementary methods until a consensus is reached.

The use of scaffolds, cements, and compounds (whether synthetic, natural, or in 3D formation) has been the focus of research aimed at developing artifacts to assist in surgical procedures for bone defects. Ma *et al*[28] evaluated the results of a CSC composed of 35% tricalcium silicate, 30% 45S5 BG (particulates with two sizes), and 35% calcium sulfate. They

Table 1 Studies published over the past 10 years involving the application of 45S5 bioactive glass in bone defects

Ref.	Objective	Type of study	Composition	Methods	Outcome measures
Souza *et al*[26], 2020	To compare the biocompatibility of a bioactive sodium calcium silicate glass containing 2.6 mol% Nb_2O_5 with that of the archetypal 45S5 BG	*In vitro* and *in vivo*	A variation of 45S5 BG in which 2.6 mol% of P_2O_5 was replaced by 2.6 mol% of Nb_2O_5, resulting in the composition named BGPN2 The glass was mixed with the precursor oxides SiO_2 (99.5%), $CaCO_3$ (99.95-100.5%), Na_2CO_3 (≥ 99.5%), P_2O_5 (≥ 99.5%), and Nb_2O_5	Biocompatibility and genotoxicity tests Bone regeneration: rat calvarial defect (5 mm). Seventy-two rats (sham group: no defect; control group: empty defect; 45S5 BG group: filled defect; BGPN2.6 group: filled defect), with 6 rats per group for 14, 28 and 56 d Qualitative and quantitative analysis of 3D micro-CT images	BGPN2.6 glass was not cytotoxic to BM-MSCs and had no mutagenic potential Micro-CT showed that BGPN2.6 almost completely regenerated a critical-sized calvarial defect within 8 wk, surpassing the performance of standard 45S5 BG. BGPN2.6 glass demonstrated more than 90% coverage compared to 66% for 45S5 BG
Souza *et al*[3], 2018	To study the bioactive properties of Nb-substituted silicate glass derived from 45S5 B	*In vitro* and *in vivo*	Compositions (mol%): 45S5 BG (46.1 SiO_2; 26.9 CaO; 24.4 Na_2O; 2.6 P_2O_5; no Nb_2O_5) BGPN2.6 (46.1 SiO_2; 26.9 CaO; 24.4 Na_2O; no P_2O_5; 2.6 Nb_2O_5) BGPN1.3 (46.1 SiO_2; 26.9 CaO; 24.4 Na_2O; 1.3 P_2O_5; 1.3 Nb_2O_5) High purity powders SiO_2, Na_2CO_3, $CaCO_3$, P_2O_5 (> 99.9%), and Nb_2O_5, optical grade, > 99.5%) Glass particles between 38-53 μm in size	Compatibility and osteogenic differentiation of hESCs. Bone formation: rods composed of different glass types (BGPN1.3, BGPN2.6, and 45S5 BG) were implanted into bone defects (2 mm) in rat tibiae. Five animals per group were analyzed after 14 and 28 d	Nb-substituted BG is non-toxic to hESCs. There was a significant increase in osteogenic capacity and biocompatibility when up to 1.3 mol% Nb_2O_5 was added to 45S5 BG. The same increase in Nb_2O_5, replacing phosphorus, increased the osteostimulation of the BG
Thomas and Anbarasu[27], 2022	To evaluate cell compatibility and regenerative potential of 45S5 BG graft in critical size defects (CSD) in rat calvaria	*In vitro* and *in vivo*	45S5 BG: 45% SiO_2; 24.5% Na_2O; 24.5% CaO and 6% P_2O_5	*In vitro* cell viability assay of 45S5 BG using MTT assay with Novabone® and 10% DMSO as positive and negative controls, respectively, whereas cells alone served as the control Bone regeneration: 20 male rats with 6 mm diameter calvarial defects (control group: empty cavity) loaded with 2.5 mg of 45S5 BG (test group). Evaluation by CBCT after 4 and 8 wk	45S5 BG achieved a cell viability rate of > 70%, confirming cell compatibility. CBCT analysis showed a significant increase in VGi and a reduction in ROI of CSD from the fourth to the eighth weeks, showing its potential for bone regeneration
Ma *et al*[28], 2017	To evaluate a silicate-based composite bone cement (CSC) in a rabbit femur defect in terms of *in vivo* bone integration and biodegradability and compare the results with those of BG particulates and a calcium phosphate cement (CPC)	*In vivo*	CSC composition: tricalcium silicate (35%) and 45S5 BG (30%) with particles < 50 μm and 90-710 μm. The ratio of the two components was 1:2 (small:large); calcium sulfate (35%)	CSC cylinders molded with a 5 mm × 10 mm diameter, and CPC cylinders. Experiments conducted on 30 adult New Zealand white rabbits with femur defects. Control groups: BG particles and CPC. Analyses were conducted after 3, 6, and 12 months	The CSC underwent slower *in vivo* degradation compared with BG and CPC. The bone contact area at the interface between the surrounding bone and CSC gradually increased over time. CSC kept its structural integrity during *in vivo* implantation because of its acceptable mechanical strength
Esfahanizadeh *et al*[29], 2022	To evaluate bone regeneration in critical defects of rabbit calvaria filled with magnesium- and strontium-doped BGs and compare it with standard 45S5 BG	*In vivo*	Standard 45S5 BG with particles of approximately 20-50 nm	Experiments on 12 male New Zealand rabbits allocated to 2 groups. Four lesions were created in each calvaria with a diameter of 8 mm spaced apart. Each lesion was filled with (1) strontium-doped BG, (2) magnesium-doped BG, (3) 45S5 BG (positive control), and (4) an empty lesion (negative control). Evaluation occurred at the end of 4 and 8 wk	At 4 wk, magnesium-doped BG showed the highest new bone formation with a mean of 11.66 ± 2.64, followed by strontium-doped BG with a mean of 11.10 ± 1.69 (P = 0.0001). At 8 wk, the highest amount of new bone was observed in the strontium-doped group with a mean of 28.22 ± 3.19, followed by the magnesium-doped group with a mean of 22.55 ± 3.43 (P = 0.0001)
Lopes *et al*[10], 2020	To evaluate the solubility, apatite-forming capacity,	*In vitro* and *in*	Composition (mol%) of 45S5 BG and Nb-substituted 45S5 BG:	*In vitro:* BMMSCs were isolated from the tibia and femur of adult Wistar rats. MTT assay was conducted for each of the	45S5 BG and BGSN1 developed an apatite layer on their surfaces within 3 h. Glasses with higher concentrations of Nb_2

	cytocompatibility, osteostimulation, and osteoinduction of Nb-containing bioactive glasses (BGNb) derived from the composition of 45S5 BG	*vivo*	45S5 BG (46.1 SiO_2; 26.9 CaO; 24.4 Na_2O; 2.6 P_2O_5; no Nb_2O_5) BGSN1 (45.1 SiO_2; 26.9 CaO; 24.4 Na_2O; 2.6 P_2O_5; 1.0 Nb_2O_5) BGSN2.5 (43.6 SiO_2; 26.9 CaO; 24.4 Na_2O; 2.6 P_2O_5; 2.5 Nb_2O_5 BGSN5 (41.1 SiO_2; 26.9 CaO; 24.4 Na_2O; 2.6 P_2O_5; 5.0 Nb_2O_5)	BG compositions. Cells were cultured in complete DMEM (positive control), and cells were previously incubated in DMSO for 30 min (negative control) *In vivo:* glass rods (4 mm length × 2 mm diameter) composed of 45S5 BG (45S5 BG or BGSN1 groups were implanted into circular defects (2 mm diameter) in the tibia of rats (5 animals/group) Evaluated after 28 d	O_5 (2.5 and 5 mol%) required at least 12 h Nb-substituted glasses were found to be compatible with BMMSCs. BGSN1 significantly enhanced cell proliferation after 4 d of treatment. Concentrations of 1 and 2.5 mol% Nb_2O_5 stimulated osteogenic differentiation of BMMSCs after 21 d of treatment
Fares *et al*[30], 2024	To evaluate the impact of different materials for filling bone defects following anterior cruciate ligament (ACL) reconstruction surgery with bone-patellar tendon-bone (BPTB) graft	In humans	Osteopure® allograft from resected human femoral head treated by sterilization at 25 kGy Glassbone® BG, 100% synthetic, a mixture of 45% SiO_2, 24.5% CaO, 25.5% Na_2O, and 6% P_2O_5 weight%) Collapat® II, a spongy bone graft composed of a collagen structure in which hydroxyapatite granules are dispersed	A prospective, monocentric cohort study was conducted with 102 adult athletes who underwent ACL reconstruction using the same arthroscopically-assisted BPTB, with a minimum follow-up of two years. Three groups based on the type of bone substitute GB group (G1): 45S5 BG ceramic Glassbone™ (n = 36; 35.29%); CP group (G2): collagen and hydroxyapatite bone void filler in sponge-shaped Collapat® II (n = 34; 33.33%); OP group (G3) treated human bone graft Osteopure® (n = 32; 31.37%). Patients were assessed based on their ability to kneel, the presence of donor site pain, and palpation of the defect	The percentage of Glassbone™ and Collapat® patients who kneeled comfortably was significantly higher than that of Osteopure® patients (77.78% and 76.5%, *vs* 65.6%, respectively)
Lu *et al*[31], 2018	To investigate the remodeling of resorbable bone cements in a stringent model of mechanically loaded tibial plateau defects in sheep	*In vivo*	Melt-derived 45S5 BG with fast- and slow-resorbing ceramic mini-granules (CG, 85% β-tricalcium phosphate/15% hydroxyapatite) ground to 100-300 μm diameter and biphasic PEUR composites Nanocrystalline hydroxyapatite (nHA) The resulting composite bone grafts were denoted as CG/nHA-PEUR and BGCG/nHA-PEUR CG/nHA-PEUR cement contained 55wt% CG, 24.3 wt% nHA, and 20.7 wt% PEUR, whereas BGCG/nHA-PEUR cement contained 37.5 wt% BG, 22.5 wt% CG, 21.6 wt% nHA, and 18.4 wt% PEUR	Eight sheep, with two types of bone defects in each posterior limb. The defects included a non-weight-bearing femoral plug defect on the medial and lateral distal condyles of both femurs (n = 16 per group, two defects with a 6 mm diameter and a 16 mm depth) and a weight-bearing tibial plateau slot defect (n = 8 per group) approximately 50% of the total anterior to posterior tibial depth with 6 mm height. Each sheep received both grafts (BGCG/nHA-PEUR or CG/nHA-PEUR) in separate extremities, with graft placement alternating between animals. Micro-CT analysis was conducted in the immediate postoperative period, and at 4, 8, 12, and 16 wk	CG/nHA-PEUR cements mechanically stabilized the tibial plateau defects and remodeled to form new bone at 16 wk, with early weight-bearing. Cements containing BG particles were resorbed and showed fibrous tissue filling the defect. These findings represent the first report of a settable bone cement that remodels to form new bone while providing mechanical stability in a stringent large animal model of weight-bearing bone defects near a joint
Diba *et al*[32], 2019	To investigate the feasibility of synthesizing novel hybrid particles by exploiting the strong interactions between alendronate and 45S5 BG	*In vitro* and *in vivo*	45S5 BG: a mean particle size of 2.0 ± 1.2 μm. Alendronic acid (4-amino-1-hydroxybutane-1,1-diphosphonic acid) powder. 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid (HEPES; ≥ 99.5%), and 2-(*N*-morpholino)ethanesulfonic acid hydrate (MES hydrate; ≥ 99.5%). Sodium hyaluronate powder (1.01-1.8 MDa) Injectable cohesive pastes: particles mixed with an aqueous solution of sodium hyaluronate (26 mg mL^{-1}). A particle/solution ratio (g/mL) of 0.75. Final composition (wt%): HP1-7 (ALN 62.3 ± 0.6; Ca 11.4 ± 0.0; Na 12.8 ± 0.0; Si < 2; P < 1) HP2-7 (ALN 25.5 ± 9.8; Ca 16.7±0.3; Na 34.7 ±	A cylindrical defect (2.5 mm diameter and 5 mm depth) was created in the bilateral femoral condyle of osteoporotic male rats (n = 8 per experimental group) and filled with HP1-7 and HP2-7 hybrid particle pastes. Positive control: 45S5 BG	The hybrid particles released alendronate and inorganic elements (Ca, Na, Si, and P) in a controlled manner, exhibited a strong anti-osteoclastic activity *in vitro*, and stimulated the regeneration of osteoporotic bone *in vivo*

			0.0; Si 7.3 ± 0.3; P 9.9 ± 0.2)		
Prado Ferraz *et al*[33], 2017	To evaluate the *in vitro* osteogenic and osteoinductive potentials of BioS-2P and its ability to promote *in vivo* bone repair	*In vitro* and *in vivo*	Biosilicate®: 23.75 Na_2O; 23.75 CaO; 48.5 SiO_2; 4 P_2O_5 (wt%), containing two crystalline phases (BioS-2P) Composition (mol%): BioS-2P (23.3 Na_2O; 25.8 CaO; 49.2 SiO_2; 1.7 P_2O_5) 45S5 BG (24.4 Na_2O; 26.9 CaO; 46.1 SiO_2; 2.6 P_2O_5)	BioS-2P and 45S5 BG were cut into 3 mm thick discs and ground with silicon carbide paper to a grit of 400 (~35 μm). MSCs were obtained from the femur of two male Wistar rats and cultured on both types of discs and on polystyrene (control group). CSDs with a 5 mm diameter were created in 15 male Wistar rats and implanted with scaffolds. Evaluation occurred at 4, 8, and 12 wk (n = 5 per period). BioS-2P scaffolds seeded with unlabeled MSCs were implanted into calvarial defects and evaluated 8 wk later	Extracellular matrix mineralization increased in cells cultured on BioS-2P compared with 45S5 BG (P = 0.029)
Zhang *et al*[34], 2017	To compare the osteogenic capacity and effects of 45S5 BG scaffolds reinforced with ZnO/B_2O_3 (ZB), called BG-ZB, with pure 45S5 BG.	*In vivo*	BG-ZB: 30 SiO_2; 28 CaO; 2 P_2O_5; 30 B_2O_3; 10 ZnO). 45S5 BG containing 4% BG-ZB 45S5/ZB*x* powders were homogeneously mixed with paraffin microspheres (porogen) of ~350 and ~500 μm diameter. BGs scaffolds manufactured with different porogens: 45S5/ZB0-350, 45S5/ZB4-350, and 45S5/ZB4-500	Thirty-six adult male rabbits were randomly separated into three groups according to the scaffolds (45S5/ZB0-350, 45S5/ZB4-350, and 45S5/ZB4-500). Each animal underwent surgery for a CSD (Ø 6 × 10 mm) in the bilateral distal femur, with two different implants inserted into the right and left femurs	Open porosity decreased with the addition of 4% ZB, but the percentage of interconnected pores (> 50 μm) increased with increasing porogen size from 350 to 500 μm. Stronger scaffolds containing 4% ZB and 500 μm porogen were beneficial for osteogenic capacity. In contrast, both scaffolds with smaller pore sizes exhibited a low level of new bone growth (< 32%) after 6-12 wk of implantation
Westhauser *et al*[35], 2019	To evaluate the effects of 0106-B1-BG and 45S5 BG on osteogenic differentiation, viability, and proliferation of MSCs *in vitro* and *in vivo* in severe combined immunodeficient (SCID) mice	*In vitro* and *in vivo*	Borosilicate glass (0106-B1-BG) (wt%): 37.5% SiO_2, 22.6% CaO, 5.9% Na_2O, 4% P_2O_5, 12% K_2O, 5.5% MgO, 12.5% B_2O_3) 45S5 BG (wt%): 45%SiO_2, 24.5% CaO, 24.5% Na_2O, 6% P_2O_5)	Ten scaffolds per BG type were seeded with MSCs. Two scaffolds per BG type were implanted without MSCs as a control (total of 24 scaffolds). Four scaffolds were implanted per animal (female SCID mice), with two subcutaneous pockets created on the forelimbs and two on the hindlimbs Evaluation occurred after 10 wk	*In vitro:* both 45S5 BG and 0106-B1-BG were comparable in terms of MSC proliferation, viability, and osteogenic differentiation *In vivo*: 0106-B1-BG scaffolds were significantly superior to 45S5 BG in terms of osteoid quantity and maturation and angiogenic gene expression patterns
Jing *et al*[36], 2018	To investigate the relationship between icariin-doped 45S5 BG seeded with ASCs and angiogenesis of rat EPCs, in rat calvarial bone defect	*In vitro* and *in vivo*	45S5 BG (wt%): 45% SiO_2, 24.5% Na_2O, 24.5% CaO, and 6% P_2O_5, in a cubic and porous format with a volume of 5 × 5 × 5 mm^3 loaded with 30 μL of icariin at a concentration of 5 × 10^{-3} mol/L Pure 45S5 BG scaffolds were used for comparison	A 8 mm diameter calvarial defect was created in the dorsal portion of the parietal bone in twenty male Sprague-Dawley rats, which were allocated into four groups: Group A (control, no implant), Group B (45S5 BG), Group C (45S5 BG/ASCs, 45S5 BG seeded with ASCs), and Group D (icariin/45S5 BG/ASCs, icariin/45S5 BG seeded with ASCs). Evaluation after 12 wk	Treatment with icariin was optimal in promoting VEGF secretion from ASCs, and it was hypothesized to promote angiogenesis of rat EPCs. This suggests a paracrine role for VEGF in mediating the interaction between icariin-induced ASCs and EPCs
Westhauser *et al*[37], 2016	To evaluate the bone formation potential of three different types of hBMSC-seeded polymer-coated 45S5 BG scaffolds in 3D using standardized protocols	*In vitro* and *in vivo*	Three types of 3D-polymer coated 45S5 BG scaffolds: Group A - scaffold coated in 5% w/v gelatin solution, (50 °C). Group B - scaffold coated in 5% w/v cross-linked gelatin-genipin (99:1) solution (50 °C) Group C - scaffold coated in 5% w/v PHBV solution (room temperature)	Each group (A-C) had four identical scaffolds differing only in the type of polymer coating. Scaffolds had a nominal size of 5 × 5 × 5 mm and were implanted subcutaneously on the back above the upper and lower extremities of three female SCID mice. Evaluated 8 wk after surgery. hBMSCs from human bone marrow aspirate were seeded onto each scaffold	All groups exhibited bone formation and good infiltration of connective tissue cells, as well as a dense vascularization network. A-group showed a greater amount of bone. C-group, and especially B-group, exhibited a high dissolution. Both B- and C-groups showed more singular bone formation with no signs of interconnectivity
Moreira *et al* [38], 2018	To evaluate the effect of low-intensity laser therapy (LLLT) on the healing of bone defects filled with autogenous bone or 45S5 BG	*In vivo*	45S5 BG Biogran® Biomet 3i	A 5 mm diameter CSD was created on the calvaria of sixty adult male rats were divided into six groups (n = 10): group C (control, blood clot); group LLLT (LLLT-GaAlAs, wavelength of 780 nm, power of 100mW, energy density of 210 J/cm^2 per point for 60 seconds/point, in five points, only once, after creation of the surgical defect); group AB (autogenous bone); group AB+LLLT (autogenous bone +	The highest ANFB was recorded in the LLLT group (47.67% ± 8.66%), followed by the AB+LLLT (30.98% ± 16.59%) and BG+LLLT (31.13% ± 16.98%) groups. There was a statistically significant difference in ANFB values between group C and the other groups, except for the BG group (P > 0.05). There was no statistically significant difference in ANFB values between group AB and the other groups, between group

		LLLT); group BG (45S5 BG); group BG+LLLT (45S5 BG + LLLT). Evaluation after 30 d	AB+LLLT and groups BG and BG+LLLT, and between groups BG and BG+LLLT. The highest area of remaining particles was found in the BG group (25.15% ± 4.82%), followed by the BG+LLLT group (17.06% ± 9.01%), and there was no significant difference between the groups

Nb_2O_5: Niobium pentoxide; 3D: Three-dimensional; micro-CT: Micro-computed tomography; BM-MSCs: Bone marrow-derived mesenchymal stem cells; hESCs: Human embryonic stem cells; CSD: Critical size defects; DMSO: Dimethyl sulfoxide; CBCT: Cone-beam computed tomography; VGi: Grayscale value in; ROI: Region of interest; CSC: Composite bone cement; CPC: Calcium phosphate cement; BGNb: Nb-containing bioactive glasses; BMMSCs: Bone marrow-derived mesenchymal stem cells; ACL: Anterior cruciate ligament; BPTB: Bone-patellar tendon-bone; PEUR: Poly(ester urethane); nHA: Nanocrystalline hydroxyapatite; BioS-2P: Biosilicate® containing two crystalline phases; MSCs: Mesenchymal stromal cells; hMSC: Human mesenchymal stem cells; MTT: 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide; SCID: Severe combined immunodeficiency; ASCs: Adipose-derived stem cells; EPCs: Endothelial progenitor cells; VEGF: Vascular endothelial growth factor; PHBV: Poly(3-hydroxybutyrate-co-3-hydroxyvalerate); LLLT: Low-intensity laser therapy; ANFB: Newly formed bone; GaAlAs: Gallium-aluminum-arsenide.

observed that this composite is suitable for clinical applications because it is a self-setting material. The authors observed that the addition of 45S5 BG increased mechanical strength and the ability to induce apatite formation. This outcome was expected, given the well-known properties of 45S5 BG. According to their results, there is evidence of *in vivo* efficacy and potential for clinical applications of silicate-based composite bone cements.

Two studies investigated the subcutaneous insertion of scaffolds. These studies caught our attention because they diverged from typical biomaterial research in bone regenerative medicine. Westhauser *et al*[35] implanted subcutaneous scaffolds in rats to observe the behavior of 45S5 BG (as described in Table 1). Interestingly, the authors found that both 45S5 BG and 0106-B1-BG had similar effects on the proliferation, viability, and osteogenic differentiation of MSCs. However, 0106-B1-BG outperformed 45S5 BG in terms of osteoid quantity and maturation, as well as angiogenic gene expression patterns. In another study, Westhauser *et al*[37] implanted subcutaneous 45S5 BG scaffolds coated with gelatin, cross-linked gelatin, and PHBV after seeding with hMSC in SCID mice. They observed bone neoformation in all groups and suggested that the gelatin coating on these implants was more stable than on group A (Table 1). This lack of stability hinders the effective interaction of the 45S5 BG surface with the surrounding tissues, thereby interfering with the formation of new tissue. Bone neoformation plays a stabilizing role for the implant. If bone neoformation is insufficient, mechanical integrity will not improve, resulting in reduced bone formation and increased mechanical destruction. Westhauser *et al*[37] then proposed conducting mechanical tests on the scaffolds to test their hypothesis linking structural deficit to reduced bone formation. Alternatively, it is likely that scaffolds with pores larger than 500 μm in diameter do not induce bone formation[42].

45S5 BG is a bioactive (osteoconductive) and versatile biomaterial capable of inducing bone growth in animal soft tissues. The findings of Yuan *et al*[43] warrant further research on the osteoinductivity of 45S5 BG, its osteoinduction mechanism, and the relationship between osteoinduction and osteoconduction.

Xynos *et al*[44] demonstrated the activation of genes involved in osteoblast metabolism and bone homeostasis. This was achieved through a specific transcriptional program activated in human osteoblasts after treatment with ionic products derived from the dissolution of 45S5 BG. These genes have multiple functions, including the induction of osteoblast proliferation, as exemplified by the RCL gene, which acts as a growth promoter. Moreover, these genes are involved in the remodeling of the extracellular matrix (such as metalloproteinases), play specialized functions (such as CD44), and facilitate cellular interactions, both between cells and with the extracellular matrix.

In regenerative therapy, the ability of scaffolds to be colonized by osteoblasts is extremely important, as a 45S5 BG substrate can serve as a model for previously modified tissues in bioengineering. As shown by Xynos *et al*[45], 45S5 BG stimulated the growth and osteogenic differentiation of primary human osteoblasts. Prado Ferraz *et al*[33] evaluated BioS-2P and 45S5 BG cylinders and found a similar cell growth pattern in both materials. Another interesting finding was that

the BioS-2P scaffold stimulated bone formation to such an extent that its combination with MSCs could not enhance it further. In another study, rat calvarial osteoblasts cultured on BioS-1P and 45S5 BG showed identical proliferation rates [46]. These findings strongly suggest that the presence of one or two crystalline phases does not affect the ability of Biosilicate® to sustain cell adhesion and proliferation. Granito *et al*[47] demonstrated osteogenic activity in 45S5 BG and Biosilicate® but found no significant difference in morphometry between them, suggesting the need for further research. In both cases, growth dynamics accompanied the growth of 45S5 BG.

Icariin seeded with ASCs is another element added to 45S5 BG to treat calvarial defects. A study[36] showed that this combination significantly improved neobone formation, while also displaying excellent osteogenic and angiogenic properties. This emphasizes the potential of this combination as a viable option for regenerating large bone defects.

In orthopedic regenerative medicine, the repair of tibial plateau fractures often requires extensive mechanical fixation and protected weight-bearing for 10 wk. This is because the lack of stability of existing grafts. For bone lesions near joints, the use of a biomaterial that hardens rapidly after implantation can stabilize the fracture with minimal use of rigid implants. Moreover, this biomaterial must stimulate the neobone formation and undergo remodelling at a rate that maintains bone integrity. Developing biomaterials that provide mechanical stability for fractures while facilitating bone remodeling remains a significant challenge in bone tissue engineering.

Lu *et al*[31] demonstrated that CG/nHA-PEUR grafts and BGCG/nHA-PEUR grafts with ceramic granules improved handling properties by reducing polymer tackiness. Both groups hardened within 20 s, resulting in a rigid cement that could not be manually compressed. We highlight the innovations of this research: the development of the first settable bone cement that not only offers mechanical stability but also remodels to form new bone in a large, stringent animal model, particularly for bone defects near a joint. In animals that tolerated the first few weeks of early loading, the CG/nHA-PEUR cements demonstrated effective mechanical stabilization of tibial plateau defects and underwent remodeling to form new bone within 16 wk. In contrast, cements containing 45S5 BG particles were resorbed and filled the defect with fibrous tissue. Additionally, CG/nHA-PEUR cements remodeled at a significantly faster rate at the full weight-bearing tibial plateau site compared to the femoral condyle site, which was mechanically protected in the same animal. These findings, along with mechanical tests, suggest that incorporating 45S5 BG into composites renders the material more brittle.

BG materials and composites may be applicable in load-bearing orthopedic injuries. Wheeler *et al*[48] observed that 45S5 BG had greater shear strength, greater bone growth, no decrease in trabecular bone thickness over time, and maintenance of mechanical integrity.

CONCLUSION

This editorial aimed to provide a comprehensive and up-to-date analysis of the applications of 45S5 BG in regenerative medicine. We have reviewed a diverse range of applications in scientific research. Below, we summarize the main findings and observations from these studies.

Several studies have compared 45S5 BG with other biomaterials. The addition of niobium and other elements generally improves osteogenesis and biocompatibility of materials. These observations demonstrate the safety and efficacy of 45S5 BG as a bone substitute for the treatment of severe defects. However, results have varied over time, suggesting that the choice of these elements may depend on the specific needs of the application. Scaffolds and cements have demonstrated potential in clinical applications because of their rapid hardening ability and their ability to induce the formation of apatite deposits. The incorporation of LLLT, subcutaneous scaffold inserts, and mechanical stabilization of fractures highlights the importance of further research to improve complementary methods in bone regenerative medicine. In summary, these studies suggest that 45S5 BG and related materials have great potential in regenerative medicine and the treatment of bone defects. Modifications and combinations of these materials may optimize bone regeneration in various clinical applications.

FOOTNOTES

Author contributions: Nogueira DMB and Rosso MPO contributed equally to this work; Buchaim DV and Buchaim RL designed the research study; Nogueira DMB and Rosso MPO performed the research; Zangrando analyzed the data; Nogueira DMB, Rosso MPO and Buchaim RL wrote the manuscript; all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Peri-articular elbow fracture fixations with magnesium implants and a review of current literature: A case series

Christopher Fang, Antony Xavier Rex Premchand, Derek Howard Park, Dong Hao Toon

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Abstract

BACKGROUND

In recent years, the use of Magnesium alloy implants have gained renewed popularity, especially after the first commercially available Conformité Européenne approved Magnesium implant became available (MAGNEZIX® CS, Syntellix) in 2013.

AIM

To document our clinical and radiographical outcomes using magnesium implants in treating peri-articular elbow fractures.

METHODS

Our paper was based on a retrospective case series design. Intra-operatively, a standardized surgical technique was utilized for insertion of the magnesium implants. Post – operatively, clinic visits were standardized and physical exam findings, functional scores, and radiographs were obtained at each visit. All complications were recorded.

RESULTS

Five patients with 6 fractures were recruited (2 coronoid, 3 radial head and 1 capitellum). The mean patient age and length of follow up was 54.6 years and 11 months respectively. All fractures healed, and none exhibited loss of reduction or complications requiring revision surgery. No patient developed synovitis of the elbow joint or suffered electrolytic reactions when titanium implants were used concurrently.

CONCLUSION

Although there is still a paucity of literature available on the subject and further studies are required, magnesium implants appear to be a feasible tool for fixation of peri-articular elbow fractures with promising results in our series.

Key Words: Magnesium screw; Fracture; Peri-articular; Elbow

Core Tip: Magnesium implants can be a useful tool in fixation of peri-articular elbow fractures with promising results.

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INTRODUCTION

In recent years, the use of Magnesium alloy implants in orthopaedic surgeries have gained renewed popularity. Apart from being bioabsorbable, negating the need for implant removal, magnesium also has good osteoconductive properties [1-4]. Biomechanically, it exhibits greater biomechanical strength than any pre-existing polymers, and reduces the stress-shielding effect associated with titanium and steel implants as it has a Young's modulus closer to bone[4].

Currently, the main utility of magnesium implants in the orthopaedic community is within the foot and ankle community where satisfactory results have been reported with its utility in forefoot osteotomies[5-7]. However, its utility in the setting of orthopaedic trauma has been steadily increasing[8].

Our study aims to document our clinical and radiographical outcomes using magnesium implants to treat peri-articular elbow fractures. To our knowledge, our study is the first study analyzing outcomes in radial head and coronoid fractures in the English literature.

MATERIALS AND METHODS

This study is a retrospective case series analyzing the clinical and radiographical outcomes of patients with peri-articular fractures of the upper limb, specifically the radial head, coronoid and capitellum, that were surgically treated with bioabsorbable magnesium screws (MAGNEZIX®, Syntellix AG, Hanover, Germany).

Domain specific review board approval was obtained prior to initiation of the study. Patients were recruited over the duration of 8 months from May 2019 to December 2019. All patients recruited were adult aged 21 years old and above, with isolated, closed peri-articular fractures of the elbow and no neurovascular compromise presenting to our institution. Pre-operatively, all patients were counselled regarding the usage of the magnesium implants and the risks and benefits of surgical fixation were extensively explained.

Surgical technique

All patients recruited underwent surgery performed by one of the senior authors of this study with a standardised surgical technique for implantation of the magnesium compression screws in accordance with the manufacturers recommendation. Intra-operatively, after temporary reduction with Kirschner-wires, a cannulated drill was utilised to create a pilot hole before the main hole is drilled and the screw inserted over the Kirschner-wire. Care was taken not to apply excessive torque during screw insertion.

Post-operative regime

Post-operatively, all patients were started immediately on a progressive occupational therapy regime. Passive range of motion was allowed immediately post operatively followed by graduated progression to active range of motion within 2-3 wk. All patients had regular therapy visits post-operatively for supervised sessions. Patients underwent a standardised follow up regime with the primary surgeon at 2 wk, 4 wk, 6 wk, 3 months, 6 months and 1 year post-operatively. During each visit, clinical notes were taken for each patient documenting relevant history and physical exam findings. Two functional scores, namely the Mayo elbow performance score (MEPS) and disabilities of the arm, shoulder and hand (DASH) score was also recorded at each visit. All complications were recorded.

RESULTS

Our study studied a total of 5 patients with 6 fractures, 2 of the coronoid, 3 of the radial head and 1 of the capitellum. The mean age at the time of surgery was 54.6 years of age ranging from 34 to 76 years old, and the mean length of follow up was 11 months, ranging from 7 to 13 months.

Table 1 Results

	Fracture sustained	Follow up	Clinical outcomes scores (At latest follow up)		ROM (Latest follow up)	Clinical outcomes
			Mayo score	DASH score		
67/F	Bryan & Morrey Type 3 capitellum fracture	7 months	100 points	0.8 points	25-130 degrees; Full prono/supination	Pain free; Went back to work as a cleaner without issues
34/M	Coronoid #: Regan and Morrey type 2	11 months	100 points	0.8 points	10–130 degrees; Full prono/supination	Pain free; Went back to recreational exercise (football)
58/M	Comminuted olecranon #; Radial head #: Mason type 2	13 months	100 points	0.9 points	0-150 degrees; 80 degrees prono/supination	Went back to work as a machine operator
38/M	Radial head #: Mason type 2	13 months	100 points	0.8 points	0–150 degrees; Full prono/supination	Pain free; Back to Gym work including weights
76/M	Terrible triad injury; Coronoid #: Regan and Morrey type 3; Radial head #: Mason type 4	11 months	100 points	10.3 points	10–130 degrees; Full prono/supination	Posterior elbow pain (Olecranon bursitis) – Resolved; Pain free from six months onwards

DASH: Disabilities of the arm, shoulder and hand.

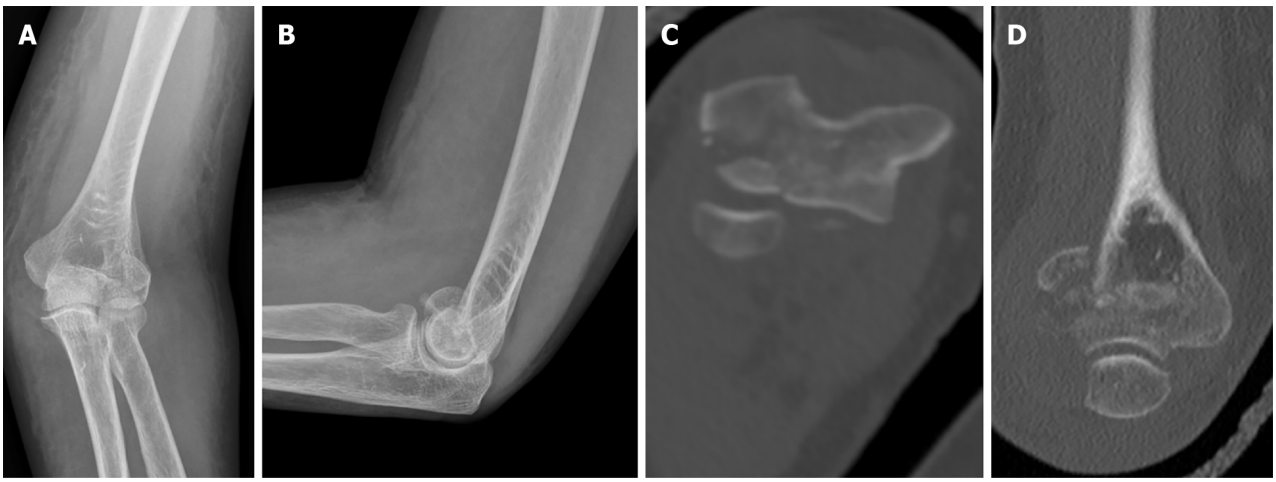

Figure 1 Injury films on presentation depicting a left Bryan and Morrey type 3 capitellar fracture. A-D: Anterior posterior (A) and lateral (B) radiographs, axial (C) and coronal (D) computer tomography cuts depicting the injury.

All 5 patients exhibited good short to medium term clinical outcomes with a mean MEPS of 100 points and a mean DASH score of 2.72 points (0.8–10.3 points) at final follow up. No fractures exhibited any loss of reduction at the point of final follow up, and there were no complications or revision surgeries required for all 5 patients. Notably, none of our patients developed any clinical signs or symptoms of synovitis of the elbow joint (Table 1).

Patient one

Patient one is a 67 year old, functionally active chinese lady with no past medical history who sustained a closed left Bryan and Morrey type 3 capitellar fracture after a mechanical fall from standing height (Figure 1).

Access to the elbow was obtained *via* a mid-axial approach after which fracture reduction was achieved under direct visualization and held with Kirschner wires. Four magnesium screws were then used to compress the fracture site before a 4 hole 1/3 tubular plate was cut and applied in a buttress fashion. Clinically, the patient was pain free by 2 wk and had obtained 25 to 130 degrees of elbow flexion and full prono/supination by the 6 months. At the point of latest follow up, she reported good functional outcomes scores, with a MEPS of 100 points and a DASH score of 0.8. She had also returned to her full time work as a cleaner without any difficulties.

One magnesium screw was noted to have broken at the 6 wk radiograph. However, there was no loss of fracture reduction and the fracture was noted to have united at 6 months post-op (Figure 2).

Patient two

Patient two is a 34 year old male with no significant past medical history who sustained an isolated closed Regan and

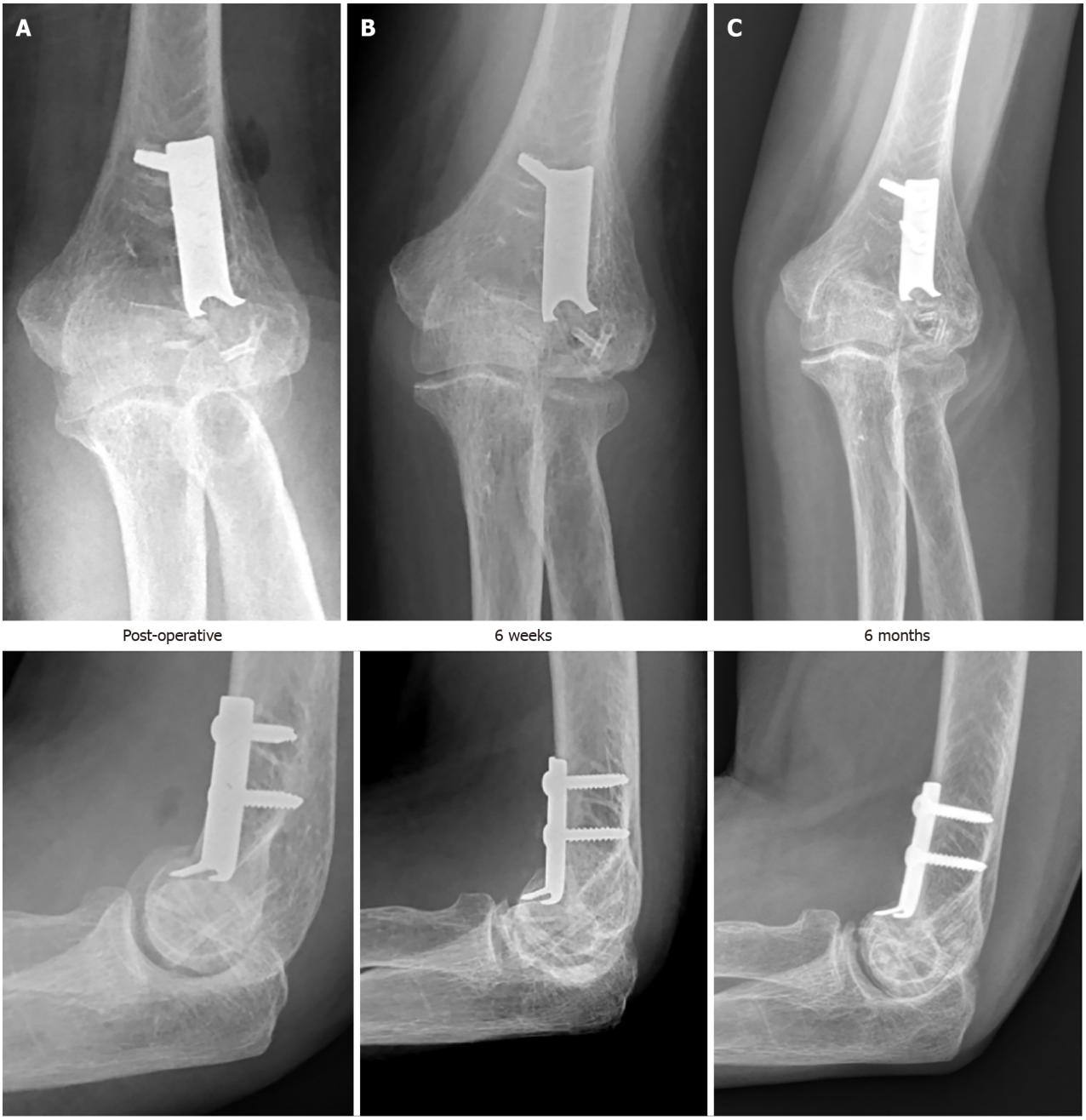

Figure 2 Post operative radiographs depicting progress. A-C: Radiographs immediately post op (A), at 6 wk (B) and at 6 months (C).

Morrey type 2 coronoid fracture. Intra-operatively the coronoid fracture was fixed using a Zimmer ALPS Coronoid plate applied in a buttress fashion and a Magnezix CS 2.7 mm compression screw for compression (Figure 3).

Fracture union was noted at 6 wk post-op, and by 6 months, he had obtained 10-130 degrees of elbow flexion, and managed to return to full work duties as well as recreational football. At the point of final follow up, he reported satisfactory functional outcome scores with a MEPS of 100 and a DASH score of 0.8 points (Figure 4).

Patient three

Patient three is a 58 year old functionally well lady with a significant past medical history of poorly controlled diabetes mellitus and hyperlipidaemia who sustained a closed Monteggia - variant fracture dislocation after a fall from standing height. (Figure 5) Pre – operatively, a computer tomography scan confirmed a comminuted olecranon fracture with a large ulnar butterfly fragment as well as a comminuted radial head fracture.

Intra-operatively, the olecranon fracture was fixed with traditional titanium implants (Zimmer ALPs system) whilst the radial head fracture was fixed with two Magnezix CS 2.7 mm headless compression screws.

By 6 wk post-operatively, she had obtained 10 to 130 degrees of elbow flexion, as well as 60 degrees and 50 degrees of pronation and supination respectively. At 6 months, this further improved to 0 to 150 degrees of flexion and 80 degrees of pronation and supination. At this point, she was pain free, and had returned to work as a machine operator without any difficulties. Fracture union was noted.

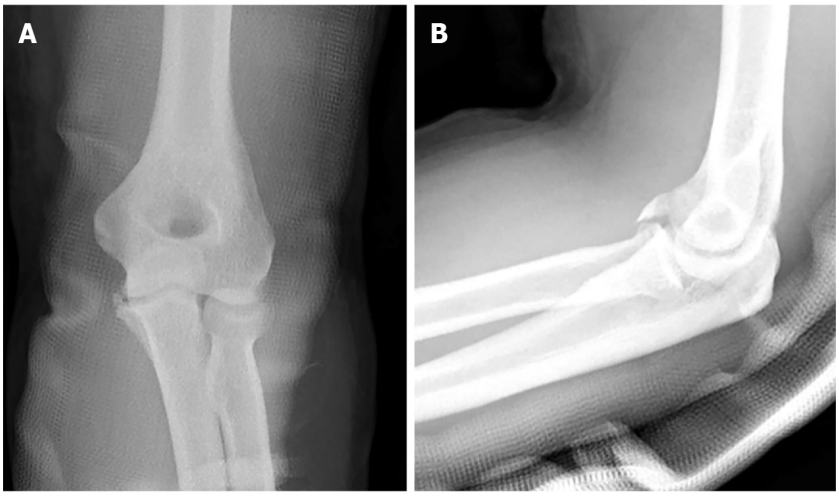

Figure 3 Injury films on presentation depicting a R&M type 2 coronoid fracture. A and B: Anterior – posterior (A) and lateral (B) views.

Radiographically, peri-implant radiolucencies became prominent around the 6 wk post-op, and gradually reduced up to the point of latest follow up at 1 year. At 6 months post-op, we noted breakage of one of the radial head screws, and by the 1 year post-op, the embedded magnesium implants were barely visible on the lateral view (Figure 6).

Patient four

Patient four is a 38 year old male with no significant past medical history who sustained a closed Mason type 2 radial head fracture after a fall from a height (Figure 7).

Intra-operatively, two Magnezix CS 2.7 mm screws were utilised for fixation and compression of the fracture. Full elbow range of motion was confirmed intra-operatively prior to closure (Figure 8).

By 6 wk post-op, he had obtained 0 to 150 degrees of elbow flexion and 90 degrees of both pronation and supination, almost identical to the contralateral limb (Figure 9).

Radiographically we noted the appearance of peri-implant radiolucencies at 2 wk post-operatively, which became more pronounced by 4 wk before reducing significantly by 6 months and almost completely disappearing by 1 year. This observation is in keeping with gradual dissipation of hydrogen produced as a result of magnesium degradation. The distal tip of one of the Magnezix CS screws was noted to have broken off at 6 months post-operatively, during which time the fracture had already healed with no loss of fracture reduction. At 1 year, the broken screw tip had resorbed and was barely visible (Figure 10).

At the point of last follow up, the patient remained clinically asymptomatic and reported no perceivable differences functionally with the contra-lateral limb with a MEP of 100 points and a DASH score of 0.8 points.

Patient five

Patient five is a 76 year old lady with good pre-morbid function who sustained a closed terrible triad injury (Regan and Morrey type 3 coronoid fracture and Mason 4 radial head fracture) (Figure 11).

Intra-operatively, both the radial head fracture and the coronoid fracture were fixed with a combination of one titanium (Medartis 2.0/2.5 mm Low Compression Screw) and one Magnezix CS 2.7 mm screw (Figure 12).

At 6 months post-op, the patient was noted to have elbow flexion from 10–130 degrees and full prono/supination which was identical to the contra-lateral limb. At the point of last follow up, she was pain free and was independent in all activities of daily living, and reported a MEPS of 100 points and a DASH score of 10.3 points (Figure 13).

In similar fashion to patient two, at the 4 wk post-op, radiolucencies were noted over both Magnezix CS screws which reduced significantly by 6 months and almost completely disappeared by 1 year. Neither of screws had broken at 1 year post-op (Figure 14).

Radiographical findings

In our series of patients, we noted the presence of radiolucencies as early as 2 wk post-operatively, which consistently became more pronounced by 4 to 6 wk post-operatively. Significant reduction in radiolucencies were noted by 6 months post-operatively, and radiolucencies were minimal and barely visible by 1 year post-operatively.

At the one year mark post-operatively, we noted screw breakage in 3 out of 6 fractures, of which 2 occurred at 6 months post-operatively and 1 occurred within the first 6 wk. Two of these breakages (Patient three and four) occurred along the distal screw threads, whilst in the remaining case (Patient one), screw breakage occurred before the 6 wk post-operatively proximally near the screw head. We postulate that a potential reason for the earlier breakage is due to the longer length of screw used.

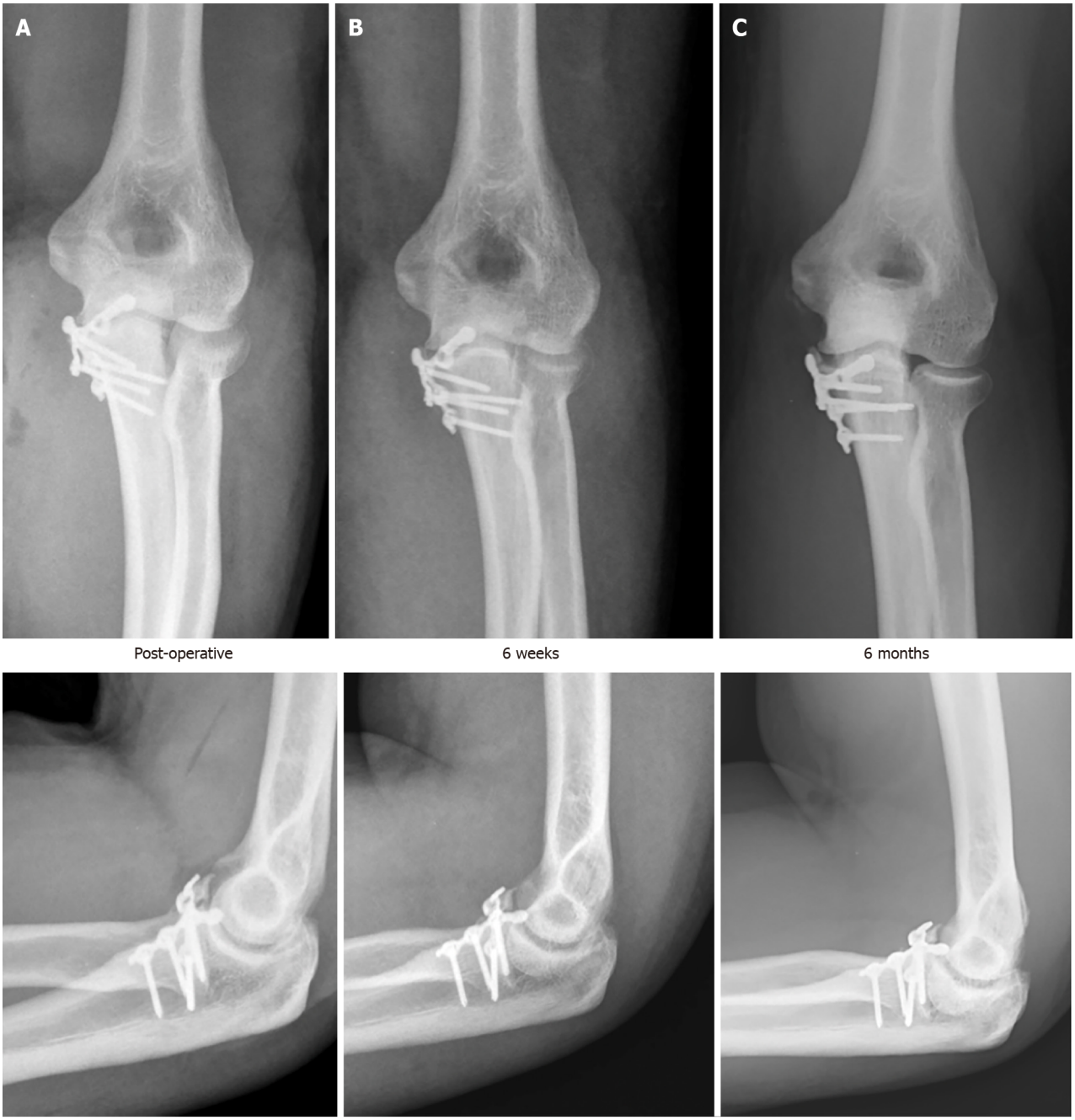

Figure 4 Post operative radiographs depicting progress. A-C: Radiographs immediately post op (A), at 6 wk (B) and at 6 months (C).

DISCUSSION

Magnesium implants were first described in an orthopaedic setting in 1906 by Lambotte[9] who then utilized a magnesium plate to treat a seventeen-year-old child with pseudoarthrosis and severe malalignment of the distal third of the tibia. Despite that, its popularity never took off due to two key reasons. Firstly, rapid corrosion of magnesium inadvertently resulted in pre-mature implant failure and secondly, contact of the magnesium implant with other metals resulted in a florid electrochemical reaction as Lambotte found out in his index experiment after his patient developed severe pain and extensive subcutaneous gas cavities post operatively due to the aforementioned reaction[9].

The advent of technologically advanced Magnesium Alloys, such as MgYREZr which solved the problem of rapid magnesium degradation, has prompted a re-birth in the utilization and popularity of these implants when the first commercially available Conformité Européenne approved magnesium implant became available in 2013 (MAGNEZIX® compression screw from Syntellix).

During this period of time, the vast majority of clinical studies published were in the setting of forefoot deformity correction surgeries such as chevron osteotomies of the first metatarsal, with only a handful of clinical studies documenting its use in the orthopaedic trauma setting.

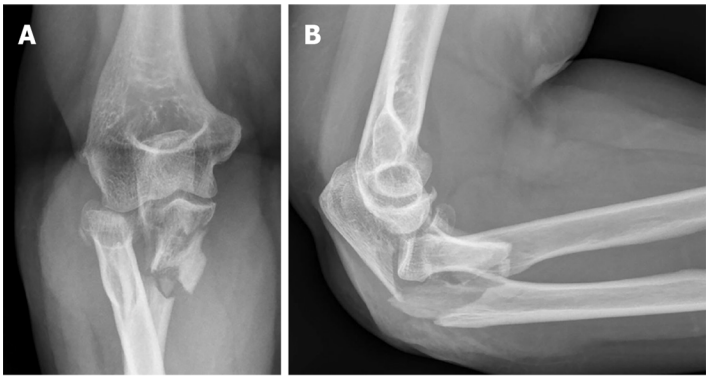

Figure 5 Injury films on presentation depicting a Monteggia variant type fracture. A and B: Anterior – posterior (A) and lateral (B) views.

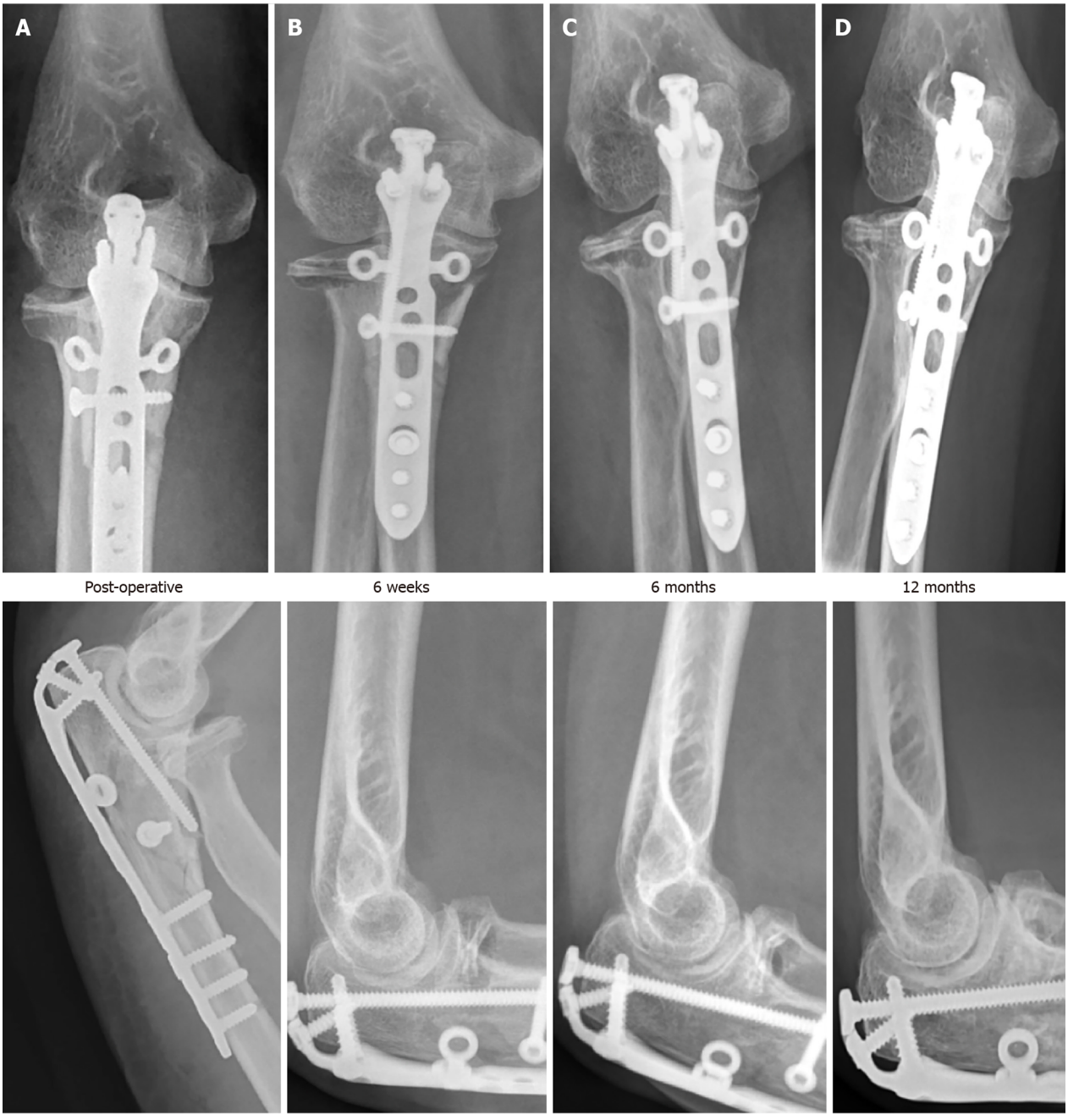

Figure 6 Post operative radiographs depicting progress. A-D: Radiographs immediately post op (A), at 6 wk (B), 6 months (C) and 12 months (D).

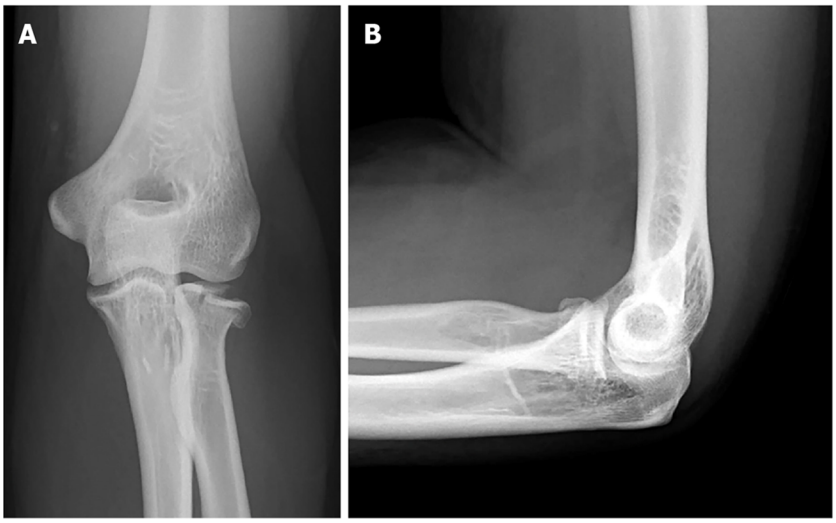

Figure 7 Injury films on presentation depicting a Mason type 2 radial head fracture. A and B: Anterior – posterior (A) and lateral (B) views.

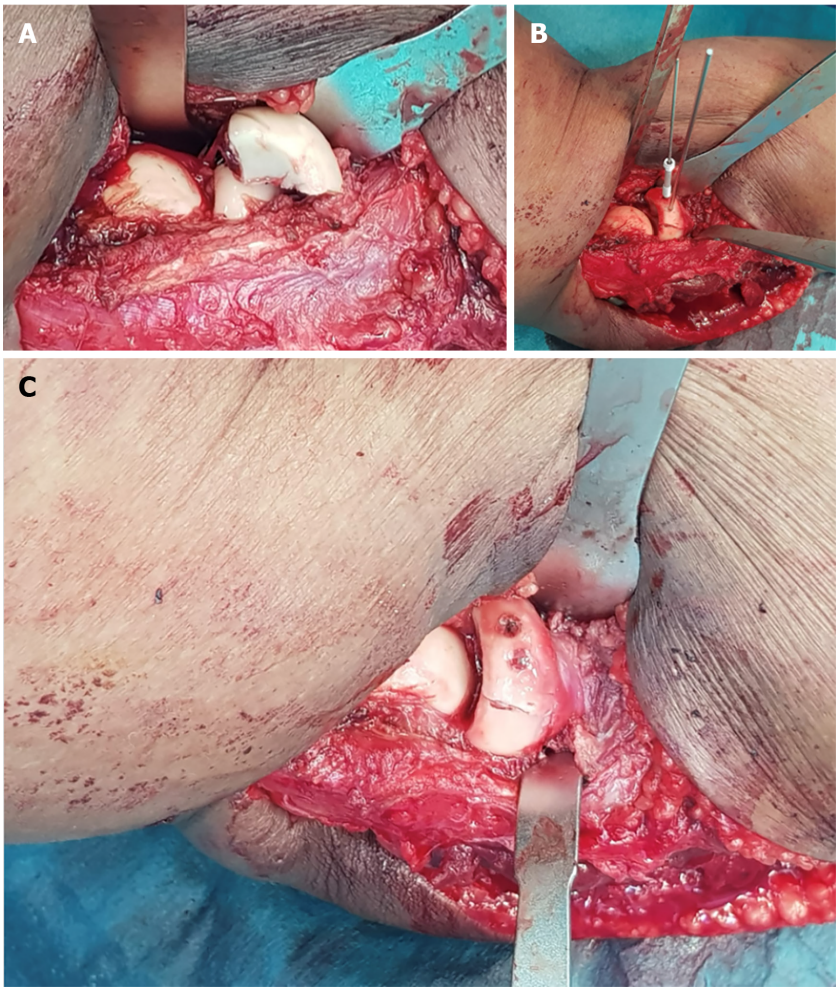

Figure 8 Intra-operative photos. A: Initial fracture configuration; B and C: Reduction and fixation with cannulated magnesium screws (B) and finally the end result (C).

In our review of the existing literature, we identified a total of 10 existing studies[10-19] reporting on the utilization of magnesium implants in the setting of orthopaedic trauma. Of these 10 studies, only 1 reported unsatisfactory outcomes [13] and did not recommend the use of magnesium implants, with 1 study still ongoing[15] (Table 2).

In fractures involving the elbow, Biber *et al*[10] and Aktan *et al*[11] both reported positive results utilizing magnesium implants intra-articular distal humerus fractures. Biber's case report documented the utility of the Magnezix CS

Figure 9 Post – operative range of motion at six wk post-operatively. A: Elbow extension; B: Flexion; C: External rotation; D: Internal rotation.

cannulated compression screw in a patient with a prior radial head replacement who suffered a capitellar fracture and Aktan *et al*[11] documented their experience utilizing two magnesium compression screws for reduction of the distal humerus articular surface in a patient with a distal humerus fracture. Both patients reported successful results with complete fracture union and functional elbow range of motion at the time of latest follow up.

Although there have been reports of magnesium screws being utilized for fractures of the phalanges mentioned, we were unable to find any case reports or studies in the English literature. Apart from Turan *et al*[12] case series documenting successful outcomes in two radial styloid fractures, the remaining existing studies in the setting of hand trauma primarily pertain to its utility in scaphoid fractures. This is natural as the Magnezix CS screw is based on a Herbert screw design (variable pitch, headless, cannulated design) which was originally developed for use in compressive osteosynthesis of scaphoid fractures[3].

In Meier *et al's* 2016 review, a single magnesium compression screw was used for fixation of various scaphoid fractures [13]. Although all patients eventually exhibited excellent wrist functional outcome scores 1 year post-operatively and all fractures eventually consolidated, he observed significant osteolysis and bone cysts in 3 out of 5 patients which resulted in a significant delay of around six months before sufficient consolidation occurred to allow return to physical work, and hence did not recommend its use in scaphoid fractures. Conversely, Grieve *et al*[14] documented positive results in his series of 3 scaphoid fractures. At present, a multi-centre, randomized control trial comparing outcomes of scaphoid fractures treated with magnesium and titanium screws by Könneker *et al*[15] is ongoing (stated to conclude by late 2020) and will hopefully shed more light on the topic.

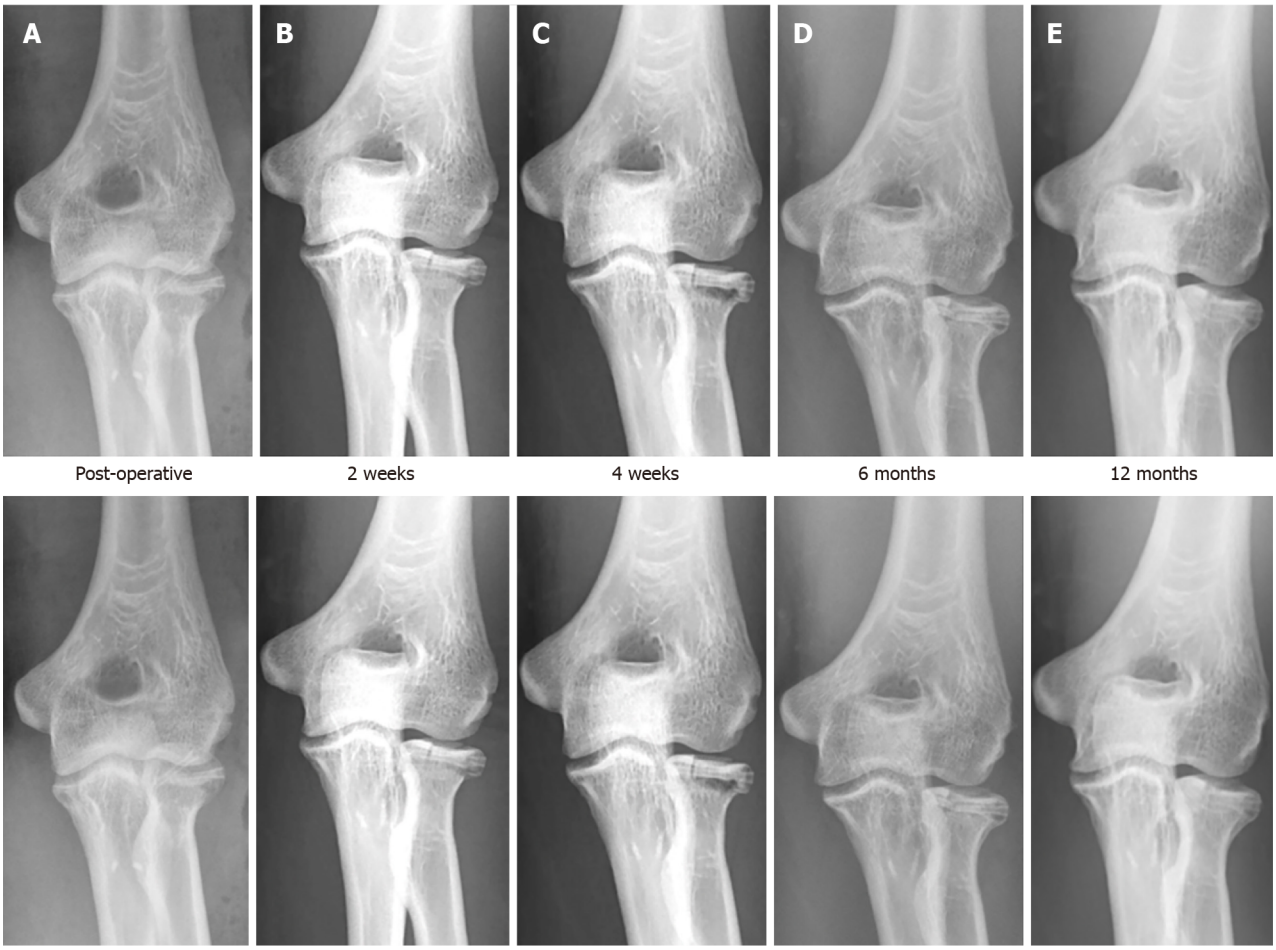

Figure 10 Post operative radiographs. A-E: Radiographs immediately post op (A), at 2 weeks (B), 4 wk (C), 6 months (D) and 12 months (E).

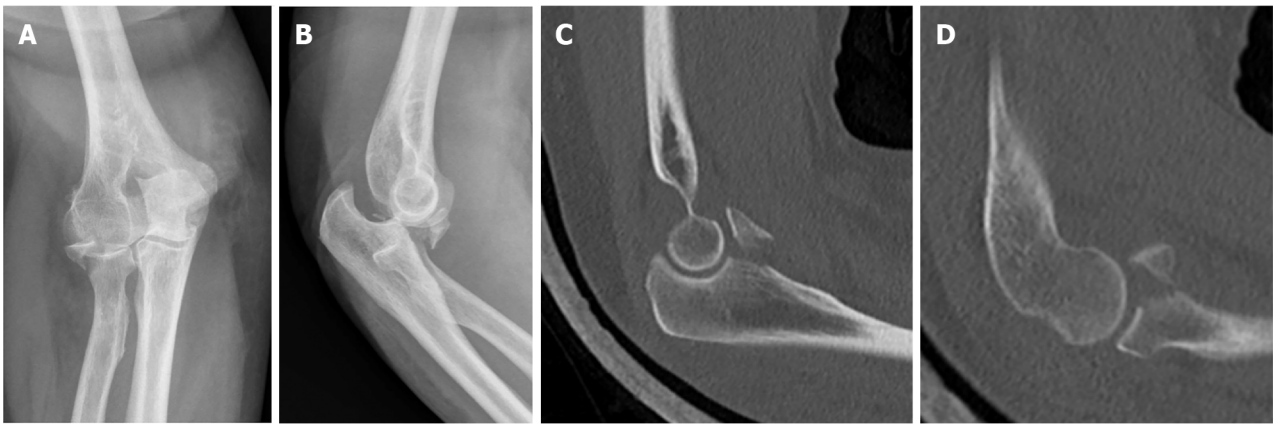

Figure 11 Injury films on presentation depicting a terrible triad fracture. A-D: Anterior posterior (A) and lateral (B) radiographs, saggital computer tomography cuts showing coronoid fracture (C) and radial head fracture (D).

In fractures involving the lower limb, there is existing literature documenting outcomes when used as an adjunct in young neck of femur fractures[16], tibial spine fractures[17] in paediatric patients, as well as isolated lateral[18] and medial malleolus[19] fractures. All reported positive clinical and radiological outcomes.

Despite the multiple benefits[1-4,20-24] of these magnesium implants (Table 3) and the emergence of these aforementioned studies citing positive outcomes, it is important to also highlight several considerations when opting to utilize these implants.

The first important consideration, and arguably the biggest disadvantage of utilizing magnesium implants are the expected production of peri-implant lucencies due to hydrogen gas produced during the process of magnesium degradation. Clinicians may find it difficult to differentiate this from post-operative complications such as infection or loosening of implants. Although studies have demonstrated that these radiolucencies do gradually disappear from

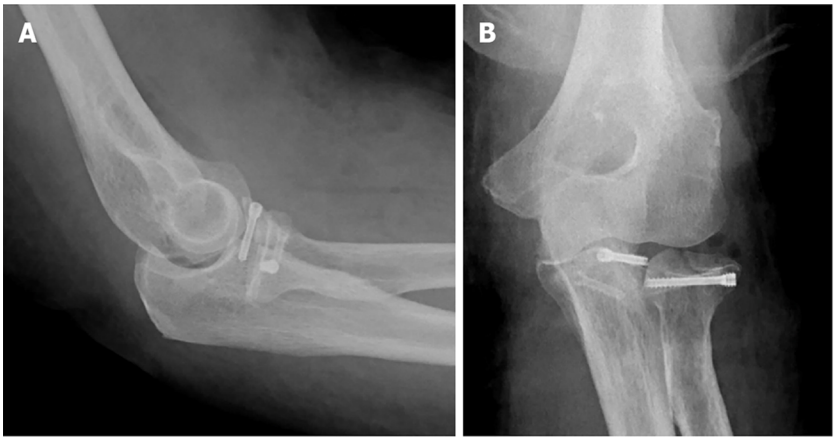

Figure 12 Immediate post-operative radiographs. A and B: Anterior – posterior (A) and lateral (B) views.

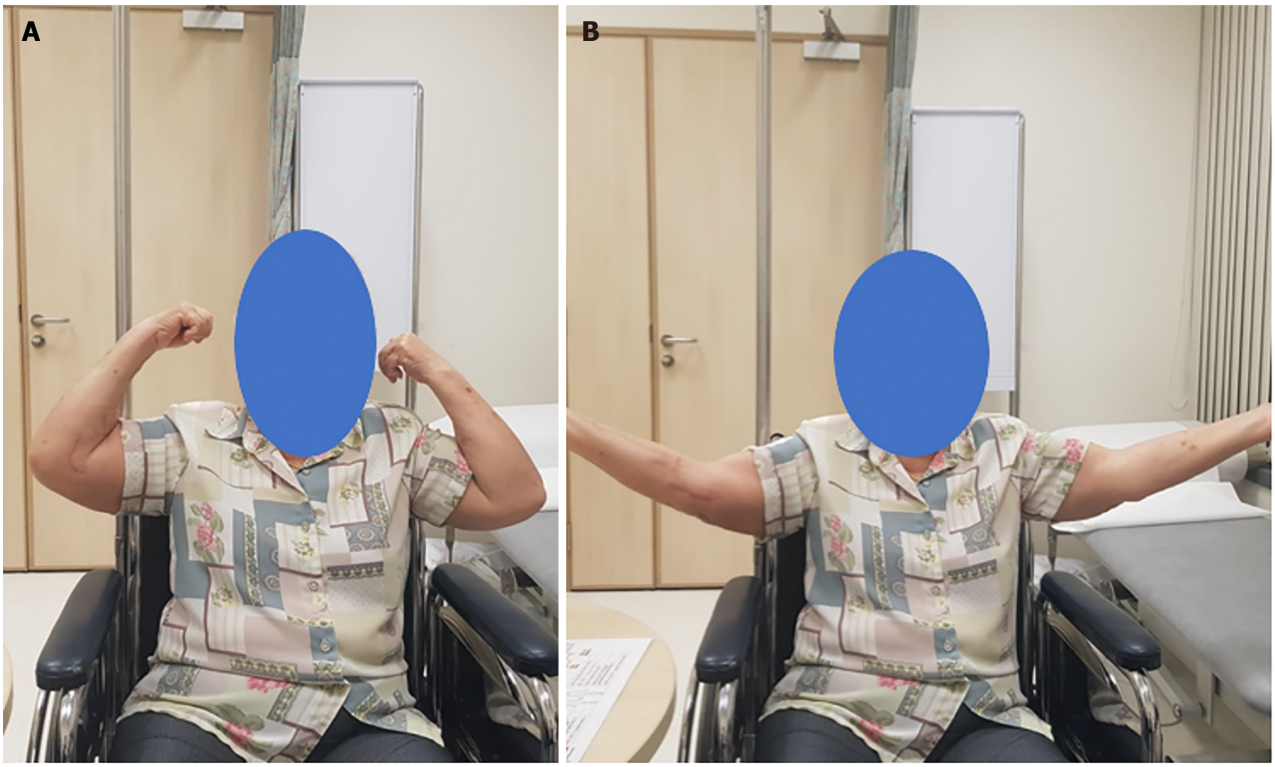

Figure 13 Post-operative range of motion at six months post operatively. A and B: Elbow flexion (A) and extension (B).

anywhere between 3 to 17 months[3], the presence of persistent radiolucencies (which appear as early as 2 wk post-operatively as seen in our series), may cause anxiety to both the clinician and the patient.

Secondly, magnesium implants are also known to be associated with osteolysis[24], which was postulated to occur when the body is unable to adequately clear the products of magnesium degeneration from the implantation site, leading to the migration of osteoclasts to the implantation site. This, coupled with the aforementioned issue of expected post-operative radiolucencies is particularly concerning given the fact that symptoms of osteolysis do not usually occur[25] until there is sufficient bone loss to result in aseptic loosening of the implant, by which point implant failure is likely to occur.

Comparison with conventional titanium implants

Our review of the literature identified 3 studies[5,26,27] comparing outcomes in magnesium and conventional implants. May *et al*'s study recruited a total of 48 patients with medial malleolus fractures undergoing compression screw fixation of which 23 had magnesium screws implanted whilst 25 had conventional screws implanted[26]. In his study, with a minimum follow up of 1 year, no differences in clinical outcomes between both groups were noted, with similar AOFAS clinical outcome scores, and a 100% union rate in both groups. Complication rates were also similar with no deep infection or osteomyelitis noted in both groups. However, 5 patients with conventional titanium implants, compared to

Table 2 Literature review

Fracture	Ref. and Journal	Methodology	Results
Elbow fractures – Capitellum fracture	Biber *et al*[10], 2016; *Case Reports in Orthopedics*	Case report of 73 yr old female with a humerus capitellum fracture	Successful results with complete fracture union and full elbow range of motion
Elbow fractures – Distal humerus fractures (Lateral column)	Aktan *et al*[11], 2018; *Cureus*	Case report of 50 yr old male with bi-column distal humerus fracture	Successful results with complete fracture union at four months, and elbow range of motion from 5-130 degrees
Hand fractures – Scaphoid fractures	Könneker *et al*[15], 2019	Multi-centre RCT: 190 patients	Pending
Hand fractures – Scaphoid fractures	Meier *et al*[13], 2016	Case series of five patients with acute scaphoid fractures treated with a single Magnesium screw	Unsatisfactory results with 3 out of 5 patients experiencing extensive osteolysis and bone cyst; All had good wrist scores and fracture union eventually
Hand fractures – Scaphoid fractures	Grieve *et al*[14], 2017; *Hand Surg Rehab*	Case series; 3 Scaphoid fractures (Two acute and one revision); 3 Intercarpal fusions	One acute scaphoid fracture lost to follow up; All other cases united except 1 case (partial union at twelve weeks)
Hand fractures – Radial styloid fractures	Turan *et al*[12]; *Thieme Medical Publishers*	Case series; 2 patients with isolated radial styloid fractures	Good fracture union in both patients with no complications
Young displaced neck of femur fractures	Yu *et al*[16], 2015; *BMC, Musculoskeletal disorders*	Case series of 19 patients; Mg screws used to fix vascularized iliac bone graft	Successful results with 94.7% union
Tibial spine avulsion fractures	Gigante *et al*[17], 2018; *Injury*	Case series of three paediatric patients treated surgically with Magnesium screws	Successful results with all three patients obtaining excellent functional recovery
Ankle fractures – Isolated lateral malleolus	Acar *et al*[18], 2018; *Cureus*	Case report of a 19 yr old female with an isolated Weber A fracture	Successful results with complete fracture union at 8 wk, AOFAS score 100 points at 2 yr
Ankle fractures – Medial malleolar fractures	Kose *et al*[19], 2018; *Archives of Orthopaedic and Trauma Surgery*	Case series of 11 medial malleolar fractures (Isolated, Bi-malleolar or Tri-malleolar)	Successful results with 100% fracture union, Mean AOFS score of 94.9 at time of final follow up

RCT: Randomised controlled trial.

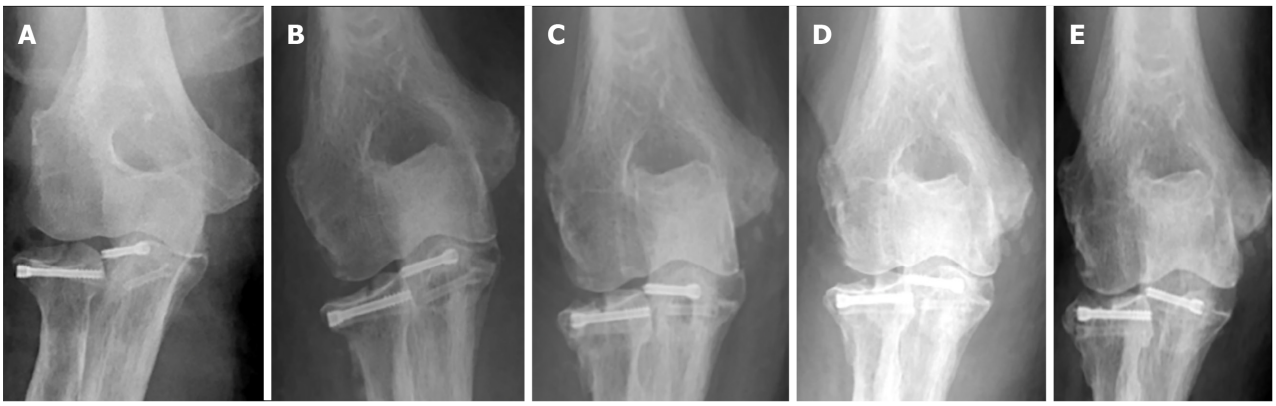

Figure 14 Post operative radiographs. A-E: Radiographs immediately post op (A), at 4 weeks (B), 4 months (C), 6 months (D) and 12 months (E).

none in the magnesium screw group required removal of implants for symptomatic hardware, highlighting the key benefit of using magnesium implants.

The remaining two studies recruited patients undergoing distal metatarsal osteotomies for hallux valgus. Acar *et al*[5] retrospectively compared two groups of 17 patients undergoing surgery with both implants, whilst Plaass *et al*[27] conducted a randomized control trial of 26 patients. Both studies reported similar therapeutic outcomes with regards to functional and radiographical outcomes, with no differences in complication rates or union rates.

Although the literature appears to suggest that these bioabsorbable magnesium screws provide similar efficacy to conventional implants, interpreting the data must performed with caution at this juncture due to the small collective number of patients analysed, and the heterogeneity of clinical indications amongst studies. In our search of the literature, there were no comparative studies analyzing the efficacy of both implants when used in peri-articular fractures around the elbow, with only two case reports[10-11] available in the literature, similarly documenting successful outcomes as reported in our series.

Table 3 Magnesium implants pros & cons

Pros	Cons
Bioabsorbable and osteoconductive[1,20]; Higher stability than existing polymers[21,22]; Similar stiffness to bone – less stress shielding[4]; Good biocompatibility[1-4]; Minimal artefacts on MRI and CT[23]	Production of hydrogen gas creates peri-implant radiolucencies[3]; Risk of osteolysis[3,24]; Unproven long term track record

CT: Computed tomography; MRI: Magnetic resonance imaging.

Limitations of study

Limitations of our study include a relatively small sample size although our case series represents one of the largest case series documenting the outcomes of magnesium screws in upper limb fractures. Furthermore, as there are few other studies on the topic, comparing and analysing our outcomes is challenging. Further studies are needed to evaluate the topic further such as a study with a control group.

CONCLUSION

Our case series serves to add to the paucity of literature on the utilization of magnesium screws in upper limb fractures. In our series, all patients exhibited good short to medium term clinical outcomes with no complications or revision surgeries required, and significantly none of our patients developed any clinical signs or symptoms of synovitis or allergic reactions. Although further larger studies with longer follow-ups are required before the implant can be unequivocally proven superior or equal to conventional existing implants, these implants appear to be a promising innovation for the modern orthopaedic surgeon.

ARTICLE HIGHLIGHTS

Research background

Larger trials such as randomized control trials with larger patient numbers should be conducted.

Research motivation

Bio-absorbable magnesium screws can be used in peri-articular fractures of the elbow.

Research objectives

All fractures healed successfully and no patient required removal of implants or suffered any major complications.

Research methods

Our paper was based on a retrospective case series design. Intra-operatively, a standardized surgical technique was utilized for insertion of the magnesium implants. Post – operatively, clinic visits were standardized and physical exam findings, functional scores, and radiographs were obtained at each visit. All complications were recorded.

Research results

Our findings will help clinicians in two main areas. Firstly, clinicians considering using the implant for their patients have a detailed case series to refer to. Secondly, clinicians considering research on the topic have a large sample size (relative to the existing literature) to aid in conducting future studies especially systematic reviews or meta–analysis.

Research conclusions

To ascertain if bio-asborbable magnesium screws are clinically efficaceous in treating peri-articular elbow fractures.

Research perspectives

Magnesium screws are gaining popularity in orthopaedic trauma surgery. No case series has been published documenting its use in peri-articular fractures of the elbow.

FOOTNOTES

Author contributions: Fang C contributed to data collection, statistical analysis and drafting of manuscript; Premchand A and Park DH contributed to invaluable guidance and providing post-operative care and documentation for post-operative patients; Toon DH contributed to performing the surgeries for the patients and overseeing all work on the original article.

Institutional review board statement: Our study was approved by our institutions local domain specific review board prior to commencement. All ethical protocols were followed.

Informed consent statement: As the study was retrospective and anonymous, no formal informed consent was deemed necessary and this was waived. Informal consent and verbal consent was documented in our hospitals electronic records system as her instruction by our IRB.

Conflict-of-interest statement: All authors declare that they have no conflict of interest.

Data sharing statement: All data collection and sharing was performed according to the methodology set out in the domain specific review board application.

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ORIGINAL ARTICLE

Retrospective Study

Subsequent total joint arthroplasty: Are we learning from the first stage?

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Abstract

BACKGROUND

With the increasing incidence of total joint arthroplasty (TJA), there is a desire to reduce peri-operative complications and resource utilization. As degenerative conditions progress in multiple joints, many patients undergo multiple procedures.

AIM

To determine if both physicians and patients learn from the patient's initial arthroplasty, resulting in improved outcomes following the second procedure.

METHODS

The institutional database was retrospectively queried for primary total hip arthroplasty (THA) and total knee arthroplasty (TKA). Patients with only unilateral THA or TKA, and patients undergoing same-day bilateral TJA, were excluded. Patient demographics, comorbidities, and implant sizes were collected at the time of each procedure and patients were stratified by first *vs* second surgery. Outcome metrics evaluated included operative time, length of stay (LOS), disposition, 90-d readmissions and emergency department (ED) visits.

RESULTS

A total of 642 patients, including 364 undergoing staged bilateral TKA and 278 undergoing bilateral THA, were analyzed. There was no significant difference in demographics or comorbidities between the first and second procedure, which were separated by a mean of 285 d. For THA and TKA, LOS was significantly less for the second surgery, with 66% of patients having a shorter hospitalization (P <

0.001). THA patients had significantly decreased operative time only when the same sized implant was utilized (P = 0.025). The vast majority (93.3%) of patients were discharged to the same type of location following their second surgery. However, when a change in disposition was present from the first surgery, patients were significantly more likely to be discharged to home after the second procedure (P = 0.033). There was no difference between procedures for post-operative readmissions (P = 0.438) or ED visits (P = 0.915).

CONCLUSION

After gaining valuable experience recovering from the initial surgery, a patient's perioperative outcomes are improved for their second TJA. This may be the result of increased confidence and decreased anxiety, and it supports the theory that enhanced patient education pre-operatively may improve outcomes. For the surgical team, the second procedure of a staged THA is more efficient, although this finding did not hold for TKA.

Key Words: Staged total joint arthroplasty; Asynchronous total joint arthroplasty; Subsequent total joint arthroplasty; Contralateral total joint arthroplasty; Perioperative outcomes

Core Tip: In this study, we investigated if surgeons and patients learn from their initial arthroplasty experience, resulting in improved outcomes following their second procedure. We showed that the second procedure of staged total hip arthroplasty has a shorter operative time, likely due to increased precision in implant sizing. However, this was not seen in total knee arthroplasty. After gaining valuable experience recovering from the initial surgery, a patient's perioperative outcomes are improved for their second total joint arthroplasty with shorter length of stay and similar discharge to facility or increased change of discharge to home.

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INTRODUCTION

The incidence of total hip arthroplasty (THA) and total knee arthroplasty (TKA) has increased dramatically, and this trend is expected to continue[1-6]. With expansion of indications, increased longevity of implants resulting in younger patients receiving arthroplasty, and patient satisfaction with these operations, it is becoming more common for patients to undergo arthroplasty of the second side when degenerative conditions progress in the contralateral hip and knee[7,8]. Patients may initially present with symptoms bilaterally and degenerative changes may progress on the contralateral side due to increased activity and time, or they may notice the pain more after the replaced side has recovered from surgery, and those with multiple joints may have higher satisfaction[7,8]. A series of 156 patients undergoing their first TKA published in 1994 reported a 37% rate of second side TKA at 7 year follow up if the other knee was arthritic at presentation and 5% if the knee was initially normal but symptoms and radiographic changes became apparent over the next 5 years[9]. Another series of 185 total knee patients eventually underwent contralateral TKA 43% of the time and this was has high as 93% if they had moderate or severe symptoms and radiographic arthritis[10]. Another series of 332 patients with primary TKA and 132 patients with primary THA reported that by 8 years, the incidence of contralateral TKA was 4% and contralateral THA 8%[8].

Despite the frequency of staged bilateral total joint arthroplasty (TJA), there is a paucity of published data on outcomes and perioperative factors comparing the second side to the first. Much of the literature is focused on whether to do simultaneous bilateral compared to staged or optimal duration[11] between stages with a focus on complications and cost effectiveness[12-29] or patient reported outcome measures (PROMs)[30-33]. However, the topic of staged subsequent arthroplasties has been mentioned in registry studies[21,23] and poses statistical challenges including immortal time bias and competing risk models[7,34,35]. In addition, some studies have demonstrated that the second THA is more similar to a unilateral THA in terms of outcome and survival[36]. Outcomes after the second stage TJA have not been thoroughly studied, with available data on operative efficiency gains particularly sparse. The purpose of this study was to determine if surgeons and patients learn from their initial arthroplasty experience, resulting in improved outcomes following their second procedure. We hypothesized there would be decreased operative time, length of stay (LOS), and discharges to skilled nursing facilities (SNF), as well as fewer 90-d emergency department (ED) visits and readmissions due to surgical team efficiency and patient expectations and preparedness for recovery.

MATERIALS AND METHODS

An institutional TJA database was retrospectively reviewed for all primary THA and TKA procedures between January 2014 and August 2017 using current procedural technology codes 27130 and 27447, respectively, resulting in 6637 procedures. Patients were included if their bilateral THA or TKA were staged on different dates, with both procedures occurring during the study period at the investigating institution. Patients were excluded if index arthroplasty was performed at an outside institution, if TJA was completed as same-day bilateral procedures, or if they were undergoing revision TJA. Patients were also excluded if the second TJA procedure was performed on a different joint from the first (that is, THA followed by subsequent TKA). The combination of these criteria led to the formation of a study group of patients who underwent primary bilateral TJA in subsequent fashion.

Patient demographics including age, sex, body mass index, and American Society of Anesthesiologists score were collected in addition to intraoperative data including operative time, anesthesia type, and implant type and sizes. Patients were stratified by first *vs* second procedure for data analysis. Outcome metrics evaluated included operative time, LOS, disposition, 90-d ED visits, and 30-d and 90-d readmissions. Statistical analysis was performed using IBM SPSS Statistics, version 24 (IBM Corp., Armonk, NY) and Wizard Pro for Mac (E. Miller, Chicago, IL). Continuous data were not normally distributed and were analyzed with Mann Whitney and are presented as median (lower quartile, upper quartile). Categorical data were analyzed with chi squared test and are presented as count (percent). A P value < 0.05 was considered statistically significant.

RESULTS

There were 1284 TJA operations performed on 642 patients, including 364 undergoing staged bilateral TKA and 278 undergoing staged bilateral THA included in this study. There was no significant difference in demographics (Table 1) or comorbidities between the first and second procedure, which were separated by a mean of 285 d [299 d (range 34-1235 d) for knees and 268 d (range 35-1267 d) for hips].

Table 2 compares outcome measures for the second joint compared to the first. THA patients had significantly decreased median operative time (102 *vs* 96 min, P = 0.011) and subgroup analysis demonstrated this to be the case only when the same sized implant was utilized. For the 278 bilateral THA patients, the stem type and size was the same in 65.5% (182 patients) and the cup type and size was the same in 66.5% (185 patients). For patients with the same stem size, the operating room (OR) time was more likely to be shorter (P = 0.025) and for patients with the same cup size, the OR time was more likely to be shorter (P = 0.001). However, there was no significant difference in OR time if the stem size (P = 0.210) or cup size (P = 0.910) were different.

For THA and TKA, LOS was significantly less for the second surgery, with 424 of the 642 patients (66%) having a shorter hospitalization (P < 0.001). At discharge, 93.3% of patients had the same disposition for both procedures with 504 discharged to home, 93 discharged to SNF, 2 discharged to rehabilitation facility. However, when a change in disposition was present, patients were significantly more likely to be discharged to home after the second procedure: 25 patients who went to SNF after their first procedure were discharged to home after their second procedure, while 12 patients who went home after the first procedure were discharged to SNF after the second (P = 0.033). Other changes of disposition included 2 rehab to home, 2 SNF to rehab, 1 rehab to SNF, and 1 home to expired in-hospital. There was no difference between procedures for post-operative readmissions (P = 0.438) or ED visits (P = 0.915).

DISCUSSION

A large percentage of patients who undergo TJA have pathology affecting the contralateral hip or knee which can progress over time and become sufficiently symptomatic and refractory to conservative therapy to warrant a second side TJA. Surgical efficiency improved on the second side for hips but was unchanged for knees. Of note the operative time was identical for TKA but was 6 min faster on the second side for THA. This is statistically significant (P = 0.011), and we would argue clinically significant in a healthcare environment where OR time is very costly. Further subgroup analysis demonstrates that this improved efficiency on the second side holds only when the same implant types and sizes as the first side are used. For the 278 bilateral THA patients, the stem type and size was the same in 65.5% (182 patients) and the cup type and size was the same in 66.5% (185 patients). For patients with the same stem size or cup size, the OR time was more likely to be shorter. However, if the stem or cup sizes utilized were different, there was no difference in OR time.

While same day bilateral TJA has been performed, many surgeons advocate recovering from the first side prior to proceeding on the other side, and many patients have degenerative joint disease at different stages when they present. With the patients' first-hand experience from the first side, postoperative expectations for pain and rehabilitation are well established. Furthermore, the medical care team including physical therapists and discharge planners may have additional insight to a patients' expected recovery needs and discharge from the hospital may occur sooner and to a different location—home rather than SNF, because of patients' comfort level. Our results were similar to another single institution study which had an increase from 69% to 74% of discharge home after first and second stage bilateral TKA but did not statistically compare this increase as their comparison was to simultaneous bilateral[12].

Surgical efficiency may be improved due to already knowing the implant sizes from the contralateral side, eliminating some uncertainty associated with a standard preoperative template. The explanation for this statistically significantly increased efficiency for THA may be due to increased confidence in starting reamer size for hips closer to the final

Table 1 Demographic data for arthroplasty patients based on procedure number

	First procedure	Second procedure	*P* value
Arthroplasty (n = 1286)			
Age (yr)	65.0 (58.0, 71.0)	66.0 (58.0, 72.0)	0.185
BMI (kg/m^2)	30.5 (26.6, 34.9)	30.4 (26.5, 35.1)	0.920
Female sex	362 (56.4)	362 (56.4)	1.000
ASA 1 or 2	373 (58.1)	370 (57.6)	0.865
Total knee arthroplasty (n = 728)			
Age (yr)	66.0 (61.0, 72.0)	67.0 (62.0, 73.0)	0.218
BMI (kg/m^2)	31.3 (27.4, 35.7)	31.5 (27.5, 36.0)	0.878
Female sex	210 (57.7)	210 (57.7)	1.000
ASA 1 or 2	193 (53.0)	192 (52.7)	0.941
Total hip arthroplasty (n = 556)			
Age (yr)	62.0 (54.0, 69.0)	62.0 (54.0, 70.0)	0.468
BMI (kg/m^2)	28.9 (25.5, 33.4)	29.2 (25.7, 33.0)	0.734
Female sex	152 (54.7)	152 (54.7)	1.000
ASA 1 or 2	180 (64.7)	178 (64.0)	0.859

Continuous data are presented as median (lower quartile, upper quartile). Categorical data are presented as count (percent). BMI: Body mass index; ASA: American Society of Anesthesiologists.

acetabular cup size and reduced need to repeat trial attempts.

A prior review reported improved ability to reduce leg length discrepancy and more accurate cup position in bilateral THA on the second side when performed in a simultaneous compared to staged fashion[18]. The present study suggests that benefit may also exist when the second side is done as a subsequent surgery. Knee pre-operative planning at our institution generally consists of using software to template cuts for the distal femur and the tibial cut and this may not be improved as much by knowledge of the other side. Other researchers have shown that postoperative medical complications or surgical site infections after the first THA or TKA are associated with recurrence of these complications with the contralateral procedure[37,38].

As with any study of this type there are important limitations to consider. Despite a large cohort of patients, ED return and readmissions are relatively rare events, making it difficult to detect clinically significant differences. This research was performed at a large tertiary referral academic medical center, and it is possible the results may be different in other practice settings due to factors like consistency of OR staff, presence of trainees including medical students, residents, and fellows, and level of complexity of cases. Of note, in this study, both sides were operated on at the same institution and the beneficial effect may be diminished if the subsequent surgery is performed by another surgeon at a different institution. We did not report perioperative variables such as blood loss and postoperative pain, due to limitations of our electronic database. Lastly, this study is not a direct comparison of simultaneous bilateral TJA to staged TJA, so conclusions regarding superiority of one technique will require additional research.

Several studies have focused on patient perceptions of functional improvement. Gazendam *et al*[33] showed that PROMs and reporting minimally clinically important difference after the first THA is predictive of a similar response on the second contralateral THA[33]. The importance of patient counseling is critical, and surgeons should avoid making assumptions about patients' expectations. Poultsides *et al*[39] showed that patients expectations had only a fair to moderate correlation between their first and second of staged TJA[39]. This seems to be particularly key in TKA. Multiple reviews have shown that the second TKA has significantly worse PROMs than the first[40,41] even in patients who were satisfied overall, and in patients who reported dissatisfaction with one of their TKAs, there was 50% greater risk of dissatisfaction at 1 year with the second TKA. However, from an objective surgical course and recovery perspective, our study demonstrates that operative time for THA, LOS, and postoperative discharge disposition can be anticipated for patients undergoing the second side TJA.

CONCLUSION

In conclusion, the second side of a staged THA is more efficient in terms of operative time, likely due to increased precision in pre-operative planning to account for implant sizing and possibly matched leg length discrepancy when the other side has already been replaced. Interestingly, this pattern was not observed for TKA. After gaining valuable

Table 2 Patient outcomes for arthroplasty patients based on procedure number

	First procedure	Second procedure	*P* value
Arthroplasty (*n* = 1284)			
OR time (min)	99.0 (86.0, 119.0)	96.0 (86.0, 113.0)	0.039
Length of stay (d)	2.26 (1.40, 3.14)	2.09 (1.28, 2.41)	< 0.001
Discharge to SNF	120 (18.7)	106 (16.5)	0.305
90-d ED return	48 (7.5)	47 (7.3)	0.915
90-d readmission	19 (3.0)	24 (3.7)	0.438
30-d readmission	14 (2.2)	15 (2.3)	0.851
Total knee arthroplasty (*n* = 728)			
OR time (min)	97.0 (85.0, 118.0)	97.0 (86.0, 113.0)	0.654
Length of stay (d)	2.3 (2.09, 3.19)	2.21 (1.33, 2.47)	< 0.001
Discharge to SNF	82 (22.5)	72 (19.8)	0.364
90-d ED return	23 (6.3)	30 (8.2)	0.318
90-d readmission	8 (2.2)	9 (2.5)	0.806
30-d readmission	7 (1.9)	7 (1.9)	1.000
Total hip arthroplasty (*n* = 556)			
OR time (min)	102.0 (88.0, 121.0)	96.0 (85.0, 112.0)	0.011
Length of stay (d)	2.21 (1.36, 2.48)	1.38 (1.23, 2.32)	< 0.001
Discharge to SNF	38 (13.7)	34 (12.2)	0.530
90-d ED return	25 (9.0)	17 (6.1)	0.199
90-d readmission	11 (4.0)	15 (5.4)	0.422
30-d readmission	7 (2.5)	8 (2.9)	0.794

Continuous data are presented as median (lower quartile, upper quartile). Categorical data are presented as count (percent). SNF: Skilled nursing facilities; ED: Emergency department; OR: Operating room.

experience recovering from the initial surgery, a patient's perioperative outcomes are improved for their second TJA, and this is likely attributable to the experience of the first procedure and reduction in anxiety. This may be the result of increased confidence, decreased anxiety, and supports the theory that enhanced patient education pre-operatively may improve outcomes. This information can be used to counsel patients who are considering bilateral TJA or who have already had one side replaced and are considering the second side.

ARTICLE HIGHLIGHTS

Research background

The volume of total joint arthroplasty is increasing rapidly and measures to decrease complications, increase efficiency and minimize resource utilization are important considerations.

Research motivation

The motivation for this project was to investigate if patients and surgeons learned or improved upon measures from the initial arthroplasty in subsequent contralateral procedures.

Research objectives

Our primary outcomes examined were operative time, length of stay, discharge disposition and 90-d emergency department visits and admissions. Length of stay was statistically significantly shorter. Total hip arthroplasty (THA) patients had a shorter operative time when the same implant sizes were utilized. There was no difference in 90-d hospital utilization.

Research methods
We utilized retrospective institutional database review for data collection and univariable analyses to compare cohorts.

Research results
Our results show that the second side of staged THA performed had shorter operative time, but there was no difference in total knee arthroplasty (TKA). There were no differences in postoperative hospital utilization. There was a shorter length of stay after the second procedure.

Research conclusions
This study reveals that patients had a shorter hospital stay after the second total joint arthroplasty (TJA) and operative time was statistically significantly shorter for the contralateral THA, but no difference was noted in TKA. This study seems to show that there is a benefit to pre and postoperative counseling in patient hospital stay and clinical course, and that there is a similar rate of postoperative hospital visits after the first and second TJA.

Research perspectives
Future studies may examine patient reported outcomes and experience of pain after first and second total joint arthroplasty, as well as if implant type or bearing type may affect patient reported outcomes or outcomes.

FOOTNOTES

Author contributions: Wu CJ revised the manuscript; Penrose C performed the data collection and drafted manuscript; Ryan SP performed data collection and analysis and drafted manuscript; Bolognesi MP, Seyler TM, and Wellman SS designed the study and provided guidance; All authors approved the final manuscript.

Institutional review board statement: Institutional review board approval was obtained prior to initiation of the study.

Informed consent statement: Consent is waived per the Duke Institutional Review Board for this retrospective review study.

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Data sharing statement: Per the institutional review board, consent was not obtained but the data are de-identified and risk of identification is low.

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ORIGINAL ARTICLE

Clinical Trials Study

Correction method for moderate and severe degrees of hallux valgus associated with transfer metatarsalgia

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Abstract

BACKGROUND

Hallux valgus (HV) is a common foot deformity that manifests with increasing age, especially in women. The associated foot pain causes impaired gait and decreases quality of life. Moderate and severe HV is a deformity that is characterized by the involvement of lesser rays and requires complex surgical treatment. In this study, we attempted to develop a procedure for this condition.

AIM

To analyse the treatment results of patients who underwent simultaneous surgical correction of all parts of a static forefoot deformity.

METHODS

We conducted a prospective clinical trial between 2016 and 2021 in which 30 feet with moderate or severe HV associated with Tailor's bunion and metatarsalgia were surgically treated *via* a new method involving surgical correction of all associated problems. This method included a modified Lapidus procedure, M2M3 tarsometatarsal arthrodesis, intermetatarsal fusion of the M4 and M5 bases, and

the use of an original external fixation apparatus to enhance correction power. Preoperative, postoperative, and final follow-up radiographic data and American Orthopaedic Foot and Ankle Society (AOFAS) scores were compared, and *P* values < 0.05 were considered to indicate statistical significance.

RESULTS

The study included 28 females (93.3%) and 2 males feet (6.7%), 20 (66.7%) of whom had a moderate degree of HV and 10 (33.3%) of whom had severe deformity. M2 and M3 metatarsalgia was observed in 21 feet, and 9 feet experienced pain only at M2. The mean follow-up duration was 11 months. All patients had good correction of the HV angle [preoperative median, 36.5 degrees, interquartile range (IQR): 30-45; postoperative median, 10 degrees, IQR: 8.8-10; follow-up median, 11.5 degrees, IQR: 10-14; $P < 0.01$]. At follow-up, metatarsalgia was resolved in most patients (30 *vs* 5). There was a clinically negligible decrease in the corrected angles at the final follow-up, and the overall AOFAS score was significantly better (median, 65 points, IQR: 53.8-70; *vs* 80 points, IQR: 75-85; $P < 0.01$).

CONCLUSION

The developed method showed good sustainability of correction power in a small sample of patients at the one-year follow-up. Randomized clinical trials with larger samples, as well as long-term outcome assessments, are needed in the future.

Key Words: Hallux valgus; Metatarsalgia; Tailor's bunion; Lapidus procedure; Proximal metatarsal osteotomy; Splayfoot

Core Tip: Although there are several methods of surgical correction for moderate and severe hallux valgus, not all patients achieve the desired treatment result. One of the reasons for this outcome is the involvement of almost all rays of the foot. To achieve a favourable treatment result in these patients, simultaneous correction of all the elements of the deformed forefoot is needed, considering the biomechanical association of this pathology, namely, high mobility of the first and fifth metatarsals.

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INTRODUCTION

Hallux valgus (HV) deformity is present in 23%-35.7% of the adult population. The incidence of HV increases exponentially with age, and HV occurs most often in women. An analysis of age subgroups showed that the disease incidence was 7.8% among individuals under 18 years of age, 23% among adults aged 18-65 and 35.7% among those aged > 65 years[1].

An increase in the degree of HV is directly associated with the development of additional problems in the forefoot, such as metatarsalgia, Tailor's bunion, and hammer toe deformity. Therefore, orthopaedists should not consider severe HV as a pathology involving only the first ray but rather as a complex problem of the entire forefoot. Metatarsalgia combined with HV deformity is a result of increased pressure and load transfer to the lateral metatarsal region. Load and pressure transfer from the big toe to the central metatarsal region has been described, indicating functional impairment of the big toe and simultaneous worsening of loading conditions at the metatarsals[2]. An increase in HV severity is significantly associated with increased metatarsalgia and decreased foot function[3]. Fifth ray deformities involving a valgus fifth metatarsal and a varus fifth toe are often associated with HV. These deformities are ascribable to the characteristics of the Lisfranc joint, allowing greater mobility of the first and fifth metatarsals in comparison to the central metatarsals[4].

Currently, there are hundreds of surgical techniques for treating HV, but arguably, no technique is significantly better than the others[5]. Arthrodesis of the first tarsal-metatarsal joint is one of these techniques. Previously, the Lapidus procedure was indicated for severe HV deformities and HV recurrence because of its ability to stabilize and correct the deformity at the first tarsometatarsal (TMT) joint[6-9]. Currently, the improved technique with multiplane correction has no restrictions in treating HV deformities, regardless of HV angle (HVA) or the magnitude of the intermetatarsal angle (IMA), and is the method of choice for all cases[10]. However, some studies have confirmed that central metatarsalgia may persist, intensify, or develop even after the most sophisticated surgery for HV[11].

Dissatisfaction with the outcomes of surgical intervention for moderate and severe HV that focuses solely on the first ray without addressing concurrent forefoot pathologies served as the impetus for the development of a comprehensive treatment approach targeting all aspects of this medical issue at the Lisfranc joint level. A distinctive aspect of the developed technique is the intraoperative utilization of an external device to augment the correction of the deformity and minimize the incidence of splayfoot.

MATERIALS AND METHODS

Patient selection

This prospective case-series study was conducted at a regional traumatology and orthopaedics centre in Kazakhstan that serves a population of 610000 people. The inclusion criteria for patients were as follows: Symptomatic moderate or severe HV according to the traditional radiographic classification[12] (HVA ≥ 20 degrees or intermetatarsal angle (IMA) ≥ 11 degrees); pain under the heads of the second or second-third metatarsals (M2, M3); hammer toe deformity; Tailor's bunion; and no previous surgical intervention.

The criteria for determining hypermobility of the first TMT joint as an indication for the Lapidus procedure are still controversial[13]. We chose the Romash classification[14] (types I and II) because, in our opinion, it is more independent and accurate than the other methods due to the use of X-rays in the assessment.

Patients with rheumatoid arthritis, gout, or osteoarthritis of the first metatarsophalangeal joint were excluded. Some of the included patients had HV deformities on both feet and underwent surgery at different times; thus, in this paper, we refer to the number of operated feet.

Information on metatarsalgia, plantar callosities, radiographic analysis, and complications was obtained before surgery, after surgery, and at the final follow-up. Clinical evaluation was performed using the American Orthopaedic Foot and Ankle Society (AOFAS) scale[15].

Operative technique

A representative case of the performance of the optimized surgical technique on a patient with moderate HV, painless Tailor's bunion, M2-M3 metatarsalgia, and hammer deformity of the second toe is shown in Figure 1. Under spinal anaesthesia, resection of the M1 head exostosis was performed using an oscillating saw. The m. adductor hallucis tendon was mobilized with sesamoid hammock realignment. Then, as in the modified Lapidus arthrodesis procedure, we resected the articular surface of the M1 base and performed wedge-shaped osteotomy of the medial cuneiform bone. For all patients, we removed the cortex of the M4 and M5 bases in the intermetatarsal space, leaving the bone chips *in situ*, as was proposed for the M1-M2 bases in the original Lapidus procedure[16]. Next, wedge-shaped resection of the articular surfaces of the M2 and M3 bases and the medial and lateral cuneiform was performed depending on the presence of metatarsalgia for the dorsal displacement of heads.

The next step of the procedure was the elimination of the metatarsus prima varus and metatarsus quintus valgus by installation of an external fixation device (developed in-house), and the K-wire was passed through the heads and necks of the metatarsal bones (Figure 2). Pronation of the first ray was manually corrected before passing through the K-wire, as proposed by DiDomenico *et al*[17]. At this time, the first metatarsal head was shifted laterally and on the plantar side. Angles M1M2 and M1M5 were corrected simultaneously. Finally, fixation in the corrected position was performed using four screws and a plate with angular stability placed on the medial surface, and one screw was used to fix M4-M5. Screws were placed through the metatarsals and cuneiform bones.

After disassembling the external fixation device, Akin osteotomy of the proximal phalanx of the first toe was performed, and a final X-ray was obtained (Figure 3). Intradermal sutures were used to close the wounds, and elastic tape and stockings were applied to improve lymphatic drainage and prevent venous thrombosis. In the early postoperative period, the patient was advised to ambulate with Barouk shoes. Passive motions in the toes and ankle joint were initiated on the second day after the operation. The patient had to wear elastic tape and Barouk shoes for 6-7 wk after surgery. Partial weight bearing was recommended as tolerated. The usual time to restore full weight-bearing was 10-12 wk.

Statistical analysis

All the statistical tests were performed and reviewed by a biomedical statistician using SPSS software (version 27.0; IBM Corp, Armonk, New York, United States). Owing to the small sample size, X-ray data before and after surgery and during the final follow-up were tested using the paired Wilcoxon criterion and independent samples *t* test at the 95% significance level. For all the data, $P < 0.05$ was considered to indicate statistical significance. Descriptive statistics for categorical variables are expressed as numbers (*n*) and percentages (%). Numerical variables are expressed as medians, standard deviations, minimum-maximum values, and interquartile ranges.

RESULTS

Thirty feet that underwent reconstruction for HV deformity between 2016 and 2021 were consecutively enrolled. HVA was prioritized over IMA for the inclusion of patients. According to the HVA, 20 (66.7%) feet had moderate HV (HVA 20-40 degrees), and 10 (33.3%) had a severe deformity (HVA ≥ 40 degrees). All feet, except for two, had an IMA > 10 degrees. In the two exceptions, the IMA was 10 degrees, but the HVAs were 25 and 28 degrees. All feet had an increased M4-M5 IMA and Tailor's bunion; all but four (13.3%) of the cases were painless. M2 and M3 metatarsalgia was observed in 21 feet, and 9 feet experienced pain only under M2. The mean age of the patients was 52.8 years (range, 19-72). The left foot was operated on in 14 patients (46.7%), and the right foot was operated on in 16 patients (53.3%). There were 21 (70%) feet classified as Romash Type I and 9 feet classified as Type II (30%).

All feet underwent surgery and had a rehabilitation period, as described previously. The mean follow-up period was 11 months (range, 9-12 months). The results of the application of the developed treatment method are presented in the boxplots in Figure 4. After surgery, the HVA was restored to normal values in all patients. In addition, the loss of correction at follow-up ($Z = -4.32$; $P < 0.001$) did not lead to clinically significant deformation or a transition from one

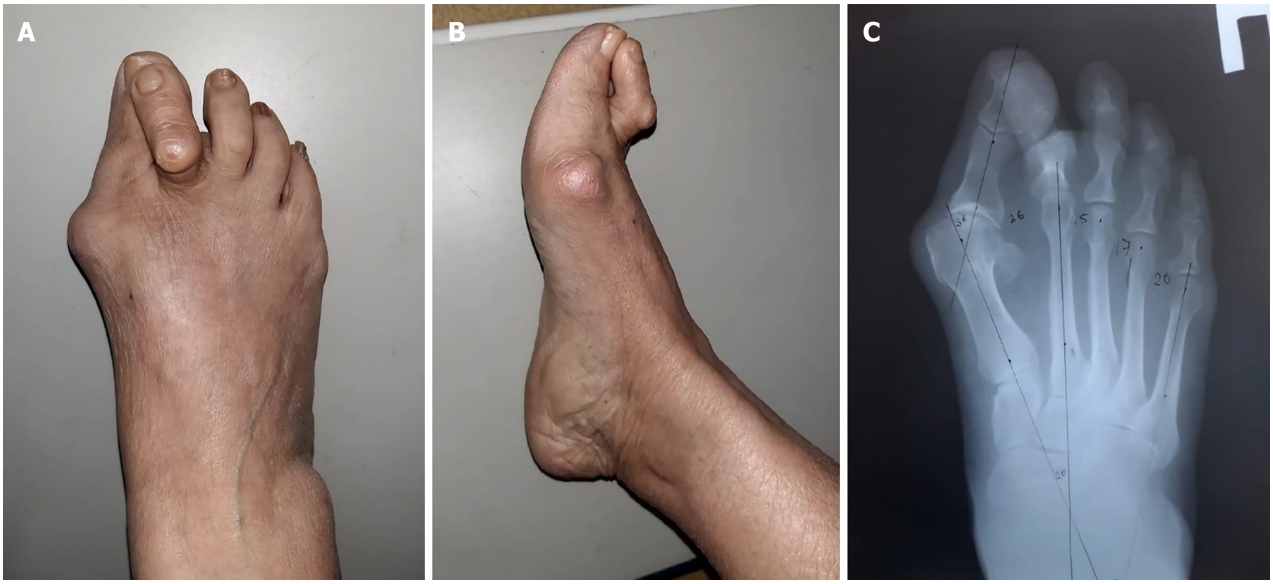

Figure 1 A 58-year-old female presented with moderate hallux valgus with painless Tailor's bunion, M2-M3 metatarsalgia, and hammer deformity of the second toe before the procedure. A: Top view of the foot; B: Medial view; C: X-ray image.

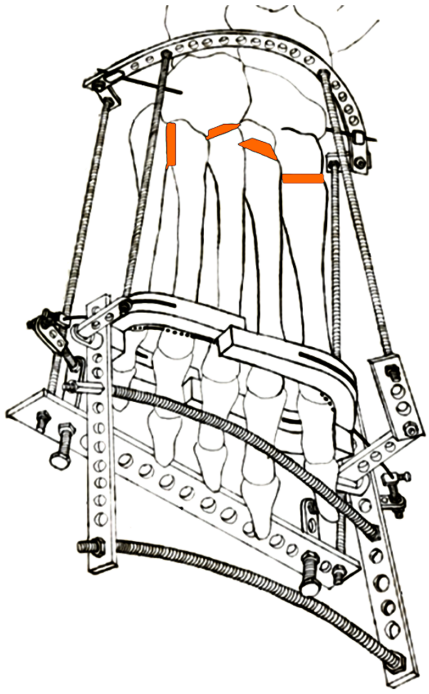

Figure 2 Scheme of the installation of the original external fixation device in a patient with moderate hallux valgus. The osteotomy is marked in orange.

degree of severity to another. The proposed surgical method significantly improved the postoperative parameters of M1M2 (decreased at follow-up Z = -3.95; P < 0.001). Notably, there was a significant decrease in the M1M5 angle (decreased at follow-up Z = -4.21; P < 0.001); one of the goals of the operation was to correct splayfoot, which is an important type of deformation leading to foot dysfunction.

With respect to the measured angles, there was an improvement in the position of the medial sesamoid bone of the first metatarsophalangeal joint relative to the axis of the first metatarsal bone in all patients after the operation. Anteroposterior X-rays were graded using the Hardy and Clapham scale[18] (Figure 5). No changes were observed between the postoperative position and final follow-up.

Accordingly, correction of the radiological parameters of the foot improved its function, resulting in an increase in the AOFAS score. The average improvement in the long term was 15 points, partly due to the correction of metatarsalgia by targeting the small rays of the foot. For plantar callosities, the grading was as follows: (1) Grade 0: No callosity; (2) Grade 1: Painless callosity underneath one joint; (3) Grade 2: Painful callosity underneath one joint; and (4) Grade 3: Painful

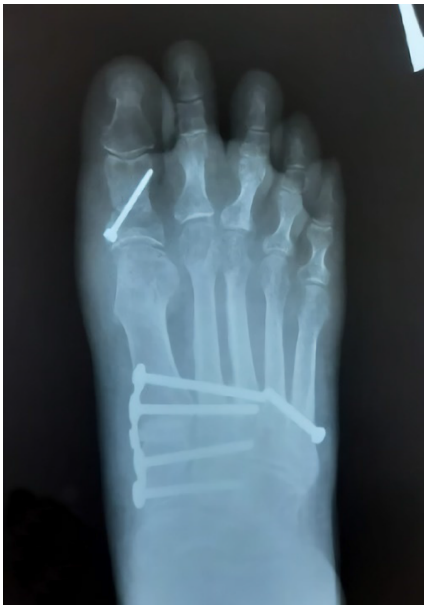

Figure 3 Final radiograph after surgery. A 58-year-old female previously presented with moderate hallux valgus with painless Tailor's bunion, M2-M3 metatarsalgia, and hammer deformity of the second toe.

callosity underneath two or more joints[19]. In the preoperative period, Grade 2-3 callosity was observed in 86.7% of patients, and in the long-term postoperative period, only five patients (16.7%) had painful callosity under the head of one metatarsal bone (Table 1).

Table 1 Preoperative and final follow-up comparison of callosity grade and presence of metatarsalgia

	Preoperative	Final follow-up
Callosity grade		
Grade 0	0	5
Grade 1	4	20
Grade 2	2	5
Grade 3	24	0
Metatarsalgia	26	5

One patient with an M1 that was shortened by 6 mm and showed partial loss of reduction had recurrent metatarsalgia; however, HVA correction was better after surgery than before surgery (43 *vs* 22 degrees). No indications for further surgery were found. Another patient developed a stitch abscess that caused redness and oedema for 3 wk, and short-term oral antibiotics were prescribed after the symptoms resolved completely. Two patients developed ligature fistulas. Recurrence of mild HV was observed in 2 feet.

DISCUSSION

The effectiveness of the Lapidus procedure for the treatment of HV, especially during multiplane correction, has been repeatedly reported[10,20]. The correction power of metatarsal osteotomy increases when performed from distal to proximal. As shown in a meta-analysis[21], the mean angular correction of the IMA for all included feet subjected to the Lapidus technique was 9.82 degrees (confidence interval: 8.82–10.82). In our study, the median delta IMA correction was 6 degrees. In the treatment of transfer metatarsalgia, the same consideration is given to the osteotomy level of the lesser metatarsals. Proximal osteotomies are more powerful than distal osteotomies because smaller corrections at the metatarsal base result in larger corrections at the weight-bearing metatarsal head, secondary to the longer lever arm. In our series, performing the concomitant procedure on lesser rays resulted in resolution of metatarsalgia in all but five patients (83.3%), and notional improvement in the AOFAS score was achieved. Favourable HV correction with osteotomy of the lesser metatarsals has also been reported[22-25].

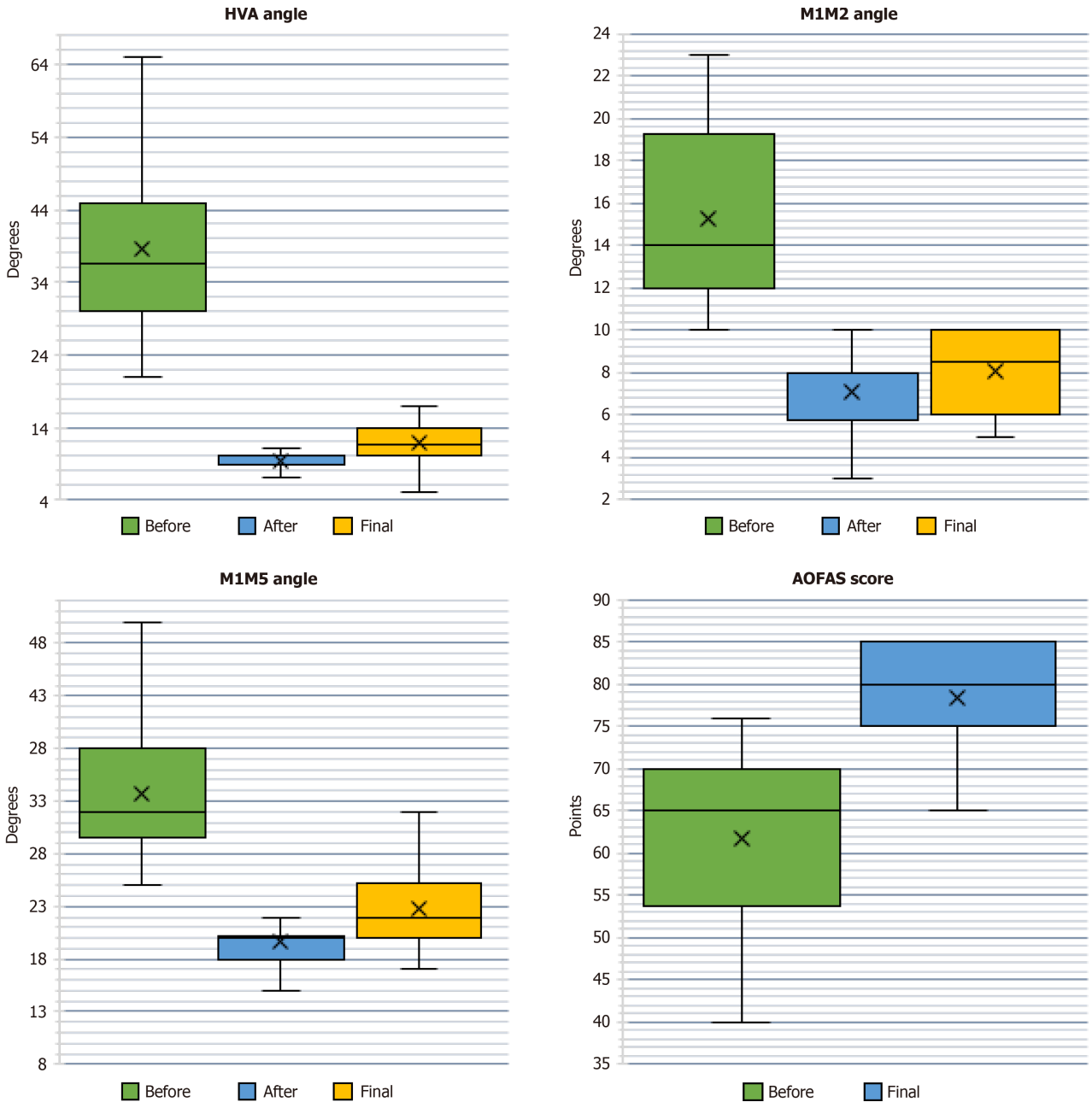

Figure 4 Boxplots before and after the operation and at the final follow-up for the hallux valgus, M1M2 and M1M5 angles and American Orthopaedic Foot and Ankle Society score. AOFAS: American Orthopaedic Foot and Ankle Society.

The absence of a negative effect of arthrodesis of the medial and middle columns of the Lisfranc joint has been reported in publications devoted to the treatment of dislocation of this joint[26]. Currently, minimally invasive surgery is the preferred surgical treatment. However, Lu *et al*[27] suggested in their meta-analysis that the use of minimally invasive surgery for the correction of HV deformity was the better choice for patients with symptomatic HV than traditional open methods, but the efficacy of minimally invasive surgery in moderate-to-severe HV (HVA ≤ 30°) was poor, and open surgery resulted in better outcomes in this cohort[28,29].

One of the disadvantages of our technique was the need to use an intraoperative corrective device, which slightly increased the overall duration of the procedure. Another disadvantage was the complexity of the surgical treatment, as the invasiveness of the procedure led to an increase in the inpatient length of stay for individual patients (mean ± SD: 5.8 ± 2.43 d; 12 d in two patients).

This study has several limitations. Our study presents the preliminary results on the use of a new method of treatment for a small number of patients and therefore has the limitations intrinsic to such research. We did not perform any biomechanical examinations, such as pedobarography, to prove a decrease in pressure below the lesser metatarsals.

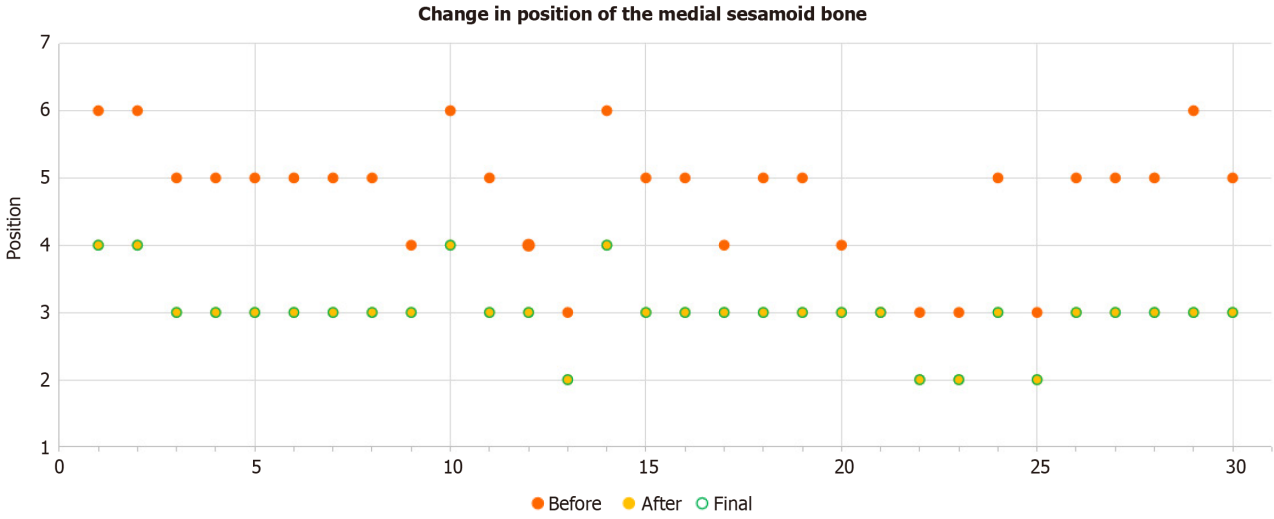

Figure 5 Change in position of the medial sesamoid bone for each operated foot. Anteroposterior X-rays were graded using the Hardy and Clapham scale: (1) Position 1: The entire sesamoid is medial to the first metatarsal bisector; (2) Position 2: The lateral aspect of the sesamoid is tangential to the metatarsal bisector; (3) Position 3: The lateral one-third of the sesamoid overlaps the bisector; (4) Position 4: The sesamoid is centred over the bisector; (5) Position 5: The medial one-third of the sesamoid overlaps the bisector; (6) Position 6: The medial aspect of the sesamoid is tangential to the bisector; and (7) Position 7: The entire sesamoid is lateral to the bisector.

CONCLUSION

The developed method of complex treatment for forefoot deformity includes a modified Lapidus procedure, M2-M3 TMT arthrodesis, intermetatarsal fusion of M4-M5 bases, and fixation with the original external apparatus, allowing for the resolution of problems caused by splayfoot.

ARTICLE HIGHLIGHTS

Research background

Until now, the treatment of hallux valgus (HV) is considered by many clinicians as an isolated problem of the forefoot, while the deformation of the first toe brings with metatarsalgia, Tailor's bunion, and hammer toe deformity. An important step is the comprehensive elimination of all the existing problems to achieve satisfactory clinical results.

Research motivation

In our study, all existing pathologies in the Lisfranc joint were eliminated simultaneously.

Research objectives

The main objective was to decrease the key angles [HV angle (HVA) and intermetatarsal angles (IMA)] and plantar callosities using a modified Lapidus procedure.

Research methods

We did a Clinical Trials Study involving 30 patients in the setting of a regional traumatology and orthopaedics centre in Kazakhstan.

Research results

The modified Lapidus procedure with intraoperative utilization of the developed external device led to a decrease in HVA, IMA, and M1M5 with correction of splayfoot and pain reduction. There was also improvement in the position of the medial sesamoid bone in each operated foot.

Research conclusions

The method used was promising and demonstrated the absence of significant drawbacks in a small sample size.

Research perspectives

Further randomized controlled trials are required to assess effectiveness in large samples.

FOOTNOTES

Author contributions: Zhanaspayev A and Bokembayev N contributed to the patient selection and main surgeon; Zhanaspayev A, Bokembayev N, and Aubakirova S were involved in the data collection; Zhanaspayev A contributed to the idea; Bokembayev N took part in the draft writing; Tlemissov A and Aubakirova S contributed to the patient rehabilitation; Zhanaspayev M was involved in the conceptualization and supervision, statistical analysis; Zhanaspayev M and Prokazyuk A contributed to the final writing.

Institutional review board statement: The study was reviewed and approved by the Local Ethics Committee of NCJSC "Semey Medical University" (Semey, the Republic of Kazakhstan) according to protocol #2 on October 25, 2018.

Clinical trial registration statement: This study was registered at Semey Medical University (Semey, Kazakhstan) with a registration ID of 05-5798 as of December 7th, 2018. No URL is available.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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ORIGINAL ARTICLE

Observational Study

Single-center experience with Knee+™ augmented reality navigation system in primary total knee arthroplasty

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Abstract

BACKGROUND

Computer-assisted systems obtained an increased interest in orthopaedic surgery over the last years, as they enhance precision compared to conventional hardware. The expansion of computer assistance is evolving with the employment of augmented reality. Yet, the accuracy of augmented reality navigation systems has not been determined.

AIM

To examine the accuracy of component alignment and restoration of the affected limb's mechanical axis in primary total knee arthroplasty (TKA), utilizing an augmented reality navigation system and to assess whether such systems are conspicuously fruitful for an accomplished knee surgeon.

METHODS

From May 2021 to December 2021, 30 patients, 25 women and five men, underwent a primary unilateral TKA. Revision cases were excluded. A preoperative radiographic procedure was performed to evaluate the limb's axial alignment. All patients were operated on by the same team, without a tourniquet, utilizing three

distinct prostheses with the assistance of the Knee+™ augmented reality navigation system in every operation. Postoperatively, the same radiographic exam protocol was executed to evaluate the implants' position, orientation and coronal plane alignment. We recorded measurements in 3 stages regarding femoral varus and flexion, tibial varus and posterior slope. Firstly, the expected values from the Augmented Reality system were documented. Then we calculated the same values after each cut and finally, the same measurements were recorded radiologically after the operations. Concerning statistical analysis, Lin's concordance correlation coefficient was estimated, while Wilcoxon Signed Rank Test was performed when needed.

RESULTS

A statistically significant difference was observed regarding mean expected values and radiographic measurements for femoral flexion measurements only (Z score = 2.67, P value = 0.01). Nonetheless, this difference was statistically significantly lower than 1 degree (Z score = -4.21, P value < 0.01). In terms of discrepancies in the calculations of expected values and controlled measurements, a statistically significant difference between tibial varus values was detected (Z score = -2.33, P value = 0.02), which was also statistically significantly lower than 1 degree (Z score = -4.99, P value < 0.01).

CONCLUSION

The results indicate satisfactory postoperative coronal alignment without outliers across all three different implants utilized. Augmented reality navigation systems can bolster orthopaedic surgeons' accuracy in achieving precise axial alignment. However, further research is required to further evaluate their efficacy and potential.

Key Words: Augmented reality; Orthopedics; Total knee arthroplasty; Robotics; Knee; Navigation

Core Tip: Augmented reality navigation systems can bolster orthopaedic surgeons' accuracy in achieving precise axial alignment. Our study unveils compelling evidence showcasing how Augmented Reality (AR) aids surgeons in achieving meticulous axial alignment. This innovative approach significantly enhances accuracy, marking a paradigm shift in surgical procedures. Surgeons leveraging AR navigation exhibit heightened precision, promising improved patient outcomes. Delve into the full manuscript to grasp the groundbreaking findings propelling orthopaedic surgery into a new era of technological advancement. Elevate your understanding and practice within the realm of AR-guided orthopaedic surgery.

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INTRODUCTION

Total knee arthroplasty (TKA) is indubitably one of the most common orthopaedic procedures ordinarily performed for knee joint osteoarthritis. In the United States, over 600000 TKAs/year are carried out, with the numbers soaring annually [1].

The preponderant goals of TKA are pain relief, joint function restoration and prostheses' longevity. TKA's success and artificial joint longevity are achieved with the restoration of limb alignment. Malalignment is recurrently associated with copious long-term complications, such as tibiofemoral and patellofemoral instability, joint stiffness, patellar fractures, increased polyethylene wear and implant loosening[2,3]. Diligent comprehension of the fundamentals and the employment of precise instrumentation are pivotal for executing reproductively a well-aligned TKA.

Computer-assisted systems acquired escalated interest in orthopaedic surgery over the last two decades, as they have been demonstrated to ameliorate accuracy over conventional instruments. The next generation of computer assistance is being developed using Augmented Reality (AR). AR systems are broadly considered to exhibit some essential advantages over traditional computer navigation platforms, as they diminish the requirement for massive external detection equipment or reflecting markers by utilizing little detectors with built-in detecting mechanisms attached to the apposite places in the operating field[3,4]. Also, AR systems compared to conventional computer navigation offer patient-specific computed tomography imaging, thus developing a personalized initial plan for the surgeon, while also being able to visualize the mechanical axis and registration points. AR systems' hardware is featured as more compact and uncomplicated contrasted to computer navigation, which could lead to reduction in associated capital expenditures and maintenance costs[4,5]. Nonetheless, the exactness of AR navigation has yet to be established[3]. These systems' utilization ranges from preoperatively surgical planning and simulation to navigation systems assisting surgeons intraoperatively[5]. With the implementation of navigation systems, orthopaedic surgeons can precisely track and visualize

surgical instruments in real-time, conforming to the anatomical structures[3].

The growingly prompt evolution of AR technologies features the prospect of attaining the exemplary form of the human-machine interface[6]. Each AR system comprises distinct hardware and software, which provides the surgeon with real-time computer-processed imaging data. AR systems project their information to the surgeon in a way that combines real-life objects with superimposed computer-generated images[7-11]. A system control software utilizes the data from a position-tracking system, transforming the input into images, which are conveyed to a display system, where the amalgamation with the real-scene view transpires in front of the surgeons' eyes[12,13].

Knee+™ AR navigation system (Pixee medical company, Besancon, France) comprises a pair of smart glasses worn by the surgeon, specific markers (QR-code) connected to the tibial and femoral cutting guides and a central laptop (Figure 1A). The Knee+™ system assists the surgeon in determining reference alignment axes in relation to anatomical landmarks for precise positioning of cutting guides regarding computed mechanical axis (Figure 1B). The smart glasses (Vuzix 2000) enable the surgeon to visualize the tibial and femoral axis superimposed on the patient in real-time during operation, providing meaningful information concerning surgical decisions. With this information, surgeons can accurately specify the distal femoral cut, flexion/extension gaps, the varus/valgus axis, and the tibial cut's posterior slope. Smart glasses can also offer real-time information to the surgeon regarding the accuracy of osteotomies according to the operative plan, combining the difference in the axis between the anatomical cut and the computerized plan. At this point, the system allows the surgeon to deliberate on the osteotomies and reach a new surgical plan.

This case series endeavors to scrutinize the accurateness of component alignment and restoration of the affected limb's mechanical axis in primary TKA, employing the Knee+™ system. Additionally, this study aims to evaluate whether such systems are substantively beneficial for a high-experienced knee surgeon.

MATERIALS AND METHODS

Study population

In our study, 30 patients underwent a primary unilateral TKA for osteoarthritis with AR guidance from May 2021 to December 2021. The average age of patients was 71.6 years, with 5 men and 25 women. Patients were included irrespective of age, diagnosis, deformity and body mass index. Revision surgery cases were excluded.

Preoperative examination

Preoperatively, radiographic exams (simple A/P and lateral knee X-rays) and full leg-length A/P X-rays were performed to all patients to assess the axial limb alignment (Figure 2A). The radiographic examinations were performed in the same center, utilizing the same software protocol. All radiological views were obtained with the patients on standing position. With regard to full leg-length A/P X-rays particulars, the images included in each set of radiographs were hip, knee and ankle views, with each image dimension being 3408 × 3320 pixels and with a resolution of 150 × 150, as well as a full-length lower limb x-ray performed by the same versed radiologist. The digital radiography system employed was the "NOVA FA" (Sedecal, Madrid, Spain), which featured a flat panel detector. The distance between the x-ray source and the patient was 160 cm. This specific system was a linear system in which the x-ray source moved from top to bottom to capture the images. It is pivotal to underline that this special preoperative imaging examination is routinely not necessary for the utilization of Knee+™ system intraoperatively, and we carried out this protocol for the purposes of our study.

Surgery

All patients were operated on by the same adept orthopaedic surgeon, under combined regional anesthesia and without a tourniquet. The following prostheses were employed: Evolution® Medial-Pivot Knee System/MicroPort Orthopedics (7 cases), BalanSys BICONDYLAR® Knee System/Mathys European Orthopaedics (12 cases) and Vanguard® Complete Knee System/Zimmer Biomet (13 cases).

All operations were conducted with the assistance of the Knee+™ AR navigation system (Pixee medical company, Besancon, France), using a standardized protocol of cutting first the tibial and then the femoral component. Concerning intraoperative soft tissue balance assessment, depending on the type of implant utilized, pertinent spacer blocks were employed for diligent evaluation of flexion and extension gaps in valgus and varus stress.

Postoperative course and imaging

Acute postoperatively, plain knee X-rays (A/P and lateral) were carried out. Subsequently, all patients were mobilized 2-3 h after the surgery with the aid of physiotherapists specialized in rapid recovery rehabilitation techniques. On the second postoperative day, following intensive physiotherapy sessions, a new full leg-length x-ray was performed in each patient, employing the same radiographic exam protocol as pre-surgery, for confirming the implants' position, orientation and alignment in the coronal plane (Figure 2B).

Data collection

We recorded measurements in three steps during the entire procedure for the femoral varus and flexion, for the tibial varus and posterior slope (Figure 1C). At first, we documented the expected values preoperatively after the evaluation of joint deformity and the mechanical axis from the AR system. Afterwards, we recorded the same measurements after each cut intraoperatively, and ultimately, we also measured these values radiologically after the operation.

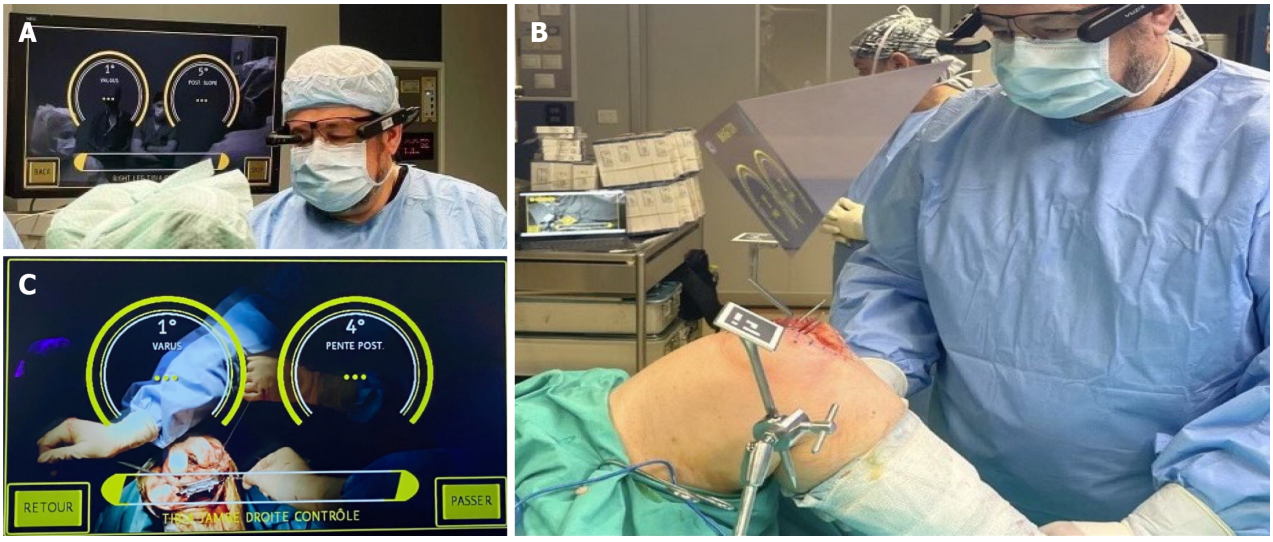

Figure 1 Knee+™ augmented reality navigation system (Pixee medical company, Besancon, France). A: It comprised of a pair of smart glasses, specific markers (QR-code) that are connected to the tibial and femoral cutting guides, and a central laptop; B: Intraoperative sensor positioning; C: Intraoperative assistance.

Statistical analysis

Lin's concordance correlation coefficient (CCC) was estimated in terms of statistical analysis. Also, results for Bland and Altman's limits-of-agreement procedure are provided as the mean of the two values, minus and plus 1.96 standard deviations. CCCs between 0.60 and 0.80 are considered substantial, while coefficients greater than 0.80 are considered excellent. As the discrepancies between the measurements could not be assumed to be normal, the Wilcoxon Signed Rank Test was also performed to examine whether there was a significant difference between the mean values of the expected values and the radiographic measures, as well as between the mean values of the expected and controlled values. If a statistically significant difference was detected, a Wilcoxon Signed Rank Test was carried out to test if the differences were significantly different from the 1 degree. The level of statistical significance was set to 0.05.

RESULTS

A total of 30 patients were included in the study. For patients' femur calculations, the difference between the controlled and the expected varus/valgus values ranged from -1 to 1 degree, whilst there was no discrepancy in terms of radiographic measurements. Regarding flexion values, the difference between expected and controlled values (which refer to the calculated varus/valgus values from the AR system after the osteotomies have been executed) ranged from -1 to 1 degree. The same was observed for the difference between expected values and radiographic measurements. The mean differences between all paired comparisons varied from 0 to 0.33 degrees (Tables 1 and 2).

Concerning tibia calculations, the discrepancy between controlled and expected values for varus ranged from -1 to 1 degree with a medium value of zero degrees, while the difference between radiographic measurements and expected values for varus ranged from 0 to 1 degree with a medium value of zero degrees. Finally, the difference between controlled and expected values for the posterior slope ranged from -2 to 1 degree and between radiographic measurements and expected values from -1 to 1 (Tables 1 and 2). The corresponding median values were equal to zero. The mean differences between all paired comparisons were narrow, varying from 0 to 0.23 degrees (Table 3).

Near-perfect CCCs were reckoned for comparisons only between estimated flexion values and controlled and radiographic measurements in the femur and between estimated posterior slope values and controlled and radiographic measurements in the tibia, varying from 0.66 to 0.89. Also, as mentioned before, no deviation was observed between expected varus values and radiographic measurements in the femur. The 95% limits of agreement were within -1.46 to 1.52 degrees, and most estimates lie within the indicating (Table 3). Low CCC was estimated for expected and controlled values of varus in the femur and tibia.

A Wilcoxon Signed Rank Test was performed to determine whether there was a statistically significant difference regarding the expected values and radiographic calculations. The test revealed a statistically significant difference in mean expected values and radiographic measurements only for femoral flexion measurements (Z score = 2.67, P value = 0.01). However, this difference was statistically significantly lower than 1 degree (Z score = -4.21, P value < 0.01). Concerning discrepancies in the values of expected values and controlled measurements, a statistically significant difference between varus values measured in tibia was noted (Z score = -2.33, P value = 0.02), which was also statistically significantly lower than 1 degree (Z score = -4.99, P value < 0.01). Finally, it is of utmost importance to mention that there was no difference between the different implants used.

Table 1 Descriptive statistics of the expected, controlled, and radiographic values from measurements in femur and tibia

	The 25th percentile	Median	The 75th percentile	Mean	SD
Femur					
Varus					
Expected values	0	0	0	0.2	0.4
Controlled values	0	0	1	0.4	0.6
Radiographic measures	0	0	0	0.2	0.4
Flexion					
Expected values	6	6	7	6.2	0.9
Controlled values	5	6	7	6.1	1
Radiographic measures	5	6	6	5.8	0.7
Tibia					
Varus					
Expected values	0	0	0	0.1	0.3
Controlled values	0	0	1	0.3	0.5
Radiographic measures	0	0	0	0	0
Posterior slope					
Expected values	5	5	6	5.4	1
Controlled values	5	5.5	6	5.7	0.9
Radiographic measures	5	5	6	5.4	0.8

Table 2 Descriptive statistics of the difference of the controlled and radiographic values from the expected values from measurements in femur and tibia

	Minimum	25th percentile	Median	75th percentile	Maximum
Femur					
Varus (degrees)					
Controlled values	-1.00	-1.00	0.00	0.00	1.00
Radiographic measures	0.00	0.00	0.00	0.00	0.00
Flexion (degrees)					
Controlled values	-1.00	0.00	0.00	0.00	1.00
Radiographic measures	-1.00	0.00	0.00	1.00	1.00
Tibia					
Varus (degrees)					
Controlled values	-1.00	-1.00	0.00	0.00	1.00
Radiographic measures	0.00	0.00	0.00	0.00	1.00
Posterior slope (degrees)					
Controlled values	-2.00	0.00	0.00	0.00	1.00
Radiographic measures	-1.00	0.00	0.00	0.00	1.00

DISCUSSION

Our study aimed to denote the reproducible accuracy of an AR system (Knee+™, Pixee Medical) in 30 TKA patients compared to their intraoperative measurements. At this time, to the best of our knowledge, this is one of the largest clinical studies of this size to examine the accuracy and efficacy of this system, but the first to include implants with different characteristics. The results indicate that good varus/valgus alignment was accomplished without outliers,

Table 3 Concordance correlation coefficient (95%CI) and 95% Limits of agreement of expected values with controlled values and radiographic measurements

	Mean (SD)	CCC (95%CI)	95% LOA	Number of differences out of the LOA
Femur				
Varus (degrees)				
Controlled values	-0.20 (0.61)	0.25 (-0.06, 0.56)	(-1.40, 1.00)	3
Radiographic measures	0.00 (0.00)	1.00 (1.00, 1.00)	-	-
Flexion (degrees)				
Controlled values	0.03 (0.56)	0.83 (0.71, 0.94)	(-1.06, 1.10)	0
Radiographic measures	0.33 (0.61)	0.66 (0.48, 0.84)	(-0.86, 1.52)	2
Tibia				
Varus (degrees)				
Controlled values	-0.23 (0.50)	0.31 (0.06, 0.56)	(-1.22, 0.76)	1
Radiographic measures	0.10 (0.31)	-	(-0.50, 0.70)	3
Posterior slope (degrees)				
Controlled values	-0.22 (0.63)	0.75 (0.59, 0.91)	(-1.46, 0.99)	3
Radiographic measures	0.03 (0.41)	0.89 (0.82, 0.95)	(-0.78, 0.84)	5

CCC: Concordance correlation coefficient; LOA: Limits of agreement.

whilst sagittal alignment was generally featured satisfactory. The procedure was performed comfortably and repeatedly by the same team. With regard to the rigorous limits and standards employed for the goals of our study, it is vitally important to emphasize that a difference of 1˚ in final implants' position is unlikely to be clinically significant, as numerous studies have demonstrated that differences in coronal alignment after TKA of up to 3˚ (or even up to roughly 6˚) result in good clinical outcomes[14]. This exact point is crucial when considering the position of AR systems in the overall context of TKA.

There is an expanding interest in surgical variables intraoperatively controlled by orthopaedic surgeons, involving lower leg alignment, component positioning and soft-tissue balancing. Punctilious control over these factors is associated with improved outcomes, which is the main reason why several computer navigation and robotic-assisted systems have emerged[11-13].

In our study, three different types of implants were used with similar characteristics as surface arthroplasties. Their main difference lies in femoral flexion and posterior tibial slope. According to the aforementioned results, the Knee+™ AR system is a repeatable open platform method, eligible to use with the same accuracy regardless of the characteristics of the implants employed.

AR solutions can potentially decrease the outcome dependence on the surgeon's parameters by providing preoperative planning in the surgeon's field of view or even indicating impeccable trajectories for placing implants with overlays[11, 12]. Diminishing cutting errors is the challenge of every AR system assisting TKA. According to literature data and the system's design, the system's accuracy lies principally in the varus/valgus tibial cut regarding the restoration of the mechanical axis.

More specifically, a recent study by Bennett *et al*[13] suggested that coronal mean error for femoral and tibial cuts is 1.3˚ and 1.1˚, respectively. That present-day paper examined total knee arthroplasties carried out with the assistance of Knee+™ AR system, as in our study. Comparing the two contemporary studies, results are featured comparatively similar, indicating that the robustness of this AR system regarding restoration of mechanical axis after primary TKA is perceptibly rigorous[13]. In a 2021 systematic review scrutinizing the accuracy of Knee+™ AR system by Iacono *et al*[15], it was deduced that this system is capable of executing cutting errors of less than 1˚ of discrepancy regarding coronal alignment and less than 2˚ in terms of posterior tibial slope and femoral extension/flexion, however, the copious limitations of this study need to be taken into consideration[15]. Perusing literature, it is patently evident that there are limited data concerning the effectiveness and accuracy of other AR systems used in TKA. Tsukada *et al*[16] examined the efficacy of another AR system regarding the exactness of bone resection in TKA, concluding that AR technology can bolster surgeons' distal femoral resection accuracy compared to traditional intramedullary-guided techniques[16]. Additionally, another study by Fucentese and Koch[17] examined the impact of "NextAR" AR TKA system (Medacta International SA, Castel San Pietro, Switzerland) in prosthesis alignment and positioning. It was inferred that, despite being employed in a low number of cases, the initial results seemed promising, requiring further research to corroborate the potency of this system[17].

The Knee+™ AR system equips the surgeon with a thorough preoperative plan projected in real-time concerning the alignment of bone components and mechanical axis restoration[18]. Notwithstanding, after initial cuts are executed, and

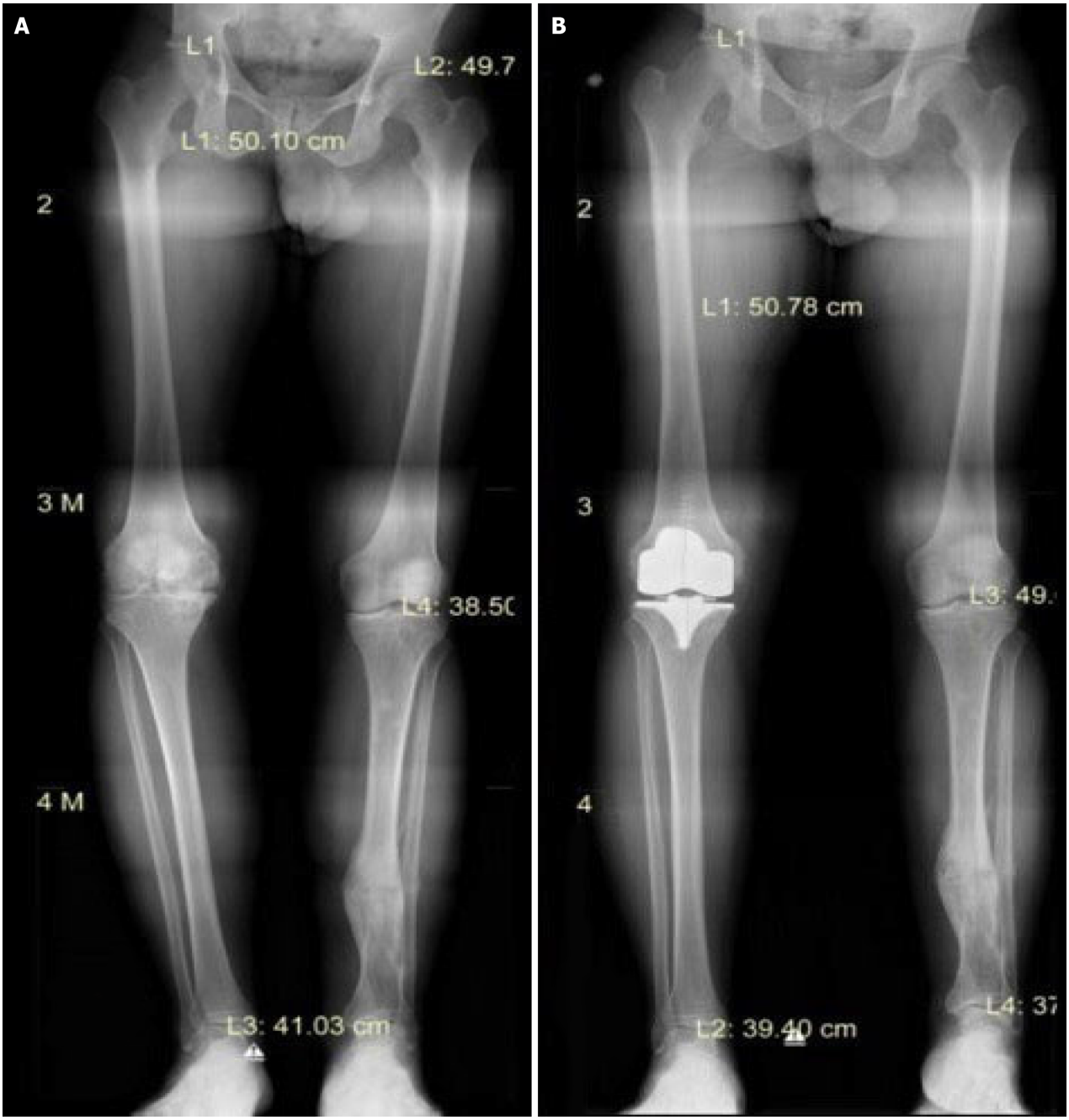

Figure 2 Radiographical evaluation and measurements. A: Preoperative of radiographical evaluation and measurements; B: Postoperative of radiographical evaluation and measurements.

the system describes a significant difference, it enables the surgeon to alter their surgical plans and correct the previously made osteotomies by contrasting the expected and controlled values. The design of this AR system does not require the utilization of intramedullary rods for femoral and tibial osteotomies, which are correlated with low-incidence intraoperative thromboembolic episodes[18].

All measurements are calculated intraoperatively, thus, there is no demand for time and cost-consuming preoperative radiographic scans that expose the patients to radiation[19,20]. During surgery, not using extra pins as markers for restoration of the mechanical axis is linked with reduced risk of periprosthetic fractures during implantation, chiefly of the femoral component, and eliminated infection risk. Marker stabilization on the cutting guides is considered safe because it decreases the risk of systemic malalignment calculations due to intraoperative pin stretching, triggering imprecise cuts[21].

Although it has been demonstrated that AR might positively impact surgeons by diminishing surgical errors, verifying the learning curve would be an engrossing aim. Nonetheless, it is a user-friendly system with an effortless intraoperative setup that guides the surgeon throughout the surgery and is versatile in amending operative plans if necessary[22,23]. In our study, operative time and blood loss were not investigated, thus further research is incontrovertibly required to evaluate the potential impact of Knee+™ and other AR systems on this area.

Concerns have been raised regarding the extent of potentially spurious and disturbing AR information displayed intraoperatively. This AR system does not require substantial space or instrumentation in the operating room. Compared with other navigation systems, this digital tool allows the surgeon to concentrate on the surgical field through smart glasses and not get distracted by other display screens, allowing precious coordination between the surgical team. Apposite contrast and clarity of the AR technology and avoidance of masking structures in real patient view are of paramount significance[23].

CONCLUSION

Present-day literature data propound that AR systems, such as Knee+™, are becoming comparable to conventional navigation techniques in terms of precision and safety for routine clinical practice. AR appears to be a robust contemporary digital tool capable of revolutionizing the field of orthopaedic surgery, providing substantive information regarding intraoperative guidance and decision-making. In the future, it will distinctly possibly serve as a transcendent human-computer interface, enabling dexterous surgeons to attain superior results. Nonetheless, further technological and medical research is requisite to achieve AR technologies' maximum potential and cost-effectiveness. Until then, it is vitally important for the orthopaedic surgeon to rely on their training and adroitness for decision-making and opting wisely to employ an AR system.

ARTICLE HIGHLIGHTS

Research background

Computer-assisted systems obtained an increased interest in orthopaedic surgery over the last years, as they enhance precision compared to conventional hardware. The expansion of computer assistance is evolving with the employment of augmented reality (AR). With the implementation of navigation systems, orthopaedic surgeons can precisely track and visualize surgical instruments in real-time, conforming to the anatomical structures. Yet, the accuracy of AR navigation systems has not been determined. This case series endeavors to scrutinize the accurateness of component alignment and restoration of the affected limb's mechanical axis in primary total knee arthroplasty (TKA), employing the Knee+™ system. Additionally, this study aims to evaluate whether such systems are substantively beneficial for a high-experienced knee surgeon.

Research motivation

This study aims to examine the accuracy of component alignment and restoration of the affected limb's mechanical axis in primary TKA, utilizing an AR navigation system and to assess whether such systems are conspicuously fruitful for an accomplished knee surgeon. Our study denotes the reproducible accuracy of an AR system (Knee+™, Pixee Medical) in 30 TKA patients compared to their intraoperative measurements, which is one of the largest clinical studies of this size to examine the accuracy and efficacy of this system. AR solutions can potentially decrease the outcome dependence on the surgeon's parameters by providing preoperative planning in the surgeon's field of view or even indicating impeccable trajectories for placing implants with overlays. In particular, the Knee+™ AR system equips the surgeon with a thorough preoperative plan projected in real-time concerning the alignment of bone components and mechanical axis restoration.

Research objectives

The results indicate satisfactory postoperative coronal alignment without outliers across all three implants. The procedure was performed comfortably and repeatedly by the same team. AR navigation systems can bolster orthopaedic surgeons' accuracy in achieving precise axial alignment. With regard to the rigorous limits and standards employed for the goals of our study, it is vitally important to emphasize that a difference of 1˚ in final implants' position is unlikely to be clinically significant, as numerous studies have demonstrated that differences in coronal alignment after TKA of up to 3˚ (or even up to roughly 6˚) result in good clinical outcomes

Research methods

From May 2021 to December 2021, 30 patients, 25 women and 5 men, underwent a primary unilateral TKA. Revision cases were excluded. A preoperative radiographic procedure was performed to evaluate the limb's axial alignment. All patients were operated on by the same team, without a tourniquet, utilizing three distinct prostheses with the assistance of the Knee+™ AR navigation system in every operation. Postoperatively, the same radiographic exam protocol was executed to evaluate the implants' position, orientation and coronal plane alignment. We recorded measurements in 3 stages regarding femoral varus and flexion, tibial varus and posterior slope. Firstly, the expected values from the AR system were documented. Then we calculated the same values after each cut and finally, the same measurements were recorded radiologically after the operations. Concerning statistical analysis, Lin's concordance correlation coefficient was estimated, while Wilcoxon Signed Rank Test was performed when needed.

Research results

A Wilcoxon Signed Rank Test was performed to determine whether there was a statistically significant difference re-

garding the expected values and radiographic calculations. A statistically significant difference was observed regarding mean expected values and radiographic measurements for femoral flexion measurements only (Z score = 2.67, P value = 0.01). Nonetheless, this difference was statistically significantly lower than 1 degree (Z score = -4.21, P value < 0.01). In terms of discrepancies in the calculations of expected values and controlled measurements, a statistically significant difference between tibial varus values was detected (Z score = -2.33, P value = 0.02), which was also statistically significantly lower than 1 degree (Z score = -4.99, P value < 0.01). There was no difference between the different implants used.

Research conclusions

Our study aimed to denote the reproducible accuracy of an AR system (Knee+™, Pixee Medical) in 30 TKA patients compared to their intraoperative measurements. At this time, to the best of our knowledge, this is one of the largest clinical studies of this size to examine the accuracy and efficacy of this system, but the first to include implants with different characteristics. The results indicate that good varus/valgus alignment was accomplished without outliers, whilst sagittal alignment was generally featured satisfactory, while the procedure was performed comfortably and repeatedly by the same team. AR solutions can potentially decrease the outcome dependence on the surgeon's parameters by providing preoperative planning in the surgeon's field of view or even indicating impeccable trajectories for placing implants with overlays. Diminishing cutting errors is the challenge of every AR system assisting TKA. The Knee+™ AR system equips the surgeon with a thorough preoperative plan projected in real-time concerning the alignment of bone components and mechanical axis restoration. It is a user-friendly system with an effortless intraoperative setup that guides the surgeon throughout the surgery and is versatile in amending operative plans if necessary. Further research is required to evaluate their efficacy and potential.

Research perspectives

In the future, it will distinctly possibly serve as a transcendent human-computer interface, enabling dexterous surgeons to attain superior results. Nonetheless, further technological and medical research is requisite to achieve AR technologies' maximum potential and cost-effectiveness. Until then, it is vitally important for the orthopaedic surgeon to rely on their training and adroitness for decision-making and opting wisely to employ an AR system.

FOOTNOTES

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ORIGINAL ARTICLE

Prospective Study

Mid-term survival of the Optimys short stem: A prospective case series of 500 patients

Bryan Hamans, Sheryl de Waard, Sjoerd Kaarsemaker, Esther R C Janssen, Inger N Sierevelt, Gino M M J Kerkhoffs, Daniël Haverkamp

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Abstract

BACKGROUND

In recent years, there has been an increase in the number of total hip arthroplasty procedures in the younger patient population. This active group has higher expectations of their prosthesis in comparison to the older population, and there is a greater physical demand for the prosthesis. Short femoral stems were introduced to retain proximal bone stock and joint biomechanics and became more common to implant in this specific population. Currently, the long-term survival and functional outcomes of various short stems are still being investigated in different clinics.

AIM

To determine the 5-year survival of the Optimys hip stem.

METHODS

This was a prospective multicenter cohort study of 500 patients conducted in two hospitals in the Netherlands. All patients received the Optimys short stem (Mathys Ltd, Bettlach, Switzerland). The primary outcome measure was survival of the hip stem, with revision as the endpoint. The secondary outcome measurements included patient-reported outcome measures (PROMs). Kaplan-Meier analysis was used to calculate the 5-year survival rate. Log-minus-log transformation was performed to calculate the 95% confidence interval (95%CI). Mixed model analyses were performed to assess the course of the PROMs during the 1st 2 years after surgery. Analyses were modeled separately for the 1st and 2nd years to calculate the yearly change in PROMs during both follow-up periods with accompanying 95%CIs.

RESULTS

The mean age of the total 500 patients was 62.3 years (standard deviation: 10.6) and 202 were male (40%). At a median follow-up of 5.5 years (interquartile range: 4.5-6.7), 7 patients were deceased and 6 revisions were registered, for infection (n = 3), subsidence (n = 2) and malposition (n = 1). This resulted in an overall 5-year survival of 98.8% (95%CI: 97.3-99.5). If infection was left out as reason for revision, a stem survival of 99.4% (95%CI: 98.1-99.8) was seen. Baseline questionnaires were completed by 471 patients (94%), 317 patients (63%) completed the 1-year follow-up questionnaires and 233 patients (47%) completed the 2-year follow-up. Both outcome measures significantly improved across all domains in the 1st year after the operation (P < 0.03 for all domains). In the 2nd year after surgery, no significant changes were observed in any domain in comparison to the 1-year follow-up.

CONCLUSION

The Optimys stem has a 5-year survival of 98.8%. Patient-reported outcome measures increased significantly in the 1st postoperative year with stabilization at the 2-year follow-up.

Key Words: Total hip arthroplasty; Femoral stem; Short stem; Optimys; Survival; 5-year survival; Revision; PROMs

Core Tip: The Optimys hip stem showed an excellent 5-year survival of 98.9%, and when excluding infections this was 99.4%. This is in line with the earlier results of the Roentgen Stereophotogrammetric analysis study completed by our group, and we expect it to be in line with the National Institute for Health and Care Excellence criteria on total hip arthroplasty for the 10-year follow-up. This study showed that in a large, varied patient population there is similar survival as other cohorts with short femoral stems.

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INTRODUCTION

Osteoarthritis has become more prevalent in recent years due to a growing and aging population[1]. According to the Dutch Arthroplasty Registry (LROI), the yearly number of total hip arthroplasties (THA) has increased from approximately 23.000 to 31.500 between 2010 and 2021[2]. As the total number of THAs has increased over the years, the number of younger patients (< 65 years) receiving THA has also increased to 20% of the total[2]. This younger group has a more active lifestyle, which results in a greater demand for hip prostheses. This makes them more susceptible to revision of their total hip, as there is an increase in wear and/or loosening of the components due to increased forces[3-7].

In recent decades, a short, curved stem as a femoral component in THA has been introduced to the market and has become more popular for implantation in this younger patient population. The philosophy behind short stems is bone-stock preservation in the proximal femur due to more proximal loading and restoration of the patient's specific anatomy [7-10]. With the introduction of new implants, it is important to monitor survival. The Optimys stem, manufactured by Mathys Ltd. Bettlach, is a meta-diaphyseal anchoring short stem and has been on the market since 2010. An earlier radiostereometric analysis study of the Optimys hip stem showed excellent results in the stabilization of the Optimys short stem at 2 years of follow-up[11]. At this time, to the best of the authors' knowledge, mid-term survival and functional outcomes have been described in only two studies, and the Optimys has an Orthopaedic Data Evaluation Panel (ODEP) rating of 7A[12].

Therefore, the aim of this study was to determine the mid-term survival of the Optimys hip stem in a large, varied patient population and to assess functional outcomes and quality of life in this patient population.

MATERIALS AND METHODS

This study was a prospective multicenter cohort study conducted in two centers in the Netherlands, the Xpert Clinics Orthopedie Amsterdam and VieCuri Medisch Centrum Venlo. This study was submitted and approved by the medical ethics research committee of Amsterdam UMC, location AMC Amsterdam (NL47055.048.13). Patients scheduled for THA between January 2014 and December 2021 were asked to participate. All patients suffered from primary or secondary osteoarthritis, which included coxarthrosis, dysplastic coxarthrosis, rheumatoid arthritis, necrosis of the head of the femur, or post-traumatic coxarthrosis. Patients were excluded in cases of revision surgery, an American Society of Anesthesiologists score > 3, sepsis, or malignant tumors. After confirmation of participation, all patients gave informed consent before they were included in this study.

Patients returned for a clinical follow-up at 6 wk, 3 months, and 1 year post surgery. Hereafter, revision status was verified using patient files and the LROI. Prior to the operation, at 6 wk, 3 months, 6 months, 1 year, and 2 years post-surgery, patients were asked to fill out a questionnaire.

Surgery

All patients received the Optimys short stem (Mathys Ltd, Bettlach, Switzerland). The Optimys stem is a calcar-guided short stem with a curved design. It is made of Ti6Al4V (titanium-aluminum-vanadium), according to ISO 5832-3, with a titan plasma spray and calcium phosphate coating for better ingrowth of the stem into the bone. The approach during THA was left to the surgeon's preference (anterior, anterolateral, or straight lateral). The day of the surgery or 1 d postoperative, patients were mobilized using two crutches and were allowed full weight bearing (Figure 1).

Outcome measurements

The primary outcome measure was survival of the hip stem, with revision as the endpoint. Revision was defined as a surgical procedure in which all or part of the previous implanted prosthesis was replaced. Reasons for revision were described. The secondary outcome measurements included patient-reported outcome measures (PROMs), which consisted of the Hip Disability and Osteoarthritis Outcomes Score (HOOS), the 36-item Short Form (SF-36), and a 5-point Likert scale for satisfaction (at 2 years post-surgery)[13-16].

Statistical analysis

IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, United States) was used for the statistical analysis. In the case of a normal distribution, all continuous outcomes were reported as the means and standard deviation (SD). In the case of a skewed distribution, the outcomes were presented as the median and interquartile range. Categorial outcomes are presented as frequencies with accompanying percentages. Kaplan-Meier analysis was used to calculate the 5-year survival rate by censoring patients at death or at the end of the observation period before 5 years. Log-minus-log transformation was performed to calculate the 95% confidence interval (95%CI).

Second, mixed model analyses were performed to assess the course of the PROMs during the 1st 2 years after surgery. Analyses were modeled separately for the 1st and 2nd years to calculate the yearly change in PROMs during both follow-up periods with accompanying 95%CIs. A P value of < 0.05 was considered statistically significant for all analyses. As PROM analyses were secondary, no correction for multiple testing was performed. Due to considerable loss of patients filling out PROMs during follow-up, a sensitivity analysis was performed according to a last observation carried forward protocol to avoid overestimation of the effect.

RESULTS

Patient characteristics

A total of 500 consecutive patients were included in this study, of whom 202 (40%) were male. The mean age was 62.3 years (SD: 10.6), and the mean body mass index was 26.5 kg/m^2 (SD: 4.1) (Table 1).

Survival

At a median follow-up of 5.5 years (interquartile range: 4.5-6.7), 7 patients were deceased with their prosthesis in situ, and 6 revisions were registered. Infection was the reason for revision in 3 patients, and they were initially treated with debridement, antibiotics, and implant retention. In 1 patient, the debridement, antibiotics, and implant retention failed, and a two-stage revision was needed. Furthermore, 2 patients were revised due to subsidence of the stem (due to an undersized stem but with good fixation), and 1 patient was revised because of malposition of the stem. This resulted in an overall 5-year survival of 98.8% (95%CI: 97.3, 99.5) in the study population (Figure 2). If infection was left out as the reason for revision, a stem survival of 99.4% (95%CI: 98.1, 99.8) was seen, with no cases of aseptic loosening.

PROMs

Of the 500 included patients, 471 patients (94%) completed the baseline questionnaires, and 317 patients (63%) completed the 1-year follow-up questionnaires. At the 2-year follow-up, this number had decreased to 233 patients (47%) (Table 2). The HOOS and SF-36 scores at all follow-up time points are presented in Table 2. Both outcome measures significantly improved across all domains in the 1st year after the operation (P < 0.03 for all domains). In the 2nd year after surgery, no significant changes were observed in any domain in comparison to the 1-year follow-up (Table 3 and Figure 3). Although

Table 1 Demographic characteristics, *n* = 500

Characteristic	Value
Male sex[1]	202 (40)
Age	62.3 (10.5)
Right side[1]	286 (57.0)
Height in cm	173.2 (9.2)
Weight in kg	79.9 (15.8)
BMI in kg/m^2	26.5 (4.1)

[1]*n* (%) or mean (standard deviation). BMI: Body mass index.

Table 2 Hip Disability and Osteoarthritis Outcome Score and 36-item short form survey baseline and follow-up scores

Outcome		Baseline, *n* = 471	6 wk, *n* = 388	3 months, *n* = 371	6 months, *n* = 355	1 yr, *n* = 317	2 yr, *n* = 233
HOOS							
	Symptoms	42.1 (18.1)	71.6 (18.2)	76.3 (17.9)	81.1 (17.7)	85.9 (16.2)	85.9 (16.7)
	Pain	42.5 (16.5)	77.4 (16.7)	83.7 (16.6)	87.1 (15.8)	89.6 (15.0)	90.2 (14.7)
	ADL	42.6 (17.5)	74.7 (17.8)	81.0 (17.8)	85.4 (16.1)	88.6 (16.4)	89.5 (15.4)
	Sports and recreation	24.3 (19.6)	51.9 (26.8)	65.6 (25.1)	71.2 (24.9)	77.1 (24.2)	77.0 (24.9)
	Quality of life	25.9 (15.7)	54.6 (20.4)	66.9 (22.3)	72.8 (21.8)	78.4 (21.6)	80.0 (21.0)
SF 36							
	Physical functioning	35.6 (18.6)	57.8 (22.8)	69.6 (22.4)	74.5 (22.4)	78.7 (22.4)	81.8 (19.8)
	Role physical	23.3 (35.7)	29.5 (36.0)	57.5 (42.5)	71.0 (40.4)	81.0 (34.9)	80.8 (34.4)
	Bodily pain	35.7 (17.2)	55.9 (22.1)	70.7 (22.1)	75.9 (21.2)	80.6 (22.4)	80.8 (22.8)
	Social functioning	61.0 (26.0)	68.1 (26.0)	79.9 (23.8)	85.0 (21.0)	88.5 (19.3)	87.7 (20.4)
	Mental health	73.4 (17.8)	80.2 (16.2)	82.0 (16.3)	81.8 (15.7)	83.1 (15.0)	83.0 (14.3)
	Role emotional	63.3 (43.7)	67.5 (41.5)	77.2 (38.2)	84.1 (33.6)	89.6 (27.0)	90.0 (27.2)
	Vitality	57.3 (19.9)	66.0 (18.4)	69.5 (18.4)	70.8 (18.2)	72.9 (17.4)	73.9 (16.7)
	General health perceptions	66.6 (18.5)	73.5 (17.9)	72.4 (19.0)	70.4 (19.7)	72.0 (19.9)	73.4 (18.5)

Data are mean (standard deviation). ADL: Activities of daily living; HOOS: Hip Disability and Osteoarthritis Outcome Score, SF-36: 36-item Short Form Survey.

sensitivity analysis showed smaller effects during the 1st year, the same comparable effect was observed during the 2-year follow-up (Supplementary Tables 1 and 2).

At the 2-year follow-up, 210 (42%) had completed the satisfaction score with results as follows: 132 patients (63%) were very satisfied; 60 patients (29%) were satisfied; 9 patients (4%) were neutral; 7 patients (3%) were unsatisfied; and 2 patients (1%) were very unsatisfied with their hip prosthesis.

DISCUSSION

This study, which included 500 patients, showed a high survival rate of 98.8% at the 5-year follow-up mark with 6 revisions. The reasons for overall revision were an infection (0.6%) in three cases, subsidence of the stem (0.4%) in two cases, and malposition of the stem (0.2%) in one case. During the revision surgery in the two cases with subsidence, it was noted that the femoral stem had good fixation in the femur, confirming that the stem was undersized during the primary placement and was now settled with bone growth around the stem for fixation. If infection as a reason for revision was left out, a survival of 99.4% of the Optimys stem was seen. No aseptic loosening was observed in this cohort.

Table 3 Yearly change in the patient-reported outcome measures (β) during the 1st and 2nd postoperative years

Outcome measure		1st yr		2nd yr	
		β (95%CI)[1]	*P* value	β (95%CI)[1]	*P* value
HOOS					
	Symptoms	34.8 (31.9, 37.6)	< 0.001	0.7 (-0.9, 2.3)	0.38
	Pain	36.8 (34.0, 39.7)	< 0.001	0.3 (-1.0, 1.6)	0.63
	ADL	36.2 (33.3, 39.1)	< 0.001	0.9 (-0.6, 2.5)	0.24
	Sports and recreation	43.3 (39.7, 46.9)	< 0.001	-0.1 (-2.6, 2.4)	0.93
	Quality of life	41.8 (38.7, 45.0)	< 0.001	1.5 (-0.7, 3.8)	0.18
SF-36					
	Physical functioning	34.5 (31.4, 37.7)	< 0.001	0.8 (-1.7, 3.4)	0.56
	Role physical	54.4 (49.0, 59.7)	< 0.001	-1.2 (-6.2, 3.8)	0.64
	Bodily pain	36.5 (33.4, 39.6)	< 0.001	-0.4 (-3.3, 2.6)	0.80
	Social functioning	22.8 (19.5, 26.0)	< 0.001	-0.9 (-3.5, 1.7)	0.49
	Mental health	6.1 (4.1, 8.1)	< 0.001	-0.7 (-2.4, 1.1)	0.45
	Role emotional	23.3 (18.1, 28.5)	< 0.001	0.0 (-4.4, 4.5)	1.00
	Vitality	10.8 (8.5, 13.1)	< 0.001	-0.6 (-2.6, 1.4)	0.56
	General health perceptions	2.4 (0.3, 4.6)	0.03	0.1 (-1.7, 1.8)	0.95

[1]Mixed model analysis. ADL: Activities in daily living; CI: Confidence interval; HOOS: Hip Disability and Osteoarthritis Outcome Score; SF-36: 36-item short form survey.

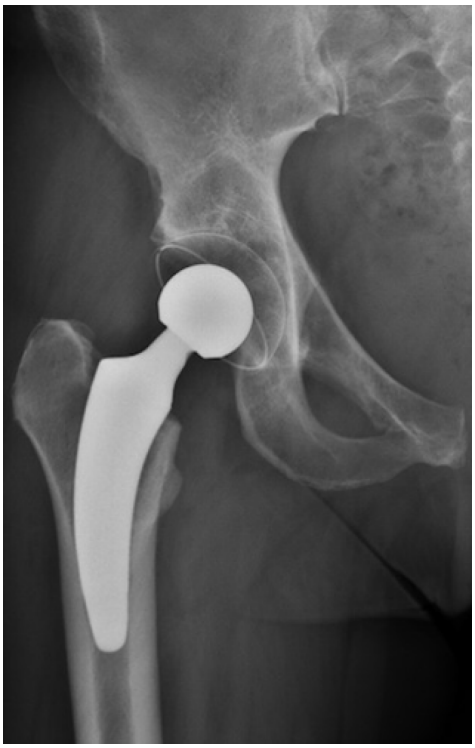

Figure 1 Optimys short stem (Mathys Ltd. Bettlach, Switzerland).

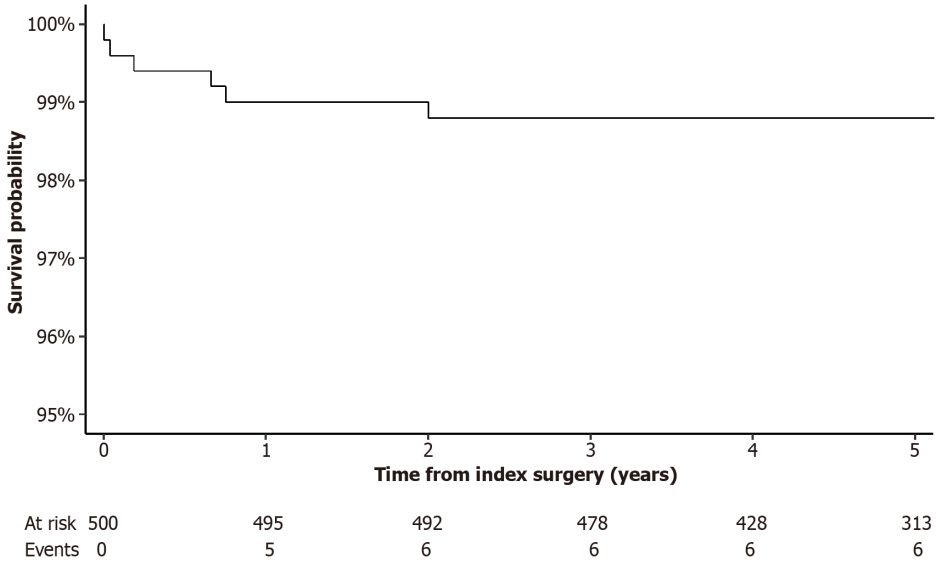

Figure 2 Kaplan-Meier survival curve illustrating 5-year survival, including all reasons for revision.

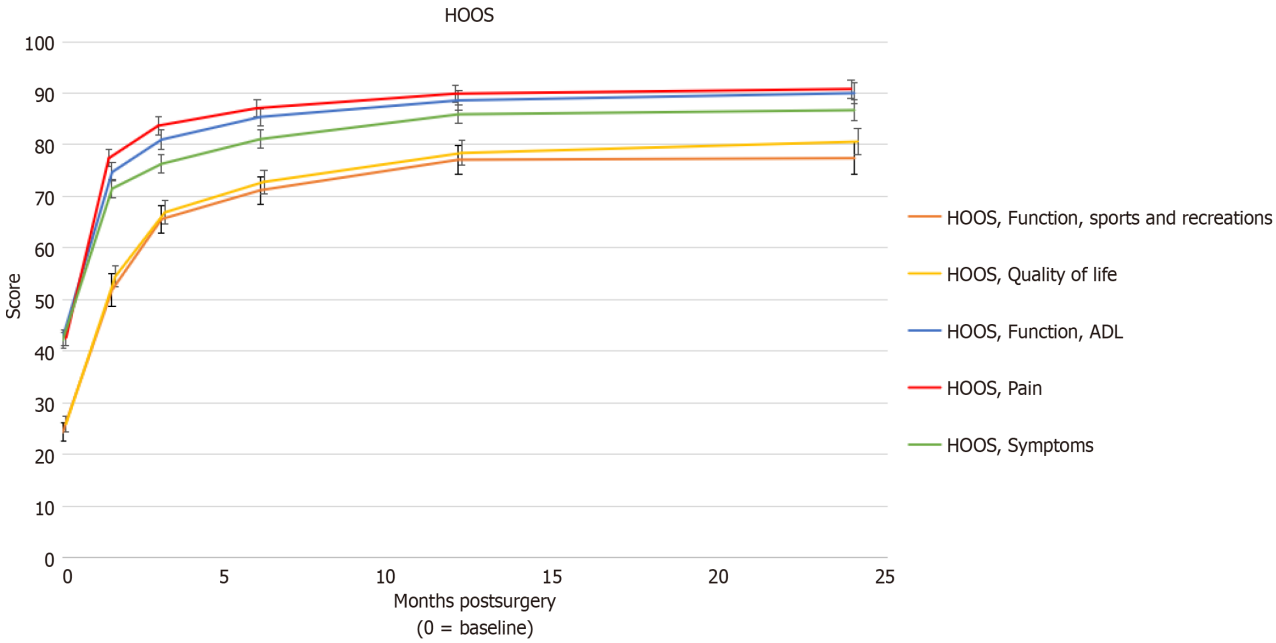

Figure 3 Follow-up graph of the Hip Disability and Osteoarthritis Outcomes Score scores from baseline to the 2-yr follow-up (means with 95% confidence interval). HOOS: Hip Disability and Osteoarthritis Outcome Score; ADL: Activities of daily living.

Furthermore, a significant increase in the PROMs at the 1st year of follow-up was observed. The HOOS scores increased by 34.8 to 43.3 points, and the SF-36 scores increased by 2.4 to 54.5 points across all subscales. After the 1st year, no significant changes in either score were observed. Almost all patients (91.4%) were very satisfied or satisfied with their THA.

The National Institute for Health and Care Excellence (NICE) criteria state that total hip replacements for patients with arthritis have revision rates or projected revision rates of 5% or less after 10 years of follow-up[17]. With a revision rate of almost 99% at the 5-year follow-up, our study results are expected to be in line with these NICE criteria.

In 2022, Kutzner *et al*[18] published a study on the mid-term results of the Optimys hip stem for 782 patients at 6 years of follow-up. It showed a survival rate of 98.4%, with 26 revisions in total (including infection and acetabular cup malposition), of which 14 were stem revisions. This is comparable to our study with a survival rate of 98.8% and 6 overall revisions, of which 4 were stem revisions in a population of 500 patients.

Furthermore, both studies had comparable baseline characteristics of the patients. Kutzner *et al*[18] used the Harris Hip Score (HHS) as a functional outcome measure. The HHS is used to evaluate the function of the hip before and after surgery for a range of different disabilities[19]. The outcome showed a large increase in the first 6 months before flattening out. At the 2-year follow-up, the HHS reached a mean of 98.2, meaning that most patients showed an excellent functional outcome after 2 years. This is similar to our study, which indicated consistent excellent survival and functional

results among the two different clinics.

Studies on comparable short stems, such as the Nanos and Fitmore stems, are in line with our results. The NANOS stem, produced by Smith and Nephew, is also a calcar-guided short stem and has an ODEP rating of 7A. A study by Ettinger *et al*[20] presented mid-term results in 65 patients receiving a NANOS short stem at 5 years of follow-up. In this study, the patient population had similar demographics compared to our study population. At the 5-year follow-up, only two infections were registered. As there were no revisions of the stem itself, a survival of 100% was observed. For functional outcomes, this study also used the HHS. The HHS increased from 47.3 before surgery to 97.6 at the final 5-year follow-up.

Another widely used short stem is the Fitmore Hip stem, produced by Zimmer Biomet. It has an ODEP rating of 10A. A study by Thalmann *et al*[21] presented clinical results in 96 patients at 5 years of follow-up. At the 5-year follow-up, only one revision was seen, resulting in a survival of 99%. The mean HHS increased from 59.3 before the surgery to 93.8 at 5 years of follow-up.

A systematic review by van Oldenrijk *et al*[22] compared the revision rate of 19 different short stems across 49 studies. These short stems were divided into three groups: Collum; partial collum; and trochanter sparing. In this study, the Optimys stem was classified as a partial collum stem. This group contained eight stem types across 24 studies in 2357 patients. Follow-up ranged from 0.5 years to 11.2 years, with a mean follow-up of 4.0 years and a mean survival rate of 99.3%. Our results for the Optimys stem were in line with these results. The results can also be compared with the trochanter-sparing group, which contained eight stem types across 20 studies in 3628 patients. Follow-up ranged from 0.3-12.0 years, with a mean of 3.4 years and a mean survival of 99.2%. Our results were also in range compared to this group of short stems. The study, however, still used the old NICE benchmark of revision rates of 10% or less at 10 years of follow-up, while the current benchmark as mentioned earlier is 5% or less at 10 years of follow-up.

This study had a few limitations. First, the use of the LROI registry has limited information about the reason for revision. As such, the reason for revision for malposition was not clear, and further information could not be obtained, as the data were anonymous. Second, the number of patients who completed the PROM questionnaire was small. This can especially be seen at the 2-year follow-up. This could lead to a bias of the presented results, as the response rate of patients can depend on the results of their prosthesis. However, as the functional outcome scores in our study did not differ between the 1-year and 2-year follow-ups and a sensitivity analysis showed similar results, it is assumed that not only the patients with lasting complaints of their hip filled out the 2-year follow-up questionnaires. A strong point in this study was the large prospective cohort. A total of 500 patients were followed for a median follow-up of 5.5 years.

Although this study shows a good survival rate at the 5-year follow-up, further research on the Optimys short hip stem is still necessary to include the long-term survival of this hip stem. This cohort will be followed for the long-term survival data.

CONCLUSION

This study showed a 5-year survival rate of 98.8% for the Optimys hip stem in a population of 500 patients. Functional outcome and quality of life increased significantly in the 1st year after implantation with subsequent stabilization at the 2-year follow-up.

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ARTICLE HIGHLIGHTS

Research background

Short stems in total hip arthroplasty are becoming more popular in the younger patient population. The philosophy behind short stems is bone-stock preservation in the proximal femur due to more proximal loading and restoration of the patient's specific anatomy. As with all new implants on the market, stepwise introduction is needed to avoid a high failure rate in patients. This study contributes to the knowledge of midterm survival data of the Optimys hip stem.

Research motivation

Short hip stems have advantages compared to the widely used conventional stems, especially in the younger and more active patient population. However, long-term survival of the conventional stems is high, so newly introduced implants must have at least a survival rate of 95% at the 10-year follow-up, according to the National Institute for Health and Care Excellence guidelines.

Research objectives

The aim of this study was to determine the mid-term survival of the Optimys hip stem in a large, varied patient population and to assess functional outcomes and quality of life in this patient population. This can show us if the hip

stem is an implant that can be commonly used in the daily practice of an orthopedic surgeon. The study can contribute to the fact that this hip stem is safe to implant in a large and varied patient population with an excellent survival rate.

Research methods

This was a prospective multicenter cohort study conducted in two hospitals in the Netherlands (Amsterdam and Venlo). This gave a large and varied patient population. The primary outcome measure was survival of the hip stem, with revision as the endpoint. Revision was defined as a surgical procedure in which all or part of the previous implanted prosthesis was replaced. Reasons for revision were described. Kaplan-Meier was used for survival rate, by censoring patients at death or at the end of the observation period before 5 years. Log-minus-log transformation was performed to calculate the 95% confidence interval. The secondary outcome measurements included patient-reported outcome measures (PROMs), which consisted of the Hip Disability and Osteoarthritis Outcomes Score, the 36-item Short Form, and a 5-point Likert scale for satisfaction (at 2 years post-surgery). Mixed model analyses were performed to assess the course of the PROMs during the 1st 2 years after surgery. Analyses were modeled separately for the 1st and 2nd years to calculate the yearly change in PROMs during both follow-up periods with accompanying 95% confidence intervals. A P value of < 0.05 was considered statistically significant for all analyses.

Research results

The survival rate of the Optimys hip stem at the 5-year follow-up was 98.8% in a group of 500 patients if all revisions were included ($n = 6$). If infection was left out ($n = 3$), a survival of 99.4% was seen. The functional outcome and quality of life was significantly improved at the 1-year follow-up and subsequently stabilized at the 2-year follow-up.

Research conclusions

Short curved hip stems had a high survival rate at the 5-year follow-up, showing that it is a safe and viable stem for common use in total hip arthroplasty.

Research perspectives

Future research includes the long-term follow-up of the Optimys hip stem to determine the survival rate at the 10-year follow-up.

FOOTNOTES

Author contributions: Hamans B and Sierevelt IN analyzed the data; Hamans B, de Waard S, Kaarsemaker S, Janssen ERC, Sierevelt IN, Kerkhoffs GMMJ, and Haverkamp D prepared the manuscript; de Waard S, Kaarsemaker S, and Haverkamp D included patients; de Waard S, Kaarsemaker S, Janssen ERC, Sierevelt IN, and Haverkamp D collected data; Sierevelt IN and Haverkamp D designed the research study; All authors read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Slotervaarziekenhuis en Reade Institutional Review Board (approval No. NL47055.048.13).

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SYSTEMATIC REVIEWS

Does progress in microfracture techniques necessarily translate into clinical effectiveness?

Sathish Muthu, Vibhu Krishnan Viswanathan, Manoharan Sakthivel, Mohammed Thabrez

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Abstract

BACKGROUND

Multitudinous advancements have been made to the traditional microfracture (MFx) technique, which have involved delivery of various acellular 2nd generation MFx and cellular MFx-III components to the area of cartilage defect. The relative benefits and pitfalls of these diverse modifications of MFx technique are still not widely understood.

AIM

To comparatively analyze the functional, radiological, and histological outcomes, and complications of various generations of MFx available for the treatment of cartilage defects.

METHODS

A systematic review was performed using PubMed, EMBASE, Web of Science, Cochrane, and Scopus. Patients of any age and sex with cartilage defects undergoing any form of MFx were considered for analysis. We included only randomized controlled trials (RCTs) reporting functional, radiological, histological outcomes or complications of various generations of MFx for the management of cartilage defects. Network meta-analysis (NMA) was conducted in Stata and

Cochrane's Confidence in NMA approach was utilized for appraisal of evidence.

RESULTS

Forty-four RCTs were included in the analysis with patients of mean age of 39.40 (± 9.46) years. Upon comparing the results of the other generations with MFX-I as a constant comparator, we noted a trend towards better pain control and functional outcome (KOOS, IKDC, and Cincinnati scores) at the end of 1-, 2-, and 5-year time points with MFx-III, although the differences were not statistically significant ($P > 0.05$). We also noted statistically significant Magnetic resonance observation of cartilage repair tissue score in the higher generations of microfracture (weighted mean difference: 17.44, 95% confidence interval: 0.72, 34.16, $P = 0.025$; without significant heterogeneity) at 1 year. However, the difference was not maintained at 2 years. There was a trend towards better defect filling on MRI with the second and third generation MFx, although the difference was not statistically significant ($P > 0.05$).

CONCLUSION

The higher generations of traditional MFx technique utilizing acellular and cellular components to augment its potential in the management of cartilage defects has shown only marginal improvement in the clinical and radiological outcomes.

Key Words: Cartilage injury; Microfracture; Mesenchymal stem cells; Platelet-rich plasma; Bone marrow aspiration concentrates; Clinical outcome; Radiological outcome; Meta-analysis; Network meta-analysis

Core Tip: Chondral lesions have been reported in 60% of patients undergoing arthroscopic procedures of the knee; and such defects are described as one of the leading causes of chronic knee pain. As compared with the other cartilage restoration strategies, microfracture (MFx) is relatively cost-effective, simple, minimally-invasive and may also be performed in a single stage. Nevertheless, recent studies have demonstrated that modifications of the traditional MFx technique, such as the use of synthetic and autologous biological adjuvants may enhance the repair tissue quality, resilience, and overall efficacy of the procedure. Based on the current network meta-analysis we could conclude that the use of acellular and cellular adjuvants has shown only marginal improvement in the clinical (pain and functional scores) and radiological outcome in patients undergoing microfracture for cartilage defects of the knee. The safety and efficacy of the higher generation MFx procedures are also clearly evident from our review. However, there is a substantial potential for further improvement in the cellular components (chondrocytes over other cellular lineage), culture or processing methodology, delivery modalities (including appropriate scaffolds); as well as better surgical techniques to achieve demonstrable significant outcome improvement.

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INTRODUCTION

Lesions of the articular cartilage of the knee remain a challenging clinical entity in view of the limited capacity of the cartilaginous tissues to heal and potential progression to chronic degenerative arthritis[1]. The deficient endogenous cartilage repair mechanism has been attributed to the poor recruitment of regenerative cells into the area of cartilage defect[2]. Based upon the theory of marrow stimulation by subchondral drilling[1], Steadman *et al*[3] popularized the concept of microfracture (MFx) technique, whereby the migration of the growth factors and mesenchymal stem cells (MSCs) across the subchondral bone stimulates the development of the hyaline-like fibrocartilage. As compared with the other cartilage restoration strategies, MFx is relatively cost-effective, simple, minimally-invasive and may also be performed in a single stage[4]. Despite still being regarded as the gold-standard first-line treatment for cartilage deficiencies of the knee, there are concerns regarding their long-term outcomes and durability of the restored fibrocartilage[5,6]. In this context, alternate cartilage restoration procedures such as autologous chondrocyte implantation (ACI), osteoarticular transfer system and osteochondral allograft transplantation have been advocated as the better treatment strategies in the recent years. In fact, the United Kingdom National Institute for Health and Care Excellence, in a recent assessment, has recommended for the abandonment of MFx in favor of ACI in the management of articular knee defects [7-11].

Nevertheless, recent studies have demonstrated that modifications of the traditional MFx technique, such as the use of synthetic and autologous biological adjuvants may enhance the repair tissue quality, resilience and overall efficacy of the procedure[7,11]. Some researchers have purported that the suboptimal efficacy of the traditional marrow stimulating techniques may be attributed to the insufficient concentrations of MSCs and growth factors getting released from

subchondral marrow. To circumvent this limitation, it has been proposed that supplementation of MFx with intra-articular adjuvants in the form of platelet-rich plasma (PRP) or hyaluronic acid (HA) can improve the outcome[12-18]. In addition, augmentation of defect with scaffolding matrix or cell-free polymer-based implant can provide a bioreactor-like structure, over which the marrow elements get trapped, concentrated and thereby, facilitate the restoration of an effective cartilage layer[19-21]. MFx has also been combined with diverse cellular additives like bone marrow aspiration concentrates (BMAC), MSCs, and peripheral blood stem cells (PBSCs). While individual studies on these biological augmentation [popularly described as "microfracture plus" (MFx+)] techniques have demonstrated encouraging histological and clinical outcomes, our understanding regarding these techniques has been limited by substantial heterogeneity among the study cohorts and paucity of high quality, prospective trials.

The purpose of our study was to consolidate the available evidence; compare the clinical, functional and radiological outcomes of three different generations of MFx techniques (traditional MFx, MFx + acellular additives, and MFx + cellular additives); and to provide the best recommendations on their relative efficacies, advantages, complications and pitfalls in the management of cartilaginous defects of the knee joint.

MATERIALS AND METHODS

PROSPERO (International prospective register of systematic reviews) registration (CRD42022338329) was obtained for the study. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) for Network Meta-analysis (NMA) guidelines[22] were followed for the conduction and reporting of the study.

Search strategy

PubMed, EMBASE, Medline, Cochrane, and Scopus electronic databases were used for literature search. The search was performed by three reviewers independently. The search strategy was built using the MeSH terms and corresponding keywords for knee cartilage defects and their different treatment methods with related complications, employing different boolean operators, as required. The model search strategy is described in Supplementary Table 1 following the PRESS guidelines[23].

The following PICOTS criteria were used for the inclusion of studies: (1) Population: Patients with cartilage defects; (2) Intervention: Treatment methods including various generations of MFx technique; (3) Comparator: Placebo or one of the alternate aforementioned treatment methods; (4) Outcome: Functional, radiological, histological outcome, or complications; (5) Time frame: Inception to 2022; and (6) Study type: Randomized controlled trials (RCTs).

Prospective non-randomized studies, retrospective studies, studies without comparator groups, and pre-clinical or animal model studies were excluded. Disagreements on decisions during the article selection were resolved through discussions among the authors. De-duplication of the articles screened from electronic databases was done using citation manager-Zotero. References of the articles included for the study were screened manually to identify the studies missed during the primary search.

Extraction of data

Cochrane Consumers and Communication Group recommendations were followed for data extraction from the included studies. The following were extracted, and a master chart was prepared: (1) Study characteristics: Author name, country, publication year, number of patients in the study; (2) Baseline characteristics: Age for the individual treatment arms, gender proportions, cartilage defect size, interventions analyzed, and duration of follow-up; (3) Functional outcomes: Visual Analog Scale (VAS) score for pain, Western Ontario McMaster Universities Osteoarthritis Index score, Tegner score, Lysholm score, International Knee Documentation Committee (IKDC) score, Cincinnati score, and Knee Osteoarthritis Outcome Scale (KOOS) score; (4) Radiological outcomes: Magnetic resonance observation of cartilage repair tissue (MOCART) score, and successful magnetic resonance imaging (MRI)-based defect filling (≥ 2/3rd of the defect); and (5) Complications: Adverse events and failures (patient requiring revision surgeries).

Data extraction was performed independently by two reviewers. The different generations of MFx techniques, described in accordance with the ORG classification, include: First-generation MFx (MFX-I) representing the traditional MFx technique; second-generation MFx (MFX-II) involving MFX-I combined with acellular additives [such as PRP, HA, collagen, and procedures such as autologous matrix-induced chondrogenesis (AMIC)]; and third-generation MFx (MFX-III) involves combining MFX-I with cellular additives such as MSCs, BMAC, PBSCs, and stromal vascular fraction (SVF) [24].

We anticipated heterogeneity among the diverse studies in the duration of follow-up for the analysis of outcome measures. Therefore, we analyzed individual outcomes at short-term (1 years and 2 years), intermediate-term (5 years), and if available long-term (≥ 10 years), based on the available data at individual time points for the outcome concerned. The risk of bias of included studies was analyzed RoB2 tool from Cochrane group[25]. It was agreed upon that studies with a high risk of bias would be excluded from the study.

Statistical analysis

Relative effects of various treatment methods used in the management of cartilage defects were compared using NMA. Any bias in the outcome reporting of pairwise meta-analyses was reduced by employing multi-variate meta-analytic strategy[26]. Stata (16.1, Stata Corp LLC) was employed for the analysis. The outcomes, adjusted for the number of studies and number of subjects involved in the individual arms, were plotted into a network map. The difference between the direct effect (obtained by head-to-head comparisons) and the indirect effect estimates for the outcomes was used to

assess the global inconsistency in the network. If a treatment belonged to a closed loop of evidence in the network (with both direct and indirect effects available), their difference was calculated along with their 95% confidence intervals (95%CI) and *P* values. The *P* values estimated the likelihood of conflict to be attributable to chance. A $P \leq 0.05$ was considered to be suggestive of inconsistency; and the inconsistency model of NMA was utilized. The inconsistency was further explored with sensitivity analysis using the network side-split method[27]. If $P > 0.05$, a consistency model of NMA was employed.

Forest plot, using the pooled log odds ratio (OR) or weighted mean difference (WMD), was constructed for reporting the events and continuous outcomes (along with their 95%CI) for the individual arms in the network in order to demonstrate their effect on the outcome analysed (as compared to a constant comparator). We also described an individual pairwise comparison within the network. Random effects model of analysis using the common variance approach was employed in view of the heterogenicity in involved treatment arms[28]. Funnel plot for the outcomes in the included studies was employed for assessing the publication bias. CINeMA approach[29] using CINeMA app[30] was employed to analyse the confidence of the evidence generated.

RESULTS

Overall, 9416 articles were shortlisted for initial screening. De-duplication resulted in 3584 articles. Title and abstract screening excluded 3231 articles. Among them, 353 articles qualified for full-text review; and 44 eligible RCTs[4,9,13,15,19,20,31-68] with 2629 included patients qualified for inclusion in the study. PRISMA flow diagram for the inclusion of studies is shown in Figure 1.

The included studies reported at least one of the generations of MFx employed in cartilage defect management. The baseline characteristics of the studies included in the network are presented in Table 1. Norway ($n = 6$), Germany ($n = 5$), and United States ($n = 5$) were the leading countries reporting the highest number of RCTs in the field. The network plot has been presented in Figure 1. The network had 36 possible pair-wise comparisons, among which, 14 had direct evidence data. The network had 42 two-armed studies and 2 multi-armed studies. We did not find significant variability among the characteristics of the included patients in the network concerning age and gender proportions. The mean age of the patients included in the trials was 39.40 (± 9.46) years. The mean follow-up in the included trials ranged between 1 and 15 years.

Quality assessment

None of the included studies demonstrated high risk of bias to warrant exclusion from the study. The risk of bias in the pairwise comparisons is presented in Supplementary Figure 1. We did not find any significant publication bias using the funnel plot for most of the outcome measures analyzed. When publication bias was noted, we adjusted using the "trim and fill" method to identify the missing studies and their effects on the overall estimate. We did not find any significant impact of the missing studies on the overall outcomes, as shown in Supplementary Figure 2.

Network analysis results

We performed a pooled NMA using a frequentist approach to every outcome of interest. Among all the treatment arms in the network, MFX-I had high data strength as compared with all the other comparators (as shown in the network plots in Supplementary Figure 3). Therefore, MFX-I is taken as the constant comparator and all the outcomes have been reported in comparison to the performance of MFX-I. The outcomes have been analyzed in terms of pain, functional outcomes, radiological outcomes, adverse effects, and failures.

Pain: Inference from the VAS score is taken into consideration for pain outcomes. VAS score was reported at one year in 13 studies[4,15,33,38,41,44,45,49,53,55-58] involving 676 patients, at two years in 10 studies[4,15,33,38,41,45,50,53,57,68] involving 690 patients and at 5 years in 3 studies[39,41,54] involving 297 patients. The pooled forest plot of the VAS score outcome based on the aforementioned follow-up time points is presented in Figures 2, 4, and 5 respectively. Although we did not note a statistically significant improvement in the pain reduction with the advancements to the traditional MFx, the SUCRA ranking of the interventions were consistent in favouring the higher generations in the following order MFX-III > MFX-II > MFX-I as shown in Table 2.

Functional outcomes: The functional outcomes were reported using KOOS, Lysholm score, IKDC score, and Cincinnati score. Figure 2 shows the pooled forest plot of various scores. KOOS score was reported at one year in 8 studies[32,33,44,46,51,55-57] involving 569 patients, and at 2 years in 4 studies[32,33,51,57] involving 361 patients. Lysholm score was reported at 1 year in 10 studies[4,33,35,41,44,47,48,53,59,65] involving 499 patients, and at 2 years in 8 studies[4,15,33,39,41,47,53,59] involving 516 patients. IKDC score was reported at 1 year in 15 studies[15,35,37,43-45,56-60,64,66,67] involving 631 patients, at 2 years in 13 studies[15,37,39,43,45,50,57-59,64,66-68] involving 782 patients, and at 5 years in 4 studies[39,54,58,59] involving 295 patients. Cincinnati score was reported at 1 year in 3 studies[31,38,65] involving 117 patients, and at 2 years in 4 studies[31,38,39,50] involving 349 patients.

The functional outcomes reported at 1, 2, and 5-year time points using the aforementioned scores were clubbed together for the sake of understanding (despite the limitation of such an approach), in view of the heterogenicity in the reporting of functional outcomes among the reviewed studies.

One-year functional outcomes: The pooled forest plot of the functional outcomes, sub-grouped based on the individual scores at 1 year, is presented in Figure 2. We observed statistically significant outcome in the higher generations of MFx

Table 1 Characteristics of included studies in the network meta-analysis, each row depicts the individual comparator arm in the studies included

Ref.	Country	Study design	Sample size		Treatment		Mean age		Female		Mean defect size		Follow-up (months)
			Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	
Volz *et al*[31], 2017	Germany	RCT	34	13	AMIC	Microfracture	40.0	36.5	7	3	3.9	2.9	60
Niemeyer *et al* [32], 2019	Germany	RCT	52	50	MACI	Microfracture	36.0	37.0	19	22	2.7	2.4	24
Fossum *et al* [33], 2019	Norway	RCT	21	20	ACI-C	AMIC	37.2	38.3	7	12	4.9	5.2	24
Ulstein *et al*[34], 2014	Norway	RCT	11	14	Microfracture	AOT	31.7	32.7	11	9	2.6	3.0	120
Visna *et al*[35], 2004	Czech Republic	RCT	25	25	Autologous chondrograft transplantation	Microfracture	29.4	32.2	7	9	4	3.3	12
Assche *et al*[36], 2010	Belgium	RCT	33	34	ACI-P	Microfracture	34.0	34.0	11	10	2.5	2.3	24
Saw *et al*[37], 2013	United States	RCT	24	25	Microfracture with HA	Microfracture with PBSC	42.0	38.0	17	15	NA	NA	18
Anders *et al*[38], 2013	Germany	RCT	22	8	AMIC	Microfracture	41.0	38.0	17	15	3.7	3.5	24
Lee *et al*[15], 2013	Republic of Korea	RCT	25	24	Microfracture	Microfracture with PRP	46.0	46.0	10	10	3.0	3.0	24
Brittberg *et al* [39], 2018	Sweden	RCT	65	63	MACI	Microfracture	38.0	34.0	23	20	5.1	4.9	60
Lim *et al*[40], 2012	South Korea	RCT	30	22	Microfracture	AOT	32.9	30.4	12	10	2.7	2.7	60
				18		ACI-P		25.1		8		2.8	60
Knutsen *et al* [41], 2007	Norway	RCT	40	40	ACI-P	Microfracture	33.3	31.1			5.0	5.0	60
Knutsen *et al* [42], 2016	Norway	RCT	40	40	ACI-P	Microfracture	33.3	31.1			5.0	5.0	180
Liu *et al*[43], 2021	Taiwan	RCT	10	5	Kartigen	Microfracture	54.8	67.8	5	3	2.9	1.0	24
Yoon *et al*[44], 2020	Republic of Korea	RCT	20	10	ACI-CCP	Microfracture	41.5	47.2	6	7	3.5	2.5	12

Kon *et al*[45], 2018	Italy	RCT	51	49	Collagen HA	Microfracture	34.0	35.2	15	18	3.4	3.4	24
Vanlauwe *et al* [46], 2011	Belgium	RCT	51	61	ACI-P	Microfracture	33.9	33.9	22	20	2.6	2.4	60
Stanish *et al*[20], 2013	Canada	RCT	41	39	Microfracture with BST-CarGel	Microfracture	35.1	37.2	18	14	NA	NA	12
Basad *et al*[47], 2010	Germany	RCT	40	20	MACI	Microfracture	33.0	37.5	15	3	7.0	7.0	24
Solheim *et al* [48], 2018	Norway	RCT	20	20	Microfracture	Mosaicplasty	35.0	31.0	6	6	4.0	4.0	180
Bisicchia *et al* [49], 2020	Italy	RCT	20	20	Microfracture with SVF	Microfracture	49.8	46.1	8	7	3.2	3.1	12
Saris *et al*[50], 2014	Netherlands	RCT	72	72	MACI	Microfracture	34.8	32.9	27	24	4.9	4.7	24
Saris *et al*[51], 2008	Netherlands	RCT	57	61	ACI-P	Microfracture	33.9	33.9	22	20	2.6	2.4	12
Saris *et al*[9], 2009	Netherlands	RCT	57	61	ACI-P	Microfracture	33.9	33.9	22	20	2.6	2.4	36
Qiao *et al*[52], 2020	China	RCT	10	10	Microfracture	Microfracture with HA	62.3	59.7	7	5	4.0	4.0	12
				10		Microfracture with MSC		62.0		7		4.0	12
Nguyen *et al* [53], 2017	Vietnam	RCT	15	15	Microfracture with SVF	Microfracture	58.6	58.2	12	12	NA	NA	18
Lim *et al*[54], 2021	Republic of Korea	RCT	43	46	Microfracture with MSC	Microfracture	55.3	54.4	28	30	4.9	4.0	60
Venosa *et al*[55], 2022	Italy	RCT	19	19	Microfracture with PRP	Microfracture with MSC	56.4	55.8	7	10	1.0	1.0	12
Shive *et al*[19], 2015	Canada	RCT	34	26	Microfracture with BST-CarGel	Microfracture	34.3	40.1	12	12	2.4	2.0	60
Koh *et al*[13], 2016	Republic of Korea	RCT	40	40	Microfracture with MSC	Microfracture	39.1	38.4	24	26	4.8	4.6	24
Knutsen *et al*[4], 2004	Norway	RCT	40	40	ACI-P	Microfracture	33.0	31.1	16	16	5.1	4.5	24
Kim *et al*[56], 2017	South Korea	RCT	14	14	Microfracture	Microfracture with Collagen	55.7	55.4	0	1	2.9	3.6	12
Kim *et al*[57],	South Korea	RCT	48	52	Microfracture	Microfracture	51.7	48.9	9	12	4.6	3.9	24

2020						with Collagen							
Kane *et al*[58], 2018	United States	RCT	21	9	Neocart	Microfracture	41.4	38.8	2	3	2.2	1.7	60
Ibarra *et al*[59], 2021	United States	RCT	24	24	MACI	Microfracture	33.7	35.8	7	10	1.9	1.7	72
Hashimoto *et al* [60], 2019	Japan	RCT	7	4	Microfracture with MSC	Microfracture	42.6	46.3	4	0	3.0	4.4	12
Gudas *et al*[61], 2006	Lithuania	RCT	28	29	AOT	Microfracture	24.6	24.3	10	12	2.8	2.7	36
Gudas *et al*[62], 2013	Lithuania	RCT	28	29	AOT	Microfracture	24.6	24.3	10	12	2.7	2.8	120
Gudas *et al*[63], 2005	Lithuania	RCT	29	28	Microfracture	AOT	24.3	24.6	12	10	2.8	2.7	36
Glasbrenner *et al* [64], 2020	Germany	RCT	12	12	Microfracture	Microfracture with BMAC	36.7	47.9	3	6	1.7	1.7	12
Dasar *et al*[65], 2016	Turkey	RCT	20	20	Microfracture	Carbon fibre rod	36.4	38.5	15	15	3.5	4.0.	24
Crawford *et al* [66], 2012	United States	RCT	21	9	NeoCart	Microfracture	41.0	39.0	2	3	2.8	2.5	24
Cole *et al*[67], 2011	United States	RCT	9	20	Microfracture	MACI	33.0	32.7	4	6	3.4	2.7	24
Chung *et al*[68], 2014	South Korea	RCT	24	12	Microfracture with BMAC	Microfracture	47.4	44.3	10	10	1.3	1.5	24

ACI: Autologous chondrocyte implantation; ACI-C: ACI with collagen cover; ACI-P: ACI with periosteal cover; AMIC: Autologous matrix induced chondrogenesis; BMAC: Bone marrow aspiration concentrate; CCP: Cultured chondrocyte pellet; HA: Hyaluronic acid; MACI: Matrix-induced autologous chondrocyte implantation; MFx: Microfracture; MSC: Mesenchymal stromal cell; NA: Not available; OAT: Osteochondral autograft/allograft transfer; PRP: Platelet-rich plasma; RCT: Randomized controlled trial; SVF: Stromal vascular fraction.

evaluated with IDKC score (WMD = 3.40; 95%CI: 0.65, 6.16; P = 0.045; without significant heterogeneity). However, the difference was not clinically relevant; and less than the minimum clinical difference for the outcome concerned. Although we did not note a statistically significant improvement in most of the functional outcomes with the advancements to the traditional MFx; we observed that (with the exception of Lysholm score) the SUCRA ranking of the interventions consistently favoured the higher generations in the following order: MFX-III > MFX-II > MFX-I (Table 2).

Two-year functional outcome: The pooled forest plot of the functional outcomes, sub-grouped based on the individual scores at 2 years, is presented in Figure 4. We did not note statistically significant difference with the higher generations of MFx with regard to the functional scores such as KOOS, Lysholm score, IDKC score, and Cincinnati score. Nevertheless, similar to the functional outcome at 1-year time point; SUCRA rankings of interventions were consistent in

Table 2 Network meta-analysis summary and ranking of interventions based on the SUCRA scores

Follow-up	Outcome	Intervention	Coeffecient	Standard error	SUCRA ranking
1 yr	VAS	mFX-II	0.139	0.296	MFX-III > MFX-II > MFX-I[1]
		mFX-III	0.023	0.457	
	KOOS	mFX-II	-2.296	2.835	MFX-III > MFX-II > MFX-I[1]
		mFX-III	-2.296	5.775	
	Lysholm score	mFX-II	-17.008	11.160	MFX-I > MFX-III > MFX-II[3]
		mFX-III	-5.660	4.427	
	IKDC score	mFX-II	2.782	1.811	MFX-III > MFX-II > MFX-I[1]
		mFX-III	4.339	2.228	
	Cincinnati score	mFX-II	4.257	4.543	MFX-II > MFX-I[1]
	MRI filling	mFX-II	0.383	0.312	MFX-III > MFX-II > MFX-I[1]
		mFX-III	1.860	1.770	
	MOCART score	mFX-II	11.950	7.419	MFX-III > MFX-II > MFX-I[1]
		mFX-III	30.700	14.168	
	Adverse events	mFX-II	-0.529	0.373	MFX-III > MFX-II > MFX-I[1]
		mFX-III	-0.138	0.546	
	Failure events	mFX-II	-0.520	0.777	MFX-II > MFX-I[1]
2 yr	VAS	mFX-II	0.377	0.452	MFX-III > MFX-II > MFX-I[1]
		mFX-III	0.690	0.795	
	KOOS	mFX-II	1.899	2.971	MFX-II > MFX-I[1]
	Lysholm score	mFX-II	0.550	6.952	MFX-II > MFX-I > MFX-III[3]
		mFX-III	-19.560	9.814	
	IKDC score	mFX-II	4.548	4.545	MFX-III > MFX-II > MFX-I[1]
		mFX-III	7.947	9.405	
	Cincinnati score	mFX-II	-6.227	3.775	MFX-II = MFX-I[2]
	MRI filling	mFX-II	0.840	0.468	MFX-II > MFX-III > MFX-I[3]
		mFX-III	0.418	0.508	
	MOCART	mFX-III	10.600	9.281	MFX-III > MFX-I[1]
5 yr	VAS	mFX-III	1.900	1.917	MFX-III > MFX-I[1]
	IKDC score	mFX-III	3.000	2.121	MFX-III > MFX-I[1]

[1]Newer generations better than older generations.
[2]Newer generations equal to older generations.
[3]Newer generations worse than older generations.
VAS: Visual Analog Scale; mFX: Microfracture; KOOS: Knee Osteoarthritis Outcome Scale; IKDC: International Knee Documentation Committee; MRI: Magnetic resonance imaging; MOCART: Magnetic resonance observation of cartilage repair tissue.

favouring the higher generations in the following order MFX-III > MFX-II > MFX-I (for all outcome measures except the Lysholm score (Table 2).

Five-year functional outcomes: We did not have sufficient data points to evaluate mid-term and long-term functional outcomes. However, based on the available data, there was no significant change in the functional outcome with the higher generations of MFx, as compared to the traditional technique (based on IKDC score; Figure 5). Nevertheless, as with the earlier time points, the SUCRA ranking of interventions favoured the higher generations (in the order MFX-III > MFX-I; Table 2).

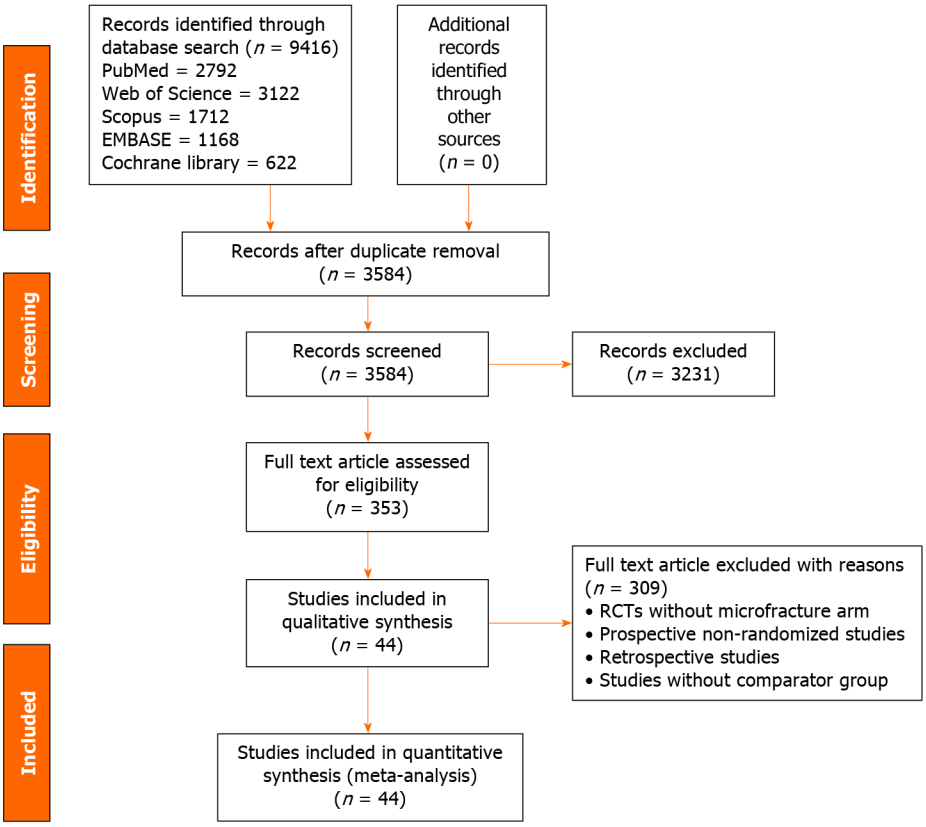

Figure 1 Preferred Reporting Items for Systematic Review and Meta-analysis flow diagram of selection of studies included in the analysis. RCT: Randomized controlled trial.

Radiological outcomes

The MOCART (magnetic resonance observation of cartilage repair tissue) Score and MRI defect filling (> 2/3rd) have been used to report the radiological outcomes in the included studies. The MOCART score was reported at 1 year in 8 studies [4,32,44,56,57,59,60,65] involving 439 patients, and at 2 years in 3 studies[13,32,59] involving 230 patients. The MRI-based defect filling was reported at 1 year in 17 studies[19,20,31,37,38,40,43-45,47,56,57,60,62-64,67] involving 847 patients, and at 2 years in 10 studies[13,19,31,38,45,47,50,64,67,68] involving 610 patients.

The pooled forest plots of the radiological outcomes, sub-grouped based on the individual scores at 1- and 2-year time points, are presented in Figures 3 and 4, respectively. We observed statistically better MOCART score in the higher generations of MFx (WMD = 17.44; 95%CI: 0.72, 34.16; P = 0.025; without significant heterogeneity) at 1 year. However, the difference was not maintained at 2 years. Although we did not note a statistically significant improvement in the MRI-filling with the advancements to the traditional MFx, the SUCRA ranking of the interventions were consistent in favouring the higher generations in the following order MFX-III > MFX-II > MFX-I (Table 2).

Complications

Adverse events: The adverse events following the compared interventions were reported in 32 studies[9,19,20,31-33,37-39,43,44,46-48,50-55,57,58,60-63,65-67,69-75] involving 1752 patients. Figure 3 shows the pooled forest plot of the reported complications for the analyzed interventions. In comparison with MFX-I, there was no statistically significant difference in the reported rates of adverse events in the higher generations. On the other hand, the SUCRA ranking of the interventions favoured the higher generations in the following order MFX-III > MFX-II > MFX-I (Table 2); thereby, highlighting the safety of the higher generations in comparison with the traditional technique.

Failures: The need for subsequent procedures following the interventions was considered as treatment failure, and the same was reported in 31 studies[4,31,33,34,38-42,46,48,57,59,61,63-65,69,72,73,76,77] involving 1059 patients. Figure 3 shows the pooled forest plot of the failure events for the reported interventions. In comparison with MFX-I, there was no statistically significant difference in the failure events among the higher generations of MFx techniques. Moreover, the SUCRA ranking of the interventions favoured the higher generations in the following order MFX-III > MFX-II > MFX-I (Table 2); thus, highlighting the reliability of the higher generations in comparison to the traditional technique.

Sensitivity & subgroup analysis

We did not observe significant heterogeneity across various outcomes analyzed in the network (based upon the heterogeneity values in the corresponding individual forest plots of pairwise comparisons of interventions). We sub-grouped and analyzed the studies based on the outcome measures and follow-up time point in order to avoid any heterogeneity in

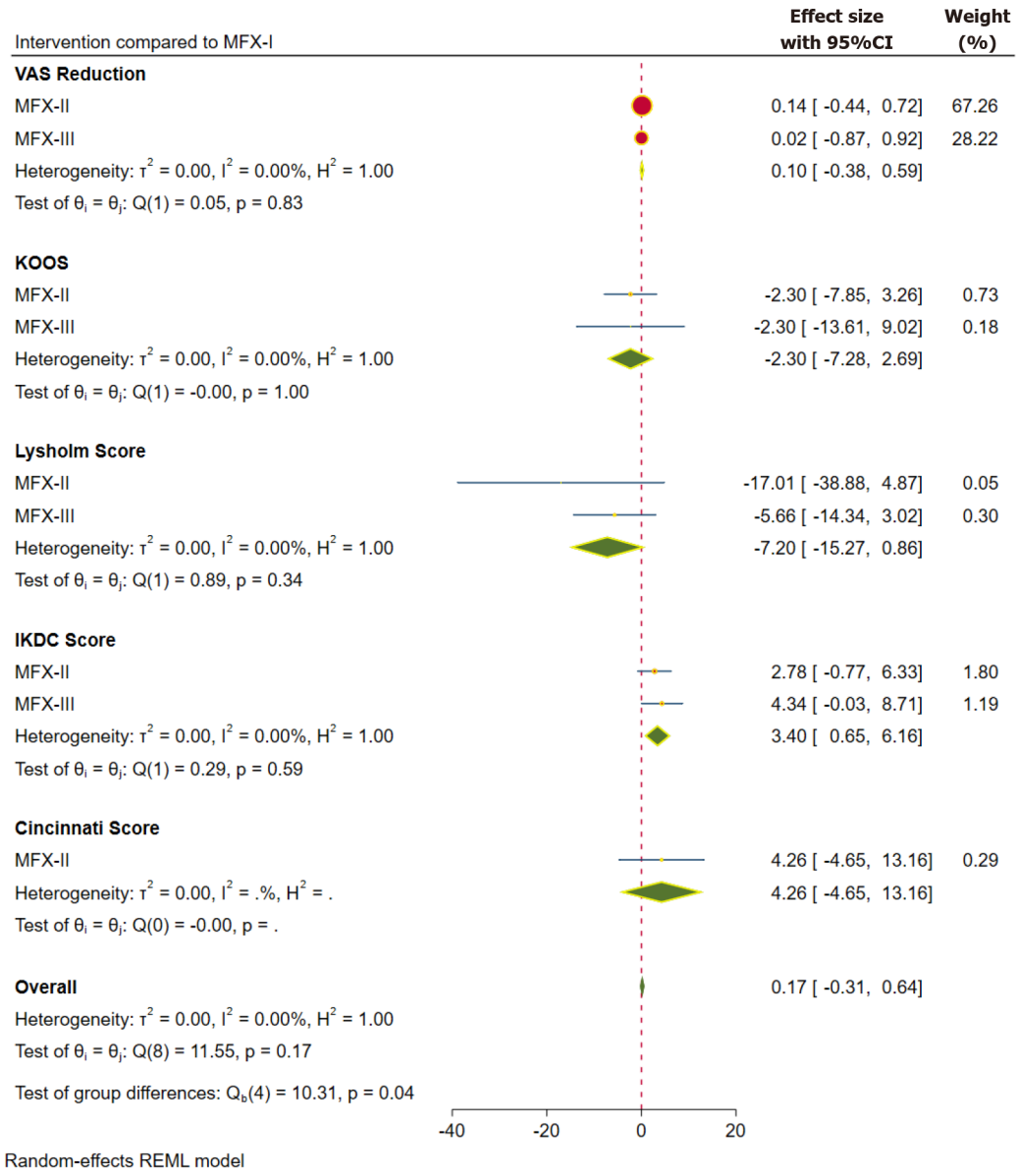

Figure 2 Forest plot comparing the generations of microfracture for the functional outcomes reported at 1 year among the included studies in the network. 95%CI: 95% confidence interval; VAS: Visual Analog Scale; MFx: Microfracture; KOOS: Knee Osteoarthritis Outcome Scale; IKDC: International Knee Documentation Committee; REML: Restricted maximum likelihood.

the pooled results.

Consistency

We did not observe any significant evidence of global inconsistency, which could have affected the transivity of the network results. The consistency analysis was performed for the individual outcomes; and the chi-square values in the corresponding pair-wise comparison forest plots were presented. We noted the indirect pooled estimates to have wider CI compared to direct estimates in some of the paired networks analysed (although without any evidence of systematic differences concerning the potential effect modifiers). We considered these apparent inconsistencies to be the effect of true differences between the direct and indirect estimates. The indirect estimates were considered to reflect a more precise estimate, since they were from a network involving a larger number of studies.

Confidence in evidence

Upon grading the paired comparisons in the network using the CINeMA approach, a "high" confidence was noted across a majority of the paired comparisons (Table 3). However, some of the comparison pairs demonstrated "moderate" confidence. The lack of precision was the most common reason, which downgraded the quality of evidence in the indirect estimates, in view of wider CIs extending on either side of the axes. We also observed some concerns due to certain "within-study bias", following selective reporting of some of the outcome measures.

Table 3 Risk of bias for all the pairwise comparisons for functional outcome from the network assessed with Cochrane's Confidence in network meta-analysis approach

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reasons for downgrading
MFx-I: MFx-II	7	Some concerns	Some concerns	No concerns	Major concerns	Some concerns	No concerns	Moderate	Imprecision in results
MFx-I: MFx - III	1	Some concerns	Some concerns	No concerns	Major concerns	Some concerns	No concerns	Moderate	Imprecision in results
MFx-II: MFx - III	1	Some concerns	Some concerns	No concerns	Major concerns	Some concerns	No concerns	Moderate	Imprecision in results

MFx: Microfracture.

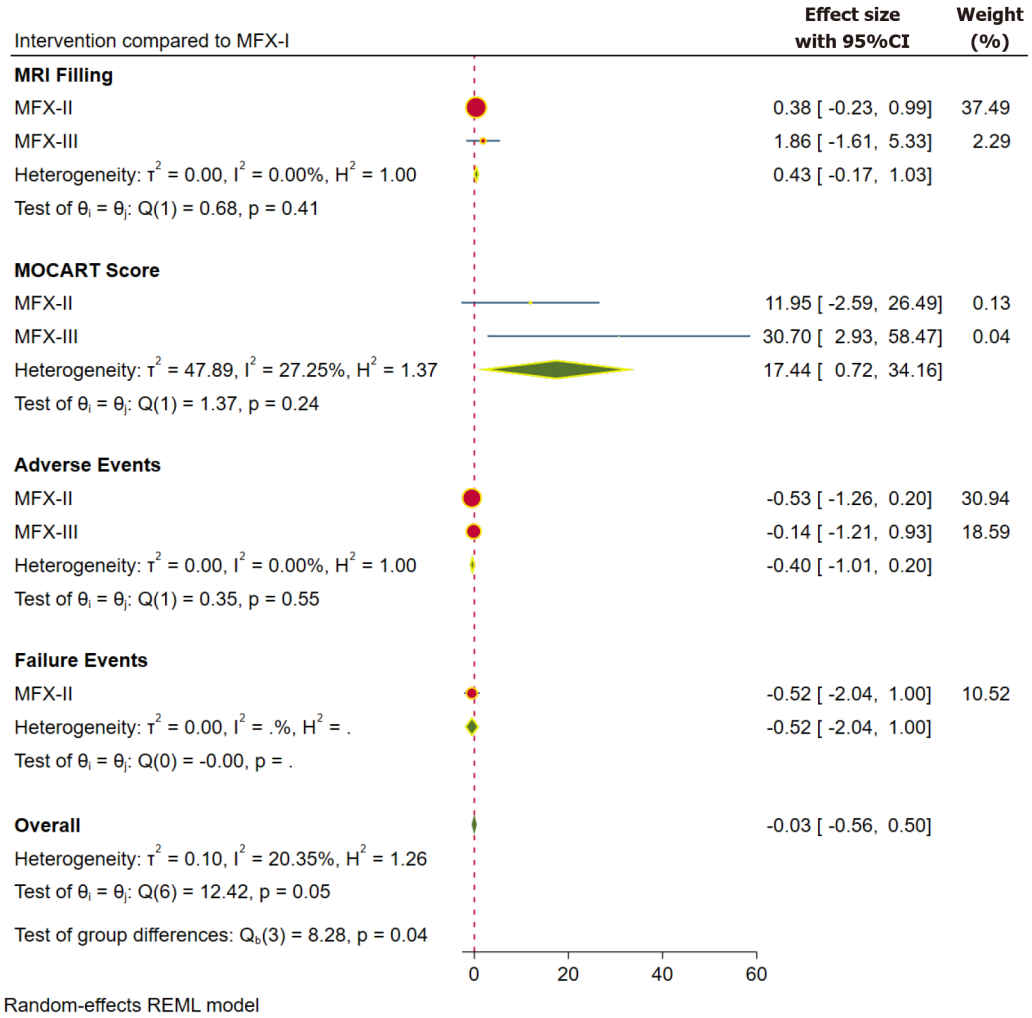

Figure 3 Forest plot comparing the generations of microfracture for the radiological outcomes reported at 1 year among the included studies in the network. 95%CI: 95% confidence interval; MFx: Microfracture; MRI: Magnetic resonance imaging; MOCART: Magnetic resonance observation of cartilage repair tissue; REML: Restricted maximum likelihood.

DISCUSSION

Chondral lesions have been reported in 60% of patients undergoing arthroscopic procedures of the knee; and such defects are described as one of the leading causes of chronic pain[78-81]. These defects may result from acute trauma, repetitive microtrauma, osteochondritis dessicans or early osteoarthritis; and can produce symptoms like pain, swelling, catching, stiffness and locking[33]. Hunter *et al*[82,83] described the challenge of cartilaginous injury by stating that, "once the cartilage is destroyed, it never recovers". These observations still hold true; and the avascular as well as aneural nature of

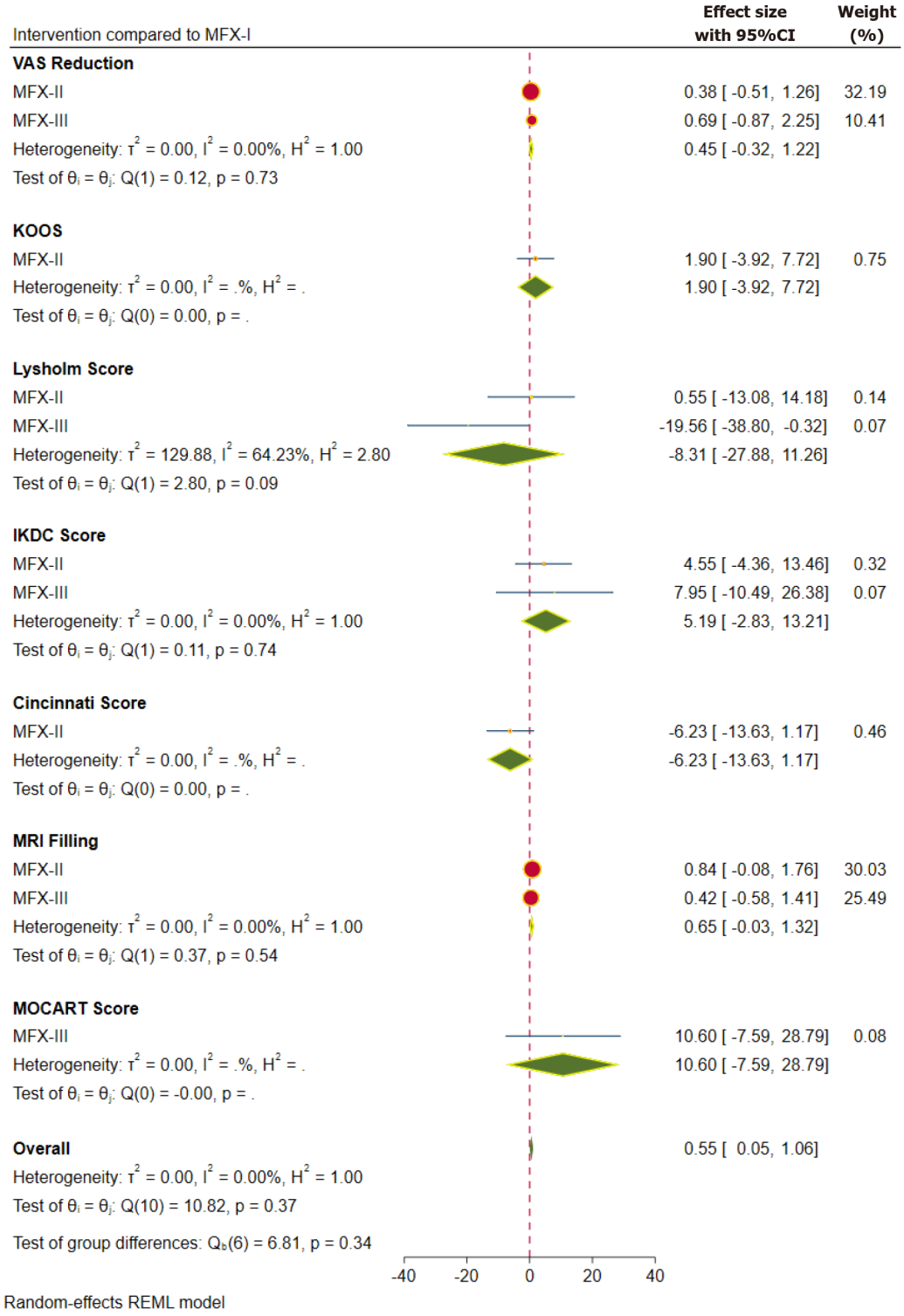

Figure 4 Forest plot comparing the generations of microfracture for the functional and radiological outcomes at 2 years reported among the included studies in the network. 95%CI: 95% confidence interval; VAS: Visual Analog Scale; MFx: Microfracture; KOOS: Knee Osteoarthritis Outcome Scale; IKDC: International Knee Documentation Committee; MRI: Magnetic resonance imaging; MOCART: Magnetic resonance observation of cartilage repair tissue; REML: Restricted maximum likelihood.

cartilage substantially limits its ability to self-regenerate[84]. If left untreated, a transgressed cartilage gradually results in severe osteoarthritis of the joint and ensuing long-standing disability[85].

Superficial cartilage deficiencies do not induce a local inflammatory response; therefore, despite proliferation of matrix molecules and chondrocytes, the surface is not adequately restored[86]. When the cartilage defect penetrates the subchondral plate, the vascularized bone marrow can enable the formation of clot rich in chondroprogenitor cells, fibrin and bioactive molecules; which in turn, facilitates the formation of type I collagen and fibrocartilage[87]. This is the rationale underlying the MFx technique, which has traditionally remained the first-line treatment for small to medium-sized defects[88]. The purported benefits of the procedure include low cost, easy technique and proven improvement in

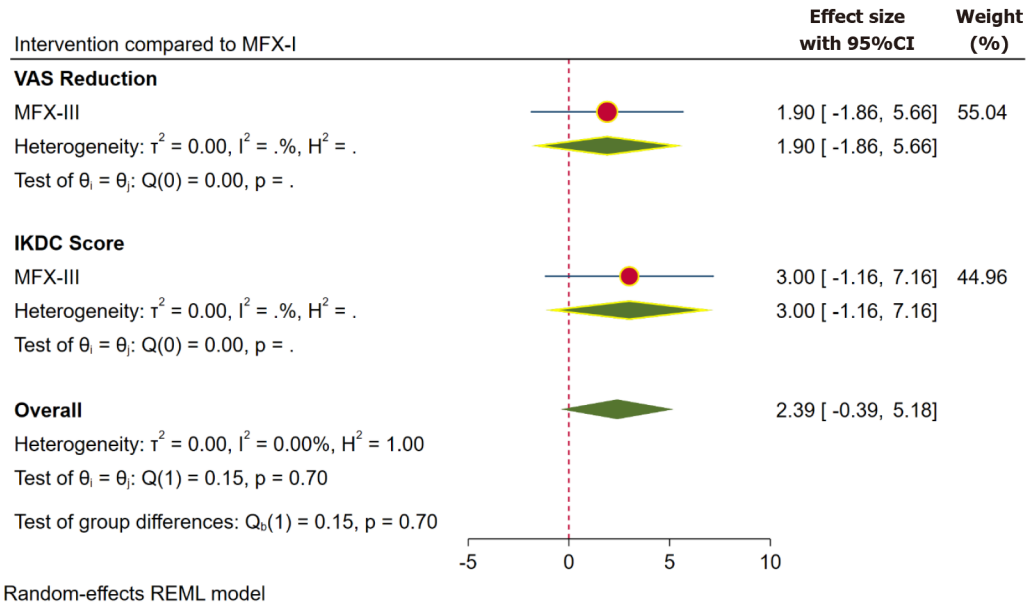

Figure 5 Forest plot comparing the generations of microfracture for the functional outcomes reported at 5 years among the included studies in the network. 95%CI: 95% confidence interval; mFX: Microfracture; IKDC: International Knee Documentation Committee; REML: Restricted maximum likelihood.

short-term outcome[87,88]. Nevertheless, 47% to 80% of patients have been reported to demonstrate substantial functional deterioration at 18 to 36 months post-surgically[10], which may be attributed to the poor viscoelastic properties of the restored fibrocartilage[89]. Since the initial description of MFx technique, multitudinous attempts have been made in the fields of tissue engineering and cartilage repair in an attempt to find the "holy grail", which enables the restoration of hyaline cartilage that can consistently integrate into the deficiency[42].

Evolution of MFx

In the traditional MFx technique described by Steadman *et al*[3], the debridement of the unstable cartilaginous tissues is initially performed arthroscopically; and a well-shouldered vertical wall is created around the periphery of the lesion. Following this, layers of calcified cartilage are removed using a curette. An arthroscopic awl is then utilized in a direction perpendicular to the bone in order to create holes in the subchondral plate around 3-4 mm apart (ascertaining that the interposed subchondral bone between the MFx perforations is maintained intact). Alternately, microdrilling using a 1.5 mm drill may be performed to perforate the subchondral plate to a depth of 1 cm.

While lesions smaller than 2 cm^2 in low-demand individuals are amenable to treatment with traditional MFx technique; lesions larger than 4 cm^2 have been purported to require additional adjuvant modalities too[90]. Diverse acellular biomaterials such as alginate, collagen, tri-copolymer and poly-lactic-glycolic acid have been utilized for engineering of cartilaginous tissues[91]. These tissues serve as carriers for delivery of cells and growth factors; as well as provide an appropriate milieu for tissue regeneration[92].

The cell therapy for cartilage repair was initially proposed in the 1980s using the technology of tissue engineering[93]; and cellular therapeutic innovation was eventually realized in 1994, when Brittberg *et al*[94] described the ACI technique. Further on, scaffold-based ACI (matrix-induced ACI-MACI: FDA-approved in 2016) technique has also been described as a modification of the traditional MFx. The discovery of adult stem cells resulted in a paradigm shift in the field of regenerative medicine[95]. A variety of stem cell-based therapies involving multipotent MSCs implantation (like bone marrow, adipose tissue, synovium, periosteum, peripheral blood, *etc*.) have been employed for cartilage repair. The chondrogenesis and development of neo-cartilaginous tissues from such undifferentiated MSCs can be guided using growth factors, and other biophysical or biomechanical stimuli[96,97].

As an alternative form of cell-based therapy, Gobbi *et al*[10] described the technique of implanting the bone marrow aspirate concentrate delivered *via* HA-based scaffold (HA-BMAC) over the micro-fractured area. Such an approach relies on the presence of MSCs and growth factors at the deficient zone so as to steer chondrogenesis. They concluded that such an approach yielded successful medium-term clinical outcome with restoration of durable cartilage, irrespective of the size and age of the lesion.

Despite such extensive publications, there has been a substantial dearth of large-scale, high-quality RCTs on this subject. In a recent systematic review; among 540 reviewed manuscripts, only 10 studies were found to be methodologically sufficient to be included for final analysis. The current evidence on this subject is therefore, still largely unclear [98]. The purpose of the current NMA was to comprehensively analyse the existing literature on chondral injuries of the knee; and comparatively evaluate the histological, radiological and clinical outcome following 3 different generations of MFx, namely traditional MFx (MFx-I), modified MFx technique using acellular adjuvant (MFx-II); and modified MFx technique using cellular adjuvant (MFX-III).

Observations from our study

Clinical and functional outcome: Overall, in our meta-analysis, we compared the pain scores and functional outcome measures (KOOS, Lysholm score, IKDC score, and Cincinnati scores) among the three generations of MFx. We could clearly observe a trend of improved pain scores and functional outcome scores (KOOS, IKDC and Cincinnati scores) with the use of cellular adjuvants (MFx-III-MSC, BMAC, PBSC, and SVF). Although the difference in the pain and functional scores improved with the use of acellular adjuvants (such as PRP, HA, collagen, and AMIC) too in comparison with traditional MFx, the differences were not as substantial as for cellular adjuvants.

This observation is in concurrence with a majority of the studies, which have demonstrated overall improved clinical outcome with acellular (MFx-II) adjuvants. In a prospective, multicenter clinical trial[31], AMIC with biodegradable type I/III collagen membrane showed significantly improved longer-term radiological (MRI defect filling) and functional outcome (as assessed by Cincinnati and modified ICRS scores) at the 5-year time point, in comparison with MFx-I. In another recent RCT, Shive *et al*[19] concluded that the use of BST-CarGel (soluble polymer scaffold containing polysaccharide chitosan dispersed in uncoagulated blood) following MFx leads to improved cartilage resurfacing and wound healing. On a similar note, various prospective studies have also reported meliorated outcome (clinical and radiological) following the use of diverse cellular components after MFx (MFx-III). Some such cellular components, which have been successfully tried in cartilage defects, include single-stage cell-based therapy using autologous cartilage fragments (cartilage autograft implantation system-CAIS)[67], collagen-covered ACI (ACI-C), AMIC[33], micro-fragmented stromal-vascular fraction (rich in adipose-derived MSCs-ADMSC)[49], and tri-layered collagen hydroxyapatite biomimetic osteochondral scaffold (CHAS) seeded intra-operatively with autologous chondrocytes (AC) or filtered bone marrow stem/stromal cells (fBMSC)[99]. In a prospective series by Liu *et al*[43], it was demonstrated that the application of Kartigen (matrix with autologous bone marrow MSC-derived chondrocyte precursors embedded in atelocollagen) enabled the restoration of columnar surface of articular cartilage, collagen type 2 and glycosaminoglycan in similar composition to native hyaline cartilage (on histology).

Radiological outcome: A majority of the studies reported on MOCART score and MRI filling defect during the follow-up. There was a statistically significant improvement in the MOCART score at the end of 1 year in patients following the use of cellular adjuvants after MFx, indicating a substantially improved cartilage tissue quality and integration. Although the radiological outcome scores at the subsequent follow-up time points were not statistically different; similar to the clinical outcome, there was a definitive trend towards better outcome after the use of cellular and acellular adjuvants following MFx (cellular > acellular).

In a prospective randomized study by Ibarra *et al*[59], it was concluded that structural outcome (as assessed by MRI-T2 mapping and MOCART score) and significantly improved clinical outcome (as evaluated by KOOS subscale and Tegner scale) at 1 to 6 years and 4 to 6 years, respectively in patients undergoing matrix-assisted autologous chondrocyte transplantation, as compared with traditional MFx. Patients undergoing adjuvant cell therapy also demonstrated higher response and lower failure rates in this series. Similar prospective cohort studies have demonstrated improved cartilage fill on T2WI MRI and mean MOCART score following surgical treatment with PRP-loaded scaffold (MFx-II)[100], scaffold augmentation using BMAC (MFx-III)[100] and transplantation of autologous BMSCs (BMSC-MFx-III)[60].

Complications and adverse events: Based on our network analysis, we could also clearly identify mitigated complication and failure rates with the higher generations of MFx (although the differences were not statistically significant. In a prospective series by Martinčič *et al*[99], tri-layered CHAS seeded intra-operatively with AC or fBMSC demonstrated significantly improved outcome, in comparison with MFx. In this study, blood soaking of the scaffold prior to cell seeding substantially reduced early post-operative complications like synovitis and arthrofibrosis.

Limitations: Though our study is one of the most comprehensively-performed reviews of the existing literature on this subject, there are certain limitations. The long-term data on histological and radiological outcomes following recent generations of MFx are limited. There is substantial paucity as well as heterogeneity in the reporting on the diverse functional outcome measures, which prevented uniform comparison of events.

Current status and future directions: Based on our comprehensive review and NMA, we could conclude that the use of acellular and cellular adjuvants (2nd and 3rd generation) marginally improves the overall clinical status (pain and functional scores) and radiological outcome (MOCART score and MRI-filling) in patients undergoing MFx for cartilage defects of the knee. The safety and efficacy of the higher generation MFx procedures are also clearly evident from our review. However, there is a substantial potential for further improvement in the cellular components (chondrocytes over other cellular lineage), culture or processing methodology, delivery modalities (including appropriate scaffolds); as well as better surgical techniques[6].

CONCLUSION

The use of acellular and cellular adjuvants (2nd and 3rd generation) has shown only marginal improvement in the clinical (pain and functional scores) and radiological outcome (MOCART score and MRI-filling) in patients undergoing MFx for cartilage defects of the knee.

ARTICLE HIGHLIGHTS

Research background

We have noted improvements in the traditional microfracture (MFx) techniques over the decades of its routine use in the management of cartilage defects. The recent generations include the addition of acellular components and cellular components to the cartilage defect. However, the effectiveness of these modifications is not explored further.

Research motivation

To explore the clinical effectiveness of the various generations of the MFx technique to understand their clinical effect in the management of cartilage defects.

Research objectives

To comparatively explore the clinical, radiological and histological outcomes along with the complications reported in the various generations of MFx in the context of the management of cartilage defects.

Research methods

We made a systematic review by utilizing the databases such as PubMed, EMBASE, Web of Science, Cochrane, and Scopus to identify the randomized controlled trials (RCTs) reporting the outcomes of utilization of various generations of MFx in the management of cartilage defects. Network meta-analysis was performed among the three generations for the outcomes analysed using Stata.

Research results

Forty-four RCTs were included in the analysis with patients of mean age of 39.40 (± 9.46) years. Upon comparing the results of the other generations with MFX-I as a constant comparator, we noted a trend towards better pain control and functional outcome (KOOS, IKDC and Cincinnati scores) at the end of 1-, 2-, and 5-year time points with MFx-III, although the differences were not statistically significant ($P > 0.05$). We also noted statistically significant MOCART score in the higher generations of MFx (WMD = 17.44; 95%CI: 0.72, 34.16; $P = 0.025$; without significant heterogeneity) at 1 year. However, the difference was not maintained at 2 years. There was a trend towards better defect filling on MRI with the second and third generation MFx, although the difference was not statistically significant ($P > 0.05$).

Research conclusions

The higher generations of traditional MFx technique utilizing acellular and cellular components to augment its potential in the management of cartilage defects has shown only marginal improvement in the clinical and radiological outcomes.

Research perspectives

Future work could focus on the improvement in the cellular components (chondrocytes over other cellular lineage), culture or processing methodology, delivery modalities (including appropriate scaffolds); as well as better surgical techniques to make the clinical impact with their further advancements.

FOOTNOTES

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META-ANALYSIS

Meta-analysis of the clinical efficacy of the Gamma3 nail *vs* Gamma3U-blade system in the treatment of intertrochanteric fractures

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Abstract

BACKGROUND

The traditional Gamma3 nail is a mainstream treatment for femoral intertrochanteric fractures. Literature reports that the Gamma3U-blade system can increase the stability of the Gamma3 nail and reduce complication incidence. However, comparative studies between the Gamma3U-blade and Gamma3 systems are limited; hence, this meta-analysis was performed to explore the clinical efficacy of these two surgical methods.

AIM

To investigate the clinical efficacy of Gamma3 and Gamma3 U-blade for intertrochanteric fractures.

METHODS

A computerized search for Chinese and English literature published from 2010 to 2022 was conducted in PubMed, Cochrane, CNKI, Wanfang, and VIP databases. The search keywords were gamma 3, gamma 3 U blade, and intertrochanteric fracture. Additionally, literature tracking was performed on the references of published literature. The data were analyzed using Revman 5.3 software. Two individuals checked the inputs for accuracy. Continuous variables were described using mean difference and standard deviation, and outcome effect sizes were expressed using ratio OR and 95% confidence interval (CI). High heterogeneity was considered at ($P < 0.05$, $I^2 > 50\%$), moderate heterogeneity at I^2 from 25% to 50%, and low heterogeneity at ($P \geq 0.05$, $I^2 < 50\%$).

RESULTS

Following a comprehensive literature search, review, and analysis, six articles

were selected for inclusion in this study. This selection comprised five articles in English and one in Chinese, with publication years spanning from 2016 to 2022. The study with the largest sample size, conducted by Seungbae in 2021, included a total of 304 cases. Statistical analysis: A total of 1063 patients were included in this meta-analysis. The main outcome indicators were: Surgical time: The Gamma3U blade system had a longer surgical time compared to Gamma3 nails (P = 0.006, I^2 = 76%). Tip-apex distance: No statistical significance or heterogeneity was observed (P = 0.65, I^2 = 0%). Harris Hip score: No statistical significance was found, and low heterogeneity was detected (P = 0.26, I^2 = 22%). Union time: No statistical significance was found, and high heterogeneity was detected (P = 0.05, I^2 = 75%).

CONCLUSION

Our study indicated that the Gamma3 system reduces operative time compared to the Gamma3 U-blade system in treating intertrochanteric fractures. Both surgical methods proved to be safe and effective for this patient group. These findings may offer valuable insights and guidance for future surgical protocols in hip fracture patients.

Key Words: Gamma3 nail; Gamma3U-Blade system; Femoral intertrochanteric fractures; Meta-analysis

Core Tip: The Gamma3U-Blade, representing the third generation of Gamma nails, possesses several notable features: the incorporation of self-tapping tension screws enhances fixation stability and lowers the risk of cutting out. Anti-screw nails are ingeniously designed to aid in compressing the fracture end. Additionally, the option of dynamic lock or static force lock is available. Despite these advancements, comparative studies between Gamma3 and Gamma3U-blade are limited. Therefore, a meta-analysis of the existing literature was conducted to compare the clinical efficacy of these two surgical methods.

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INTRODUCTION

Intertrochanteric fractures are commonly seen lower limb fractures in elderly patients[1-4], with an increasing incidence [5]. Previous studies have indicated that early surgical intervention for intertrochanteric fractures can reduce mortality[6, 7]. The prevalent clinical classification for these fractures includes the Evans and AO types[8,9]. Intramedullary fixation, characterized by its minimally invasive approach, reduced soft tissue damage, and high healing rate, has become the preferred surgical method for intertrochanteric fracture treatment[10].

Key representatives of this approach are the Gamma Nail, proximal femoral nail, proximal femoral nail antirotation (PFNA), TriGen InterTan hip fracture nailing system (InterTan), and trochanteric fixation nail advanced[11]. PFNA is particularly suitable for elderly patients with osteoporosis, but its usage has been extending to younger patients. During penetration, the PFNA spiral blade anchors in pressurized cancellous bone, but penetration can be challenging in patients with robust bone. PFNA surgery does not allow for pulp enlargement, and in cases of marrow cavity stenosis, there's a risk of shifting the fracture end during insertion, thus increasing operation time. The InerTAN system, with its superior anti-rotation capability, might not be appropriate for patients with small or thin bone marrow cavities. The use of two interlocking nails in InerTAN can lead to more bone loss at the femoral neck, leaving a large residual cavity post-fixation and heightening the risk of refracture. Additionally, the InerTAN system demands high technical skill and has a steep learning curve. The Gamma nail, designed by Halder in 1988, is considered a pioneering product for modern pulp nails. The Gamma3 nail, however, does not possess the robust anti-pulling effect of the PFNA spiral blade. To enhance this aspect of the Gamma3 nail, Lenich introduced the "U" type blade pull screw for Gamma nails, known as the Gamma3U-Blade system[12]. As the third-generation Gamma nail, the Gamma3U-Blade has distinctive features: it uses self-tapping tension screws to bolster fixation stability and mitigate the risk of cutting out. Its anti-screw nails are engineered to assist in compressing the fracture end, and it offers the choice between dynamic lock and static force lock[13,14].

The conventional Gamma3 nail remains the primary treatment for femoral intertrochanteric fractures. However, reports in the literature[15] suggest that the Gamma3U-blade system enhances the stability of the Gamma3 nail and lessens complication rates. Yet, comparative studies between the Gamma3U-blade and Gamma3 systems are sparse. This meta-analysis was thus conducted to investigate the clinical efficacy of these two surgical methods.

MATERIALS AND METHODS

Inclusion criteria

This study included Chinese and English clinical studies comparing the Gamma3 nail and Gamma3U blade in treating femoral intertrochanteric fractures, published between 2010 and 2022. The focus was on adult cases of femoral intertrochanteric fractures. The literature considered provided measurements such as operation time, intraoperative blood loss, postoperative hip function Harris score, postoperative tip-apex distance value (TAD), and functional recovery (Figure 1).

Exclusion criteria

Excluded from the study were cases involving pathologic fractures, polytrauma combined with intertrochanteric fractures, treatment measures integrated with other surgical methods, repeatedly published literature, reviews, systematic evaluations, case reports, letters, basic research, and finite element analysis models.

Statistical indicators

General information: Authors, year of publication, sample size.

Main outcome indicators: Operative time, Harris hip score (HHS), TAD, and union time.

Literature search

Data collection and analysis: The PRISMA statement guidelines were adhered to for conducting and reporting meta-analysis data. The data were analyzed using Revman 5.3 software. Two reviewers ensured the accuracy of data input. Continuous variables were reported using mean difference and standard deviation, and outcome effect sizes were expressed using ratio OR and 95% confidence interval (CI). High heterogeneity was defined as ($P < 0.05$, $I^2 > 50\%$), moderate heterogeneity as I^2 ranging from 25% to 50%, and low heterogeneity as ($P \geq 0.05$, $I^2 < 50\%$).

KEY ("Gamma3" or "Gamma3 nail" or "Gamma3 U-blade" or "U-blade") and Femoral intertrochanteric fractures ("Femoral intertrochanteric fractures" or "intertrochanteric fractures").

RESULTS

Search results

After a thorough search, review, and analysis of the literature, six articles were ultimately included in this study. These comprised five articles in English and one in Chinese, published between 2016 and 2022 (Supplementary Table 1, Figure 2). The study with the largest sample size, authored by Seungbae in 2021, encompassed a total of 304 cases (Figures 3 and 4).

Statistical results

The meta-analysis included a total of 1063 patients. The primary outcome indicators were as follows: Surgical time: The surgical time for the Gamma3U blade system was longer compared to Gamma3 nails ($P = 0.006$, $I^2 = 76\%$). TAD: No statistical significance or heterogeneity was observed ($P = 0.65$, $I^2 = 0\%$). HHS: No statistical significance was found, with low heterogeneity ($P = 0.26$, $I^2 = 22\%$). Union time: No statistical significance was noted, accompanied by high heterogeneity ($P = 0.05$, $I^2 = 75\%$) (Figure 5).

DISCUSSION

The limited availability of controlled studies on Gamma3 and Gamma3 U-blade has restricted the number of comparisons in this meta-analysis. Variations in the focus of comparative follow-up across existing references also impacted the number of comparisons. Additionally, regional differences in fracture diagnosis among clinicians pose a risk of inclusion bias in the study.

Elderly patients are particularly susceptible to osteoporotic intertrochanteric fractures. Early surgical intervention for these fractures, along with hip joint functional exercises, can reduce complications like deep vein thrombosis, pressure ulcers, and joint stiffness[16]. Intramedullary fixation of intertrochanteric fractures offers effective anti-rotational stability. For unstable fractures (31-A2, 31-A3), intramedullary nailing fixation is the preferred treatment, a consensus in clinical practice[17]. Gamma3 nails, an evolution from Gamma nails for treating intertrochanteric fractures, address some limitations of the earlier design. However, some clinical studies have noted that the head nail of Gamma3 screws demonstrates poor stability and a higher risk of screw withdrawal[18]. The Gamma3 U-blade system incorporates a U-shaped blade, increasing the contact area between the femoral head, neck, and the screw, thereby enhancing head nail stability and reducing the risk of nail dislodgement. This meta-analysis revealed that the Gamma3 U-blade method required longer operative time compared to the Gamma3 nail method ($I^2 = 76\%$, $P = 0.006$).

The observed differences in operative time were statistically significant. However, no statistically significant difference was found in fracture healing time between the two internal fixation systems ($P = 0.05$). Presently, no literature conclusively states that the postoperative stability of the Gamma3 U-Blade system surpasses that of Gamma3 nails[19].

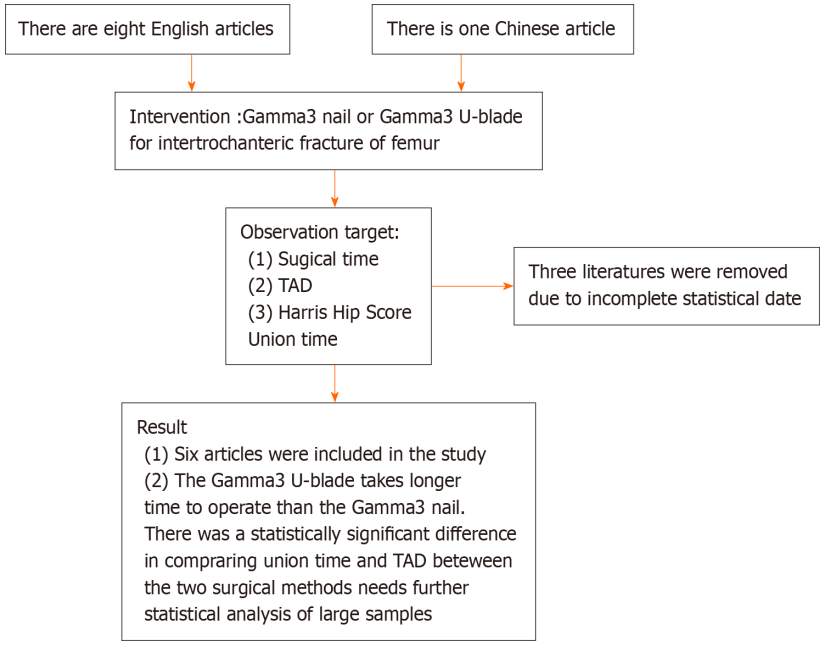

Figure 1 Study selection. TAD: Tip-apex distance.

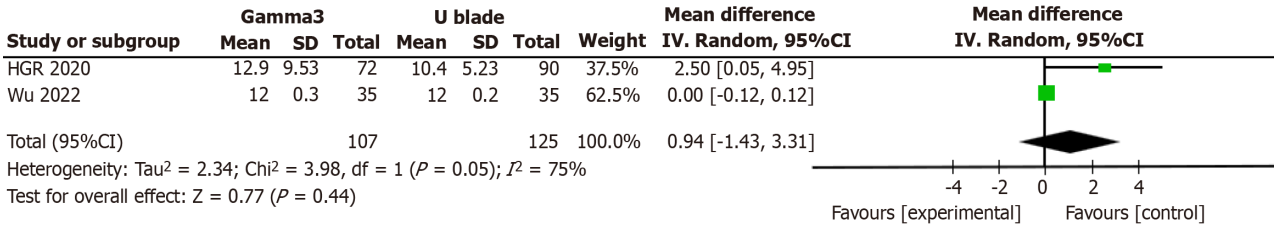

Figure 2 Literature selection process: Six English literature and one Chinese literature were included in the study.

Therefore, patients undergoing intertrochanteric fracture treatment with intramedullary nailing can commence early functional exercises of the affected limb to reduce complications like joint stiffness. The literature selected for this meta-analysis did not systematically analyze when patients began functional exercises or their limb function scores, nor did it provide specific clinical analysis of functional exercise impacts. Patients with intertrochanteric femur fractures often have associated osteoporosis, necessitating further clinical analysis to determine if postoperative anti-osteoporosis treatment can expedite fracture healing and influence the timing of functional exercise commencement. This meta-analysis indicates that the Gamma3 U-blade system has a longer operative time compared to Gamma3 nails, with a statistically significant difference (P = 0.006). Gamma3 nails are preferable for frail patients with multiple underlying conditions who cannot withstand lengthy surgery. However, the Gamma3 U-blade offers superior postoperative stability and a lower risk of revision surgery due to internal fixation loosening and nail withdrawal, making it more suitable for elderly patients who can tolerate extended surgery.

Intertrochanteric fractures are susceptible to screw cutting after intramedullary nail fixation, which is closely related to three factors: the TAD, the greater trochanter, and the posterolateral wall. Literature suggests that a TAD value of 20-25 mm is safest, but debates on the optimal TAD value persist. The average TAD value in the literature included in this study ranged from 19.1-20.3 mm, with patients showing favorable clinical outcomes during follow-up. It can be inferred that an average TAD of 20 mm can yield good clinical results, but further large-scale studies are required to ascertain the precise upper and lower limits of this value.

This meta-analysis revealed no statistically significant difference in postoperative fracture healing time between the two surgical methods. Intertrochanteric fractures, primarily unstable, benefit from the abundant vascularity at the fracture ends, leading to a low rate of nonunion. The literature[20] highlights that effective reduction is key to the healing of intertrochanteric fractures. Both Gamma 3 nails and Gamma U-blade nails proficiently restore the force line at the fracture end and maintain stability of the fracture ends. Consequently, it can be inferred that both surgical methods positively impact fracture healing.

Clinical studies have determined that elderly and underweight patients, having lower bone mineral density (BMD), are more susceptible to intertrochanteric femur fractures[21]. These patients often present with preoperative anemia, while obese patients tend to experience more intraoperative blood loss. This study found no statistically significant difference in body mass index (BMI) and BMD values, possibly due to the wide age range of the patients involved, leading to non-significant differences in comparisons. Patients from different age groups exhibit varying metabolic rates, and their BMI

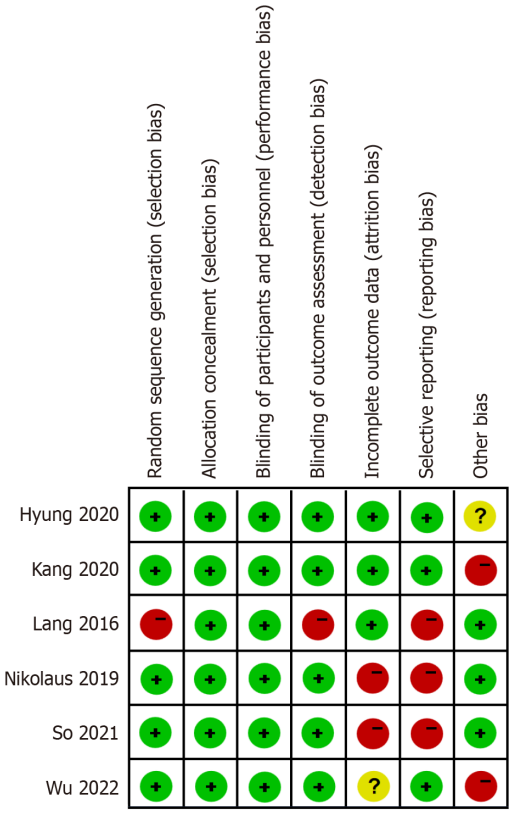

Figure 3 Risk of bias summary: Review author's judgements about each risk of bias item.

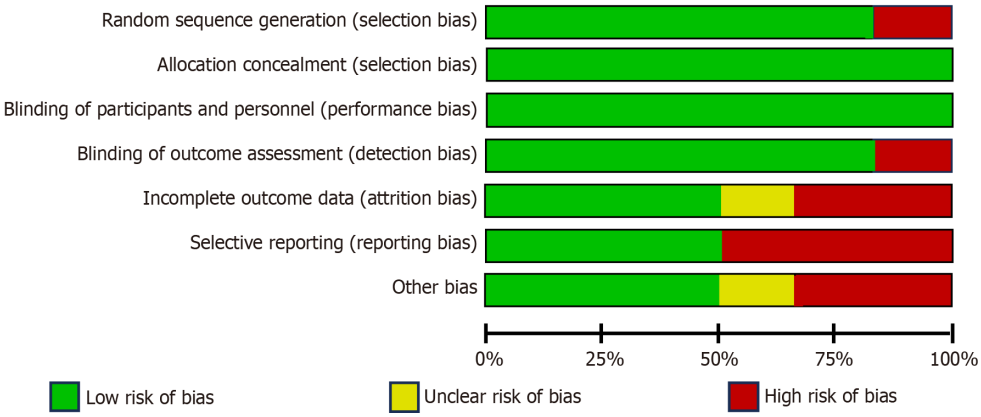

Figure 4 Risk of bias graph.

and BMD values differ accordingly. For enhanced clinical relevance, dividing patients into age groups for comparative analysis could yield more significant insights.

The literature included in this meta-analysis indicates that operations using the U-blade tend to have longer durations compared to those with Gamma3, attributed to the additional steps required in the Gamma3U-blade procedure. Given that the Gamma3U-blade has been in use for a shorter time than Gamma3, advancements in clinical procedures and increased clinical experience may address the issue of prolonged surgical time. However, further statistical analysis regarding operation time necessitates a substantial number of clinical samples for a robust research foundation. Limitations of the Included Research Articles: While surgical intervention enhances survival quality in patients with intertrochanteric fractures, reports[22] indicate that the one-year postoperative mortality rate for these patients ranges from 11.9%-18.5%. It is plausible that long-term follow-up data may be skewed due to postoperative mortality, particularly in older patients, contributing to statistical bias in the study. Large-sample studies are required to minimize data bias related to mortality. Union time and TAD, vital scoring criteria post-intertrachanteric fracture, were accounted for in only two articles each, with no statistically significant differences observed in comparisons (P = 0.05 for Union time and P > 0.05 for TAD). Given the limited number of articles included, the data on Union Time and TAD may be biased. Currently, no prospective studies compare these two types of internal fixation methods. Therefore, the aim of this study is a meta-analysis of the efficacy of femoral trochanteric surgery, limited to clinical efficacy indicators for surgical outcome

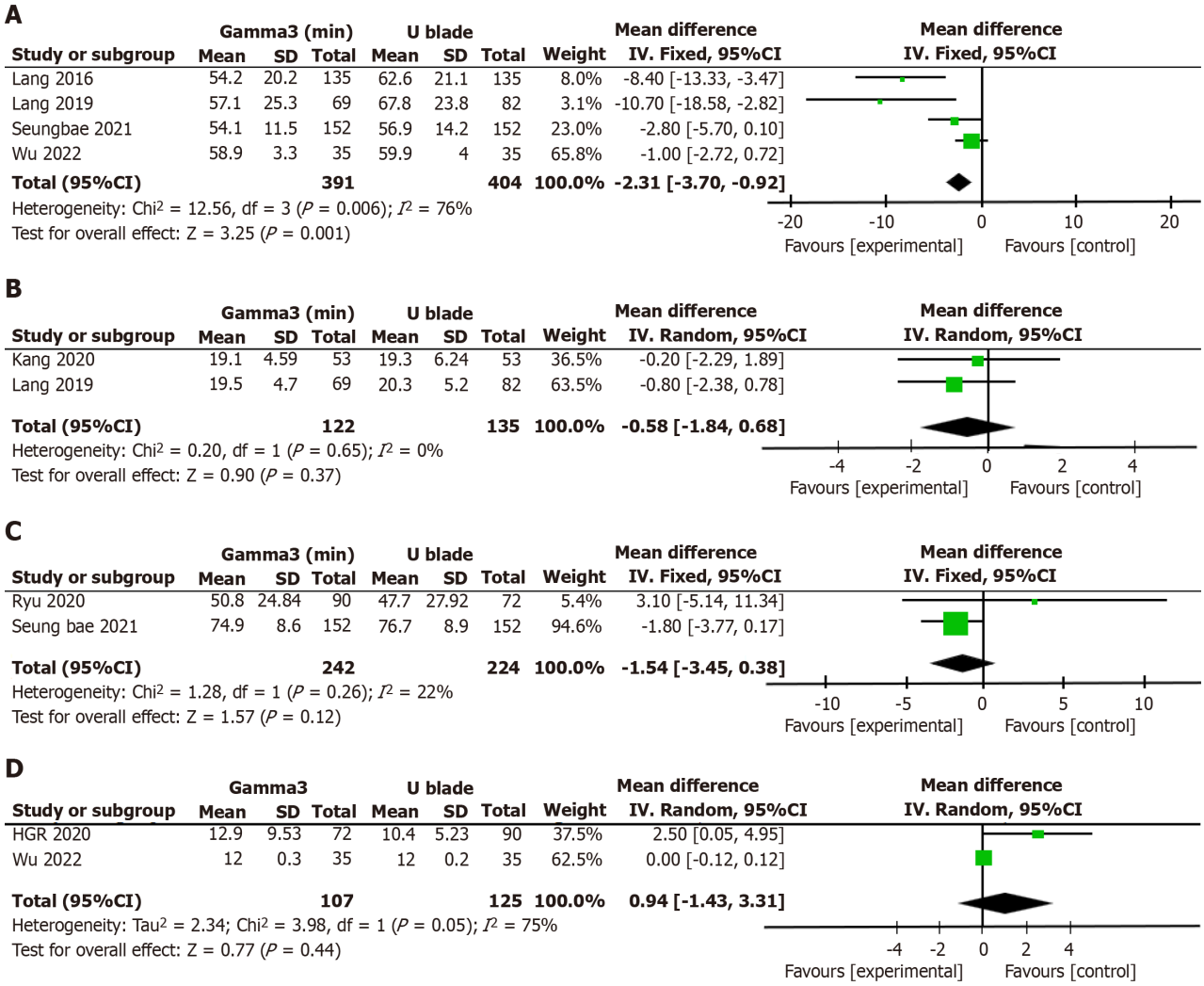

Figure 5 Comparison of the Gamma3 and U blade clinical data. A: Meta-analysis of operative time between gamama3 nail and Ublade; B: Meta-analysis of tip-apex distance indicators between gamama3 nail and Ublade; C: Meta-analysis of Harris hip score indicators between gamama3 nail and Ublade; D: Meta-analysis of union time indicators between gamama3 nail and Ublade.

assessment. To ascertain whether significant differences exist in comparing Union Time and TAD between the two surgical methods, further statistical analysis with large samples is warranted.

CONCLUSION

Our study demonstrated that the Gamma 3 system is associated with reduced operative time in comparison to the Gamma 3 U-blade for treating intertrochanteric fractures. Both surgical approaches are safe and effective for this patient group. These insights may offer valuable recommendations and information for future surgical protocols in hip fracture patients. Nevertheless, to enhance the evidence base, further extensive multicenter prospective trials are necessary. A randomized controlled trial focusing on documented and quantified osteoporosis patients with extended follow-up periods is required.

ARTICLE HIGHLIGHTS

Research background

The conventional Gamma3 nail remains the primary treatment for femoral intertrochanteric fractures. However, reports in the literature suggest that the Gamma3U-blade system enhances the stability of the Gamma3 nail and lessens complication rates. Yet, comparative studies between the Gamma3U-blade and Gamma3 systems are sparse. This meta-analysis was thus conducted to investigate the clinical efficacy of these two surgical methods.

Research motivation
To compare the clinical efficacy of Gamma3 and Gamma3 U-blade, and then to guide the clinical treatment.

Research objectives
Whether Gamma3 U-blade can replace Gamma3 nails, and whether there is room for further improvement.

Research methods
The article chooses the traditional meta-analysis, and its main purpose is to analyze the existing data and guide the clinical treatment.

Research results
The Gamma3 U-blade procedure is longer than the Gamma3, but both surgical procedures are safe and effective, and further clinical studies are needed to optimize the Gamma3 U-blade procedure.

Research conclusions
These insights may offer valuable recommendations and information for future surgical protocols in hip fracture patients. Nevertheless, to enhance the evidence base, further extensive multicenter prospective trials are necessary. A randomized controlled trial focusing on documented and quantified osteoporosis patients with extended follow-up periods is required.

Research perspectives
Comparative surgical studies of Gamma3 U-blade and Gamma3 are missing, and numerous clinical surgery and prospective studies are needed.

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FOOTNOTES

Author contributions: Wu X Collect all the literature required for the study, provided the data analysis of the article, and put forward important opinions and suggestions on the discussion part of the article; Gao B participated in the study of the background part of the article, collated and revised the content of the article; Bo G provided financial support as the host of the project.

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META-ANALYSIS

Pulsed lavage in joint arthroplasty: A systematic review and meta-analysis

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Abstract

BACKGROUND

Knee and hip osteoarthritis affects millions of people around the world and is expected to rise even more in frequency as the population ages. Joint arthroplasty is the surgical management of choice in these articulations. Heterotopic ossification and radiolucent lines formation are two frequent problems faced in hip and knee replacements respectively. Some studies show that the usage of pulsed lavage may prevent their formation.

AIM

To compare pulsed lavage to standard lavage in joint arthroplasty.

METHODS

PubMed, Cochrane, and Google Scholar (page 1-20) were searched till December 2023. Only comparative studies were included. The clinical outcomes evaluated were the heterotopic ossification formation in hip replacements, radiolucent lines formation, and functional knee scores in knee replacements.

RESULTS

Four studies met the inclusion criteria and were included in this meta-analysis. Pulsed lavage was shown to reduce the formation of radiolucent lines (P = 0.001). However, no difference was seen in the remaining outcomes

CONCLUSION

Pulsed lavage reduced the formation of radiolucent lines in knee replacements. No difference was seen in the remaining outcomes. Furthermore, the clinical significance of these radiolucent lines is poorly understood. Better conducted randomized controlled studies and cost-effectivity studies are needed to reinforce these findings.

Key Words: Knee arthroplasty; Hip arthroplasty; Pulsed lavage; Syringe lavage; Heterotopic ossification; Radiolucent lines

Core Tip: Pulsed lavage may be important in total knee arthroplasty but has no added benefit in total hip arthroplasty.

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INTRODUCTION

With the advancements in medicine, people's average life expectancies are rising[1]. Between 2000 and 2050, there will be a 135% increase in the population above the age of 65[2]. The World Health Organization has identified four chronic musculoskeletal illnesses as conditions whose prevalence will increase as the population ages. Two of these conditions are osteoarthritis (OA) and rheumatoid arthritis (RA), which both affect millions of individuals worldwide[3]. When conservative treatment for RA and OA has failed and a person's overall quality of life is continuing to decline, total hip arthroplasty (THA) and total knee arthroplasty (TKA) is the surgical management of choice[4-10]. In fact, Joint arthroplasty is as an effective intervention to relieve pain and improve joint function[11-13]. Furthermore, gait is the most common activity to be affected in patients prior to undergoing joint replacement surgery[14-18]. Different prosthetic materials can be used in joint replacement which can also impact the gait and functional outcomes post-operatively, and can be assessed by computational simulation[19-23]. The By 2030, it is predicted that the United States would undertake over 3.5 million primary TKA procedures yearly and close to 600000 main THA procedures[1].

The lifespan of the implants depends on improvements in cement penetration and implant stability in hip and knee arthroplasty[24]. Pulsed lavage (PL) can be used to achieve this[24]. Radiolucent lines are a common observation at the cement-bone interface in TKA[25]. However, the clinical outcome does not appear to be impacted by the radiolucent lines, though[26]. The majority of radiolucent lines are 1 mm wide and have a radioopaque sclerotic border. Pathological radiolucent lines, on the other hand, are larger than 2 mm and have ill-defined edges[27]. Another problem in THA is the formation of heterotopic ossification (HO). PL may stop HO development by removing the nascent mesenchymal cells from the hip joint and gluteal muscles[28].

Despite numerous publications about the efficacy of PL in the field of surgery, there is no meta-analysis about its effectiveness in Joint Arthroplasty (JA). Therefore, this meta-analysis is designed to compare PL to standard lavage (SL) in JA.

MATERIALS AND METHODS

Search strategy

This study followed the PRISMA guidelines. PubMed, Cochrane, and Google Scholar (page 1-20) were searched updated to December 2023 for the qualified studies in order to study the efficacy of PL in JA using the following keywords and Boolean operators "puls*" AND "knee" OR "hip". Literature was also identified by tracking reference lists from papers and Internet searches. One investigator (MD) extracted the data, and another investigator (AS) confirmed the choice of the articles. The process is summarized in the PRISMA flowchart (Figure 1).

Inclusion criteria were: (1) Comparative studies: randomized controlled trails, retrospective comparative studies, prospective clinical trials; (2) patients operated with a total or partial knee or hip replacement; and (3) Pulsed lavage was used in the first group compared to standard lavage in another group. The studies with the following characteristics were excluded from this study: (1) Case reports, narrative or systematic reviews, theoretical research, conference report, meta-analysis, expert comment, and economic analysis; and (2) non-relevant outcomes.

Data extraction

Two reviewers determined the eligibility of the studies independently. Extraction of the analyzed data was made from the included studies and it consisted of two parts. The first part consisted of the basic information containing the name of the authors, the title, the publication year, the journal, the volume, the issue, the pages, the study design, the sample size along with the size of each group of management, and the different types of bias suspected in each study. The second part consisted of the clinical outcomes the formation of HO, radiolucent lines formation, and functional knee scores. Any arising difference between the investigators was resolved by discussion.

Risk of bias assessment

The Cochrane risk-of-bias tool was used by two writers (MD and AS) to independently assess the risk of bias. The following factors were taken into consideration when determining whether a trial had a high, low, or unclear risk of bias: Random sequence generation, allocation concealment, blinding of participants and study workers to the research

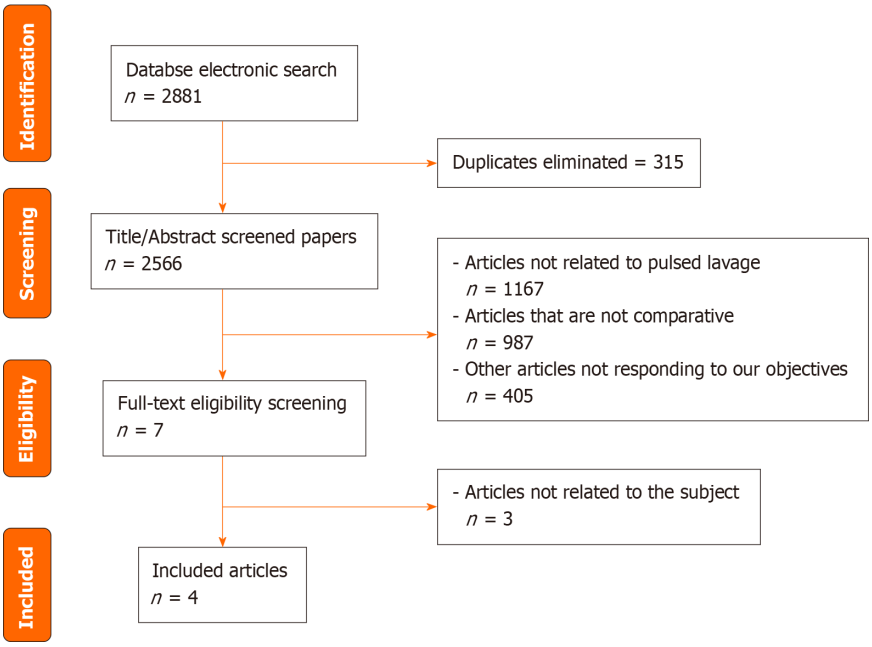

Figure 1 PRISMA flowchart for article selection process.

procedure, blinding of outcome assessment, inadequate outcome data, and selective reporting (Figure 2A and B). Trials that had a high risk of bias for more than one key domain were deemed to have a high risk of bias, while those that had a low risk of bias for every key domain were deemed to have a low risk of bias. If neither of these conditions were met, the trials were deemed to have an unclear risk of bias. For non-randomized studies, the ROBINS-I tool for assessing risk of bias in non-randomized studies of interventions was used[29]. Studies that had a critical risk of bias were excluded.

Statistical analysis

The statistical analysis was performed using Review Manager 5.4 (The Cochrane Collaboration, 2020). For continuous data, 95% confidence intervals (CI) and standardized mean differences were utilized, while risk ratio with 95%CI was used for dichotomous data. Q tests and I^2 statistics were used to evaluate heterogeneity indicating considerable heterogeneity if $P \leq 0.10$ or $I^2 > 50\%$. High levels of variability were handled by the use of the random-effects model. On the other hand, the fixed-effect model was chosen if $P > 0.10$ or $I^2 < 50\%$. Statistical significance threshold was chosen at $P = 0.05$.

RESULTS

Characteristics of the included studies

Four studies[24,28,30,31] met the inclusion criteria and were included in the meta-analysis with 2 randomized controlled trials and 1 prospective non-randomized study, and 1 retrospective comparative study. It involved 185 subjects in the PL group and 182 subjects in the SL group. The main characteristics of the included studies are summarized in Table 1.

Bias results

The risk of bias assessment is presented in Figure 2A and B and Table 2. There were no high bias risks, they were either low, moderate, or unclear.

Heterotropic ossification

Two studies on 181 subjects (87 PL *vs* 94 SL) reported data on post-operative HO formation. The results showed no differences between PL and SL in overall HO formation (Odds ratio = 0.76; 95%CI = 0.42–1.36, $P = 0.35$, Figure 3A), Brooker grade 1 HO formation (Odds ratio = 1.02; 95%CI = 0.39–2.67, $P = 0.96$, Figure 3B), Brooker grade 2 HO formation (Odds ratio = 1.23; 95%CI = 0.49–3.08, $P = 0.65$, Figure 3C), Brooker grade 3 HO formation (Odds ratio = 0.36; 95%CI = 0.12–1.08, $P = 0.07$, Figure 3D), and Brooker grade 4 HO formation (Odds ratio = 0.76; 95%CI = 0.14–4.05, $P = 0.75$, Figure 3E).

Radiolucent lines

Two studies on 186 (98 PL *vs* 88 SL) subjects reported data on radiolucent lines formation. The results showed that when compared to SL, PL significantly reduces the formation of radiolucent lines (Odds ratio = 0.29; 95%CI = 0.14–0.61, $P = 0.001$, Figure 4).

Table 1 Main characteristics of the included studies

Ref.	Methods	Participants		Mean age (SD)		Measured outcomes	Follow-up time
		PL	SL	PL	SL		
Abdeldayem *et al* [24], 2018	Prospective randomized comparison	44	42	64, NA	64, NA	Knee society score, knee function score, radiolucent lines	12 months
Clarius *et al*[30], 2009	Prospective non-randomized comparison	54	46	63, NA	68, NA	Knee society score, knee function score, Oxford knee score, radiolucent lines	22 months
Mellema *et al*[28], 2011	Retrospective comparison	39	48	62; 9	55; 10	Rate of heterotopic ossification	14 months
Sneath *et al*[31], 2001	Prospective randomized comparison	48	46	71, NA	73, NA	Rate of heterotopic ossification	12 months

PL: Pulsed lavage; NA: Not available; SL: Standard lavage.

Table 2 Bias assessment of the included studies

Studies	Confounding bias	Selection bias	Classification bias	Bias due to deviation from interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results	Results
Clarius *et al* [30], 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
Mellema *et al*[28], 2011	Low risk	Low risk	Low risk	Low risk	Low risk	low risk	Low risk	Low risk

Knee functional scores

Two studies on 186 subjects (98 PL *vs* 88 SL) reported data on knee functional scores. The results showed no difference between PL and SL in knee society score (Mean difference= -0.01; 95%CI = -4.85–4.84, P = 1.0, Figure 5A) and knee function score (Mean difference = 3.85; 95%CI -2.53–10.23, P = 0.24, Figure 5B).

DISCUSSION

Total joint arthroplasties are expected to increase over time due to the aging population and obesity. A commonly faced adverse events in such procedures is the formation of HO in hip replacements and radiolucent lines formation in knee replacements. The efficacy of PL and preventing such problems has been studied in JA. However, this is the first meta-analysis assessing the efficacy of PL in both knee and hip replacements. The outcomes of this meta-analysis can be divided into three section: HO formation, radiolucent lines, and knee functional scores. Pulsed Lavage reduced the formation of radiolucent lines. However, no differences were seen in the remaining outcomes.

Our results showed no difference in HO formation between PL and SL. A study by Mellema *et al*[28] showed a beneficial effect of PL in preventing Brooker grade 3-4 HO however this may be limited by the low numbers in such high HO grades. The etiology of this pathology is still unclear. It is said that it might be from the mesenchymal pluripotential stem cells that are released by the bone during the surgery acting as a stimulus[32,33]. If that was the case, then PL should have a beneficial effect on HO formation. The lack of correlation between HO formation and PL suggests another mechanism. Pellegrini *et al*[34] showed that a pre-operative radiotherapy directed at the soft tissue around the hip reduced the rate of HO formation which may draw the conclusion that the osteogenic precursors responsible of HO are derived from the soft tissue and not the bone debris.

No difference in knee functional scores were seen between SL and PL, however the latter reduced the formation of radiolucent lines in knee replacement. After cemented TKA, there are two types of tibial radiolucency that can be found. In the first year post-operatively, physiological radiolucency is a frequent but common observation[24]. It does not progress or compromise the stability of the implant. Physiologic radiolucency has a sclerotic border and a thickness of no more than 1 mm on radiographs. On the other hand, pathological radiolucency typically has edges that are not sclerotic and is thicker than 2mm. These radiolucent lines are signs of septic or aseptic loosening and influence implant stability because they progress over time[24]. Abdeldayem *et al*[24] and Clarius *et al*[30] showed that the cement penetration was deeper in the PL group which could explain the lower rate of radiolucency observed when PL was used. This can be explained by the cancellous bone becoming more porous following jet lavage and then becoming much more thoroughly penetrated by bone cement[24]. However, the clinical significance of these radiolucent lines is still poorly understood[26].

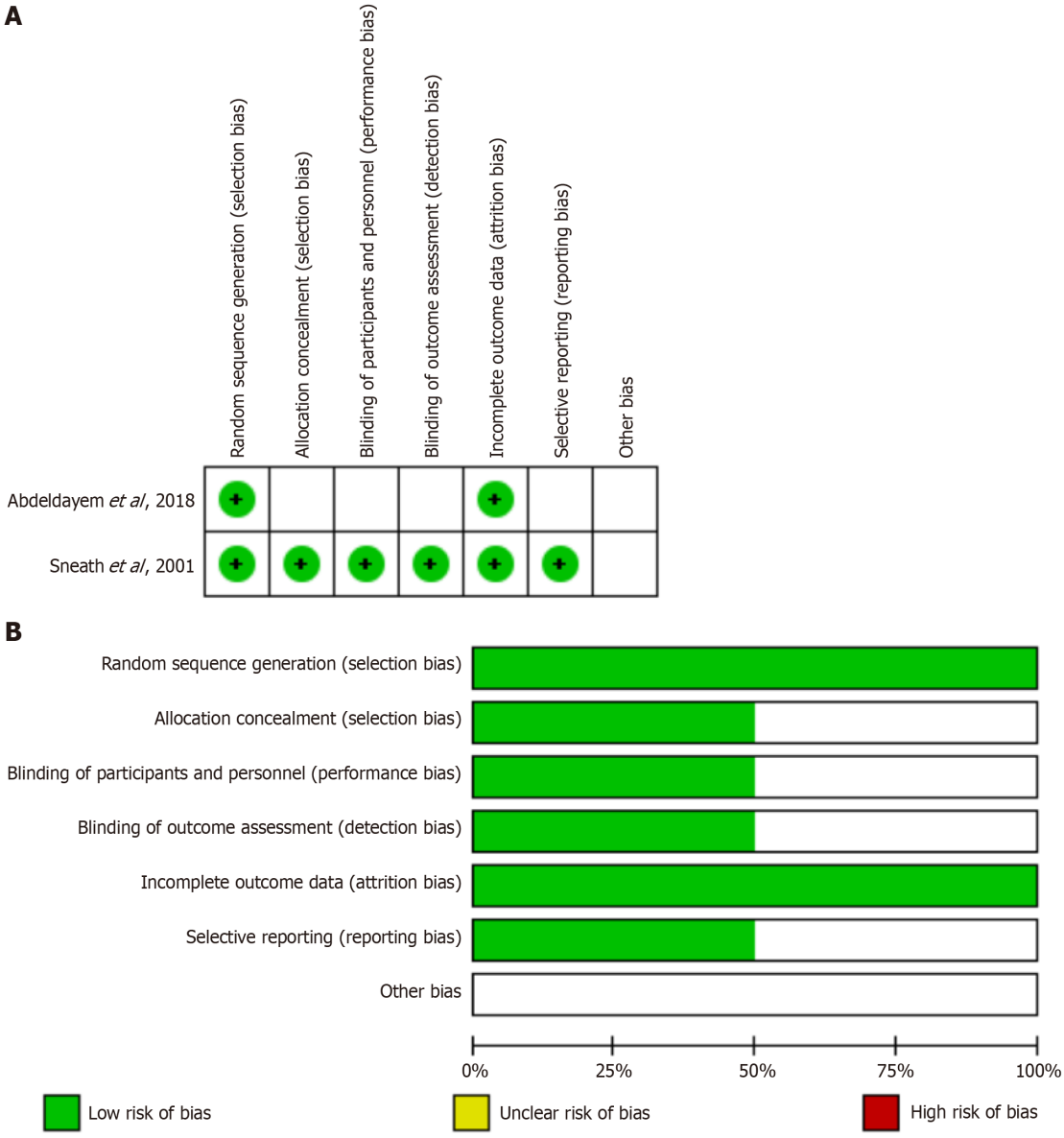

Figure 2 Risk of bias. A: Risk of bias summary: review authors' judgements about each risk of bias item for each included study; B: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

In fact, radiolucency is present in all loose knee implants, but not all implants that have radiolucency are loose[26]. And seeing that there are no differences in the functional scores, one might wonder about the benefit of using PL in knee replacement.

Strengths and limitations

This study has several strengths: It is the first meta-analysis comparing PL to SL in JA. Moreover, only comparative studies were included reducing the risk of operative and matching bias. Finally, the selection process was more selective. This makes the study less heterogenous and decreases the risk of bias. However, this study had also limitations: There weren't that many comparative studies in the literature to include; Inclusion and exclusion criteria for patients were different; the number of included studies is limited and the data used for analysis was pooled and individual patients' data were unavailable, and this could limit more comprehensive analyses.

CONCLUSION

This is the first meta-analysis comparing pulsed lavage to standard lavage in partial or total knee and hip arthroplasty. It showed that pulsed lavage reduced the formation of radiolucent lines in knee replacement. No difference was seen in the remaining outcomes when compared to standard lavage. The decrease in radiolucent lines formation may be associated to a better cement penetration however, the clinical significance of these lines is still questionable. Nevertheless, more randomized controlled studies and cost-effectivity studies are needed to confirm the benefits of this lavage technique.

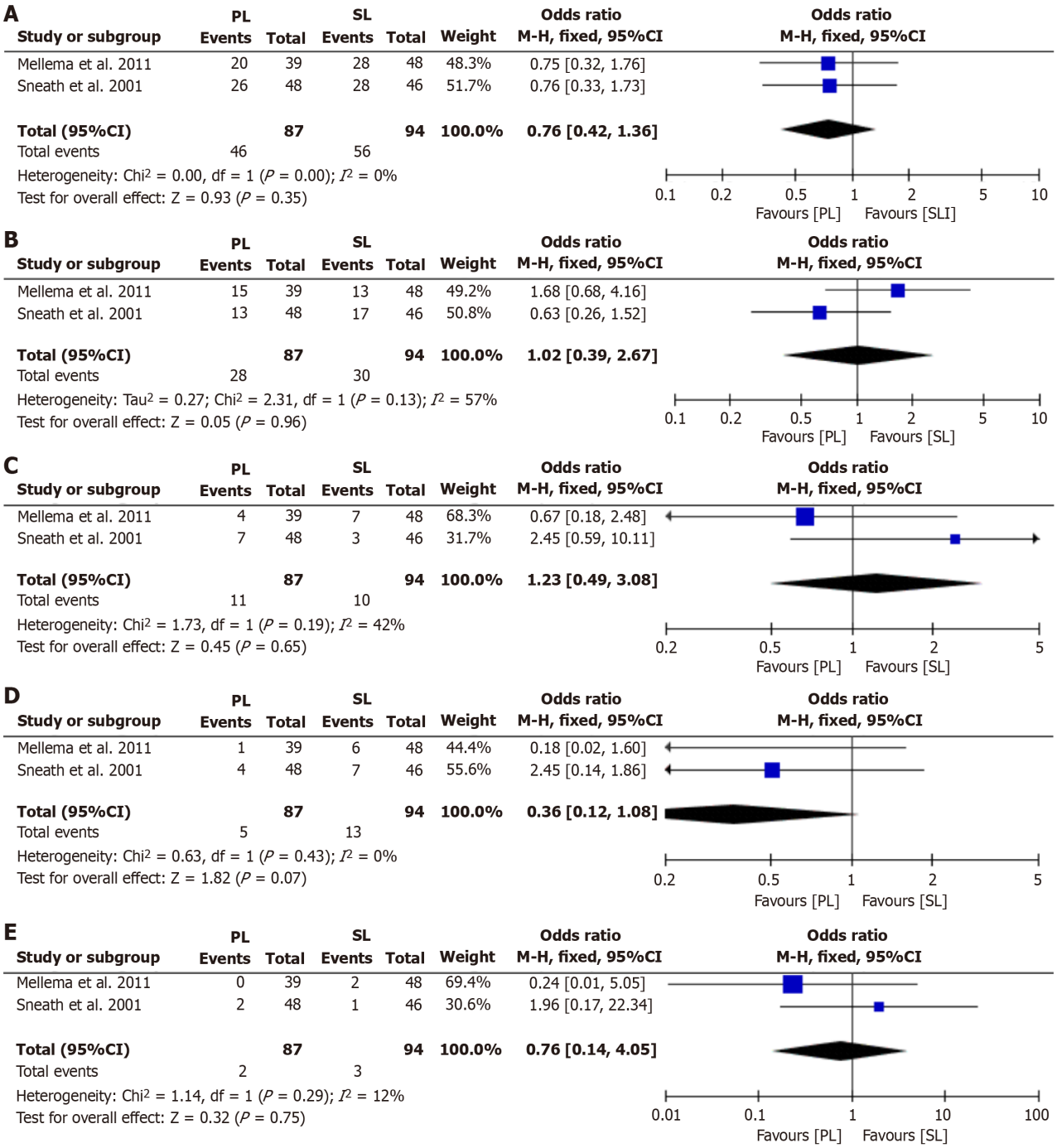

Figure 3 Forest plot. A: Forest plot showing the overall heterotopic ossification (HO) formation in pulsed lavage (PL) and standard lavage (SL); B: Forest plot showing the Brooker grade 1 HO formation in PL and SL; C: Forest plot showing the Brooker grade 2 HO formation in PL and SL; D: Forest plot showing the Brooker grade 3 HO formation in PL and SL; E: Forest plot showing the Brooker grade 4 HO formation in PL and SL.

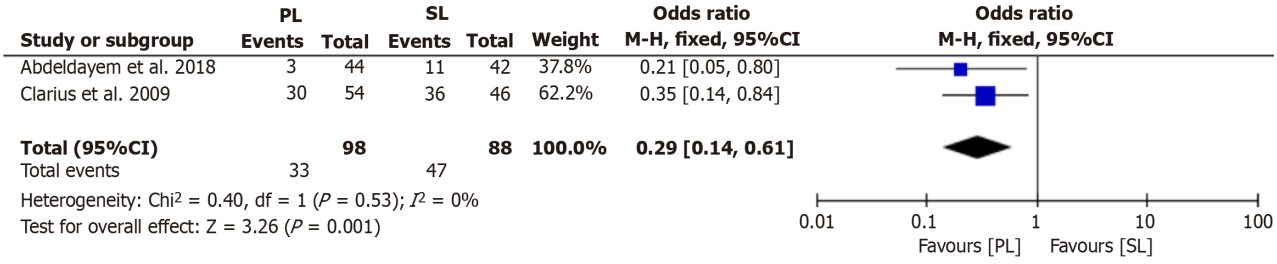

Figure 4 Forest plot showing the formation of radiolucent lines in pulsed lavage and standard lavage.

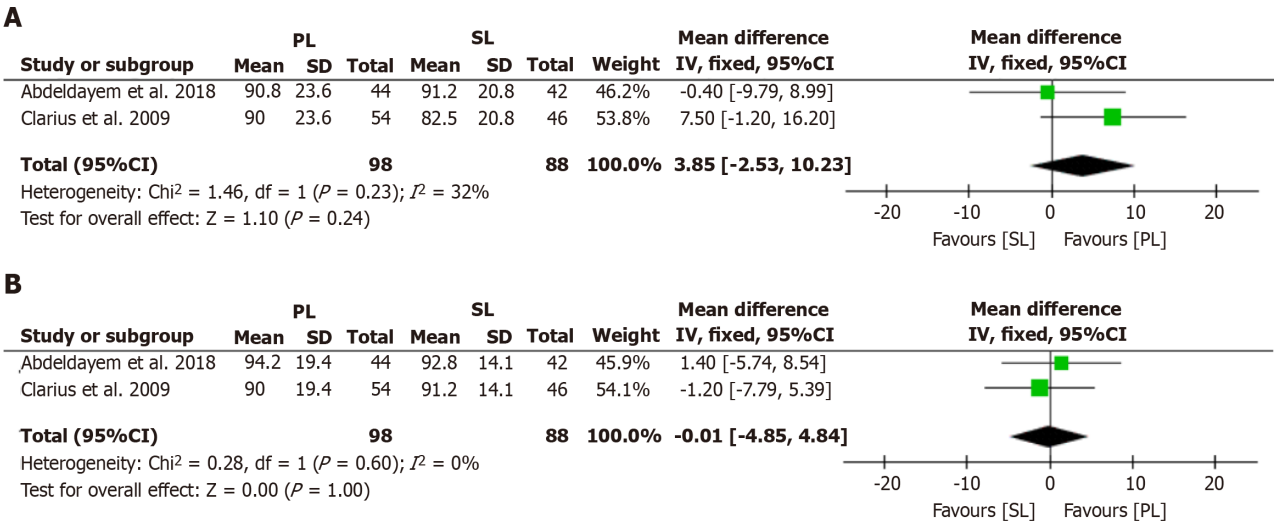

Figure 5 Forest plot. A: Forest plot showing the knee society score in pulsed lavage (PL) and standard lavage (SL); B: Forest plot showing the knee function score in PL and SL.

ARTICLE HIGHLIGHTS

Research background

Many studies compared pulse lavage to standard lavage in the setting of joint replacement but no meta-analysis is present to assess the overall utility of pulse lavage.

Research motivation

This study will be the first to assess the utility of pulse lavage in the setting of total hip and total knee replacements.

Research objectives

In the setting of hip replacement, we assessed the formation of heterotopic ossification whereas in knee replacement, we assessed the formation of radiolucent lines and functional outcomes.

Research methods

PubMed, Cochrane, and Google Scholar (page 1-20) were searched till December 2023 including only comparative studies comparing pulsed lavage to standard lavage in total knee or total hip replacements.

Research results

We found no difference in heterotopic ossification in hip replacement and no difference in functional outcomes in knee replacement. However, we found a reduction in the formation of radiolucent lines in total knee replacement.

Research conclusions

We conclude that pulsed lavage may be beneficial in the setting of total knee replacement but has no added benefit in total hip replacement.

Research perspectives

Future research should assess the costs/benefits of pulsed lavage in the setting of total joint replacement.

FOOTNOTES

Author contributions: Daher M contributed to writing draft; Haykal G contributed to editing; Haykal G and Sebaaly A contributed to supervision; Aoun Mand Moussallem M contributed to data collection; Aoun M, Moussallem M, Ghoul A, Tarchichi J, and Sebaaly A contributed to writing; Sebaaly A contributed to editing.

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CASE REPORT

New method of local adjuvant therapy with bicarbonate Ringer's solution for tumoral calcinosis: A case report

Takashi Noguchi, Akio Sakamoto, Kensaku Kakehi, Shuichi Matsuda

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Abstract

BACKGROUND

Tumoral calcinosis is a condition characterized by deposits of calcium phosphate crystals in extra-articular soft tissues, occurring in hemodialysis patients. Calcium phosphate crystals are mainly composed of hydroxyapatite, which is highly infiltrative to tissues, thus making complete resection difficult. An adjuvant method to remove or resolve the residual crystals during the operation is necessary.

CASE SUMMARY

A bicarbonate Ringer's solution with bicarbonate ions (28 mEq/L) was used as the adjuvant. After resecting calcium phosphate deposits of tumoral calcinosis as much as possible, while filling with the solution, residual calcium phosphate deposits at the pseudocyst wall can be gently scraped by fingers or gauze in the operative field. A 49-year-old female undergoing hemodialysis for 15 years had swelling with calcium deposition for 2 years in the shoulders, bilateral hip joints, and the right foot. A shoulder lesion was resected, but the calcification remained and early re-deposition was observed. Considering the difficulty of a complete rection, we devised a bicarbonate dissolution method and excised the foot lesion. After resection of the calcified material, the residual calcified material was washed away with bicarbonate Ringer's solution.

CONCLUSION

The bicarbonate dissolution method is a new, simple, and effective treatment for tumoral calcinosis in hemodialysis patients.

Key Words: Tumoral calcinosis; Adjuvant therapy; Bicarbonate; Ringer's solution; Surgery; Case report

Core Tip: Tumoral calcinosis, which occurs in 2%-3% of hemodialysis patients, involves calcium phosphate deposits, thus making surgical resection challenging. Hydroxyapatite, the main component of tumoral calcinosis, infiltrates tissues extensively. A bicarbonate Ringer's solution is used post-resection. A 49-year-old hemodialysis patient with calcified shoulder, hip, and foot lesions underwent the bicarbonate dissolution method. After resection, the operative field was washed with the solution. This simple and effective treatment offers a novel approach for managing tumoral calcinosis in hemodialysis patients.

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INTRODUCTION

Tumoral calcinosis is a condition characterized by solitary or multifocal calcium phosphate deposits in extra-articular soft tissues. The joints of the hips, shoulders, and elbows are most often involved; the hands, feet, and knees are less often involved. Tumoral calcinosis often presents as painful tumor-like masses that limit joint range of motion; cosmetic problems also occur[1-5].

Tumoral calcinosis has a primary type with no associated disease, which is due to a genetic abnormality, and a secondary type that is associated with other disorders, especially chronic renal failure[1,6]. The prevalence of tumoral calcinosis has been reported to range from 0.5%-3% among dialysis patients[7-9]. The exact mechanisms underlying tumoral calcinosis are unclear. The role of repeated joint microtrauma has been suggested to cause tumoral calcinosis[10]. Previous studies have reported that elevated calcium phosphate production is closely associated with soft tissue calcification[11,12]. Regardless of the etiology, hyperphosphatemia is associated with tumoral calcinosis. Medical treatment for tumoral calcinosis in hemodialysis patients includes dietary phosphorus restriction, calcium-free phosphate binders, and frequent dialysis with low-calcium dialysis solutions; however, these treatments are usually ineffective[7,13,14].

Surgical resection is only used when these treatments are insufficient[15]. Surgical resection of tumoral calcinosis lesions has been the primary treatment[13] but surgical resection is not curative. In contrast, it has been reported that tumoral calcinosis is reduced or resolved with improved systemic symptoms following parathyroidectomy[16-18]. Parathyroidectomy is effective for tumoral calcinosis patients, especially patients with secondary hyperparathyroidism [5]. Following a parathyroidectomy, calcified tissue is significantly resorbed; however, bone renewal is reduced following parathyroidectomy because of lower parathyroid hormone (PTH) levels, resulting in increased circulating calcium and promotion of vessel and soft tissue calcification[19,20].

Calcium phosphate deposits in tumoral calcinosis have been shown to be comprised of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$][21]. Experimentally, hydroxyapatite is known to be insoluble; however, hydroxyapatite is easily dissolved by blowing carbon dioxide (CO_2) into a hydroxyapatite suspension, in which the dissolution amount is 200 times that found without CO_2. Calcium carbonate ($CaCO_3$) is an insoluble calcium salt. Hydroxyapatite co-exists with CO_2; $CaCO_3$ changes into the highly-soluble calcium hydrogen carbonate [$Ca(HCO_3)_2$][22,23]. We therefore assumed that hydroxyapatite in tumoral calcinosis could be soluble with co-existing CO_2 or HCO_3^-.

A bicarbonate Ringer's solution was used. The solution had a pH of 7.0 and an osmotic pressure of approximately 1.0. The solution contained HCO_3^- (28 mEq/L) (Tables 1-3). After resecting calcium phosphate deposits of tumoral calcinosis as much as possible, while filling with bicarbonate Ringer's solution, residual calcium phosphate deposits at the pseudocyst wall are gently scraped with fingers or gauze in the operative field. Because the concentration of HCO_3^- (28 mEq/L) is normal *in vivo*, the amount to be used is not restricted, but we use approximately 1000 mL of the solution for 1 operation. The use of the solution as a washing solution is explained to the patients and consent is obtained.

Herein we report the successful treatment of a patient with tumoral calcinosis by local adjuvant therapy with bicarbonate Ringer's solution. The procedure, chemical background, and safety are discussed.

CASE PRESENTATION

Chief complaints

The patient is a 49-year-old woman with a diagnosis of tumoral calcinosis.

History of present illness

She had noticed swelling in her right shoulder 2 years before the initial assessment. Nine months later, there was bilateral hip and right foot swelling. The size of the right shoulder swelling had increased to be from the supraclavicular fossa to the maxilla, and the size of the swelling was > 20 cm in diameter.

Table 1 Composition bicarbonate solution

Ion	mEq/L
Na^+	130
K^+	4
Mg^{2+}	2
Ca^{2+}	3
Cl^-	109
HCO_3^-	28
$Citrate^{3-}$	4

Table 2 Property of bicarbonate solution

Bicarbonate solution	
Appearance	Colorless and transparent
pH	6.8-7.8
Osmotic pressure	Apraxia 1

Table 3 Component of bicarbonate solution

Component		500 mL	1000 mL
Sodium chloride	NaCl	2.92 g	5.84 g
Potassium chloride	KCl	0.15 g	0.30 g
Calcium chloride hydrate	$CaCl_2 \cdot 2H_2O$	0.11 g	0.22 g
Magnesium chloride	$MgCl_2$	0.10 g	0.20 g
Sodium bicarbonate	$NaHCO_3$	1.175 g	2.35 g
Sodium citrate hydrate	$C_6H_9Na_3O_9$	0.10 g	0.20 g
Citric acid hydrate moderation	$HOC(COOH)(CH_2COOH)_2 \cdot H_2O$	Moderate	Moderate

History of past illness
She has a history of hemodialysis for 15 years.

Personal and family history
There was no specific personal or family history.

Physical examination
The size of the bilateral hip swelling was > 20 cm in diameter and that of the sole of the foot was 3 cm. Each mass was elastic and soft with fluid palpitation.

Laboratory examinations
The leukocyte count was normal [7140/mm^3 (normal range, 3300-8600/mm^3)]. The differential was as follows: neutrophils, 68.8% (normal range, 46%-62%); lymphocytes, 22.4% (normal range, 30%-40%); monocytes, 6.7% (normal range, 4%-7%); eosinophils, 1.7% (normal range, 3%-5%); and basophils, 0.4% (normal range, < 1%). Laboratory data showed the following: corrected Ca^{2+}, 9.7 mg/dL (normal range, 8.8-10.1 mg/dL); inorganic phosphorus, 5.5 mg/dL (normal range, 2.7-4.6 mg/dL); creatinine, 5.16 mg/dL (normal range, 0.16-0.79 mg/dL); estimated glomerular filtration rate, 7.8 mL/min/1.73 m^2 (normal range, < 90 mL/min/1.73 m^2), and PTH-intact, 1110 pg/mL (reference value, 10-65 pg/mL). The serum phosphorus level was elevated, even after medical treatment. The serum PTH level was also elevated, suggesting secondary hyperparathyroidism.

Imaging examinations
Plain radiographs and computed tomography (CT) showed that the lesions were multilocular, opaque, and homogeneous. Axial CT showed various densities of calcium crystals and a liquid level within an elementary formation related

to the sedimentation of calcium crystals with a serous supernatant (sedimentation sign)[4,10] (Figure 1). In the right shoulder lesion, erosions of the bone cortex of the clavicle were noted. Magnetic resonance imaging showed that the cystic lesions had a homogenous low-signal intensity on T1-weighted images and high-signal intensity at the top of the cyst and low-signal intensity at the bottom of the cyst on T2-weighted images. Brachial plexus and vessels were located between the cyst and chest wall (Figure 2).

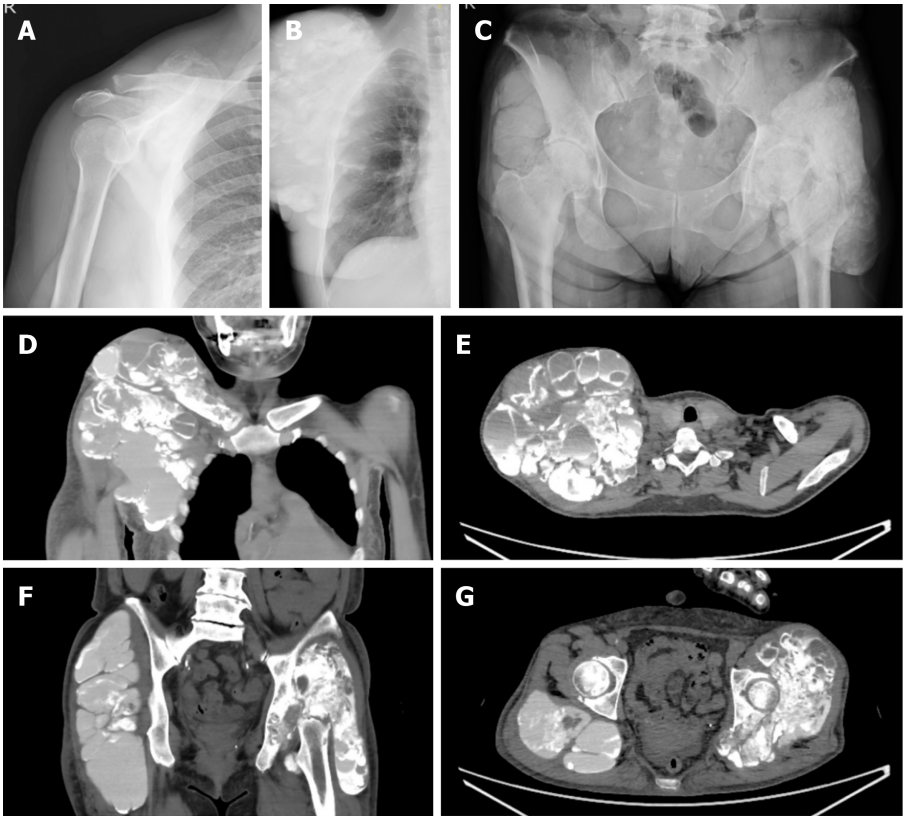

Figure 1 Plain radiograph and computed tomography of tumoral calcinosis. A-C: The images have an opaque and nodular appearance in the right shoulder 12 months (A) and 3 months before the operation (B) and the bilateral hips (C); D-G: Computed tomography (CT) shows calcified multi-cystic lesions in the right shoulder (D and E) and the bilateral hips (F and G); E and G: Axial CT shows each cyst has fluid-fluid level with a dense CT value at the bottom.

FINAL DIAGNOSIS

The diagnosis was based on the clinical course and the imaging findings were tumoral calcinosis associated with hemodialysis.

TREATMENT

Because growth of the lesion after medical treatment with low-calcium dialysis failed, surgical intervention was considered. The right shoulder lesion was not acceptable esthetically and the foot lesion caused discomfort when walking. Although a parathyroidectomy was an option, given the side effects, surgical resection was selected.

Under general anesthesia, an incision was made from the supraclavicular region to the axilla. A pseudofibrous capsule was noted and white fluid and muddy material extended to the subcutaneous tissue. The fluid material was removed. A solid white material was entrapped in the fibrous wall and the fibrous wall was removed as much as possible. The fibrous wall was continuous with the surrounding tissue without a clear border. Because the brachial plexus and vessels were located between the cyst and chest wall, complete resection was not possible. A curettage was performed for the calcified tissue in the fibrous wall and a massive, calcified lesion was removed. The operative field was routinely washed with normal saline to reduce the possibility of infection. A postoperative plain radiograph showed a diffuse, calcified intensity in the operative field (Figure 2). The fluid collection at the right shoulder gradually increased, and the swelling returned to the preoperative size within 2 months.

Because of the unsatisfactory results of the resected shoulder lesion, adjuvant therapy was added to the foot lesion resection. Under general anesthesia, a tourniquet was used. The calcified lesion was located on the sole and an incision

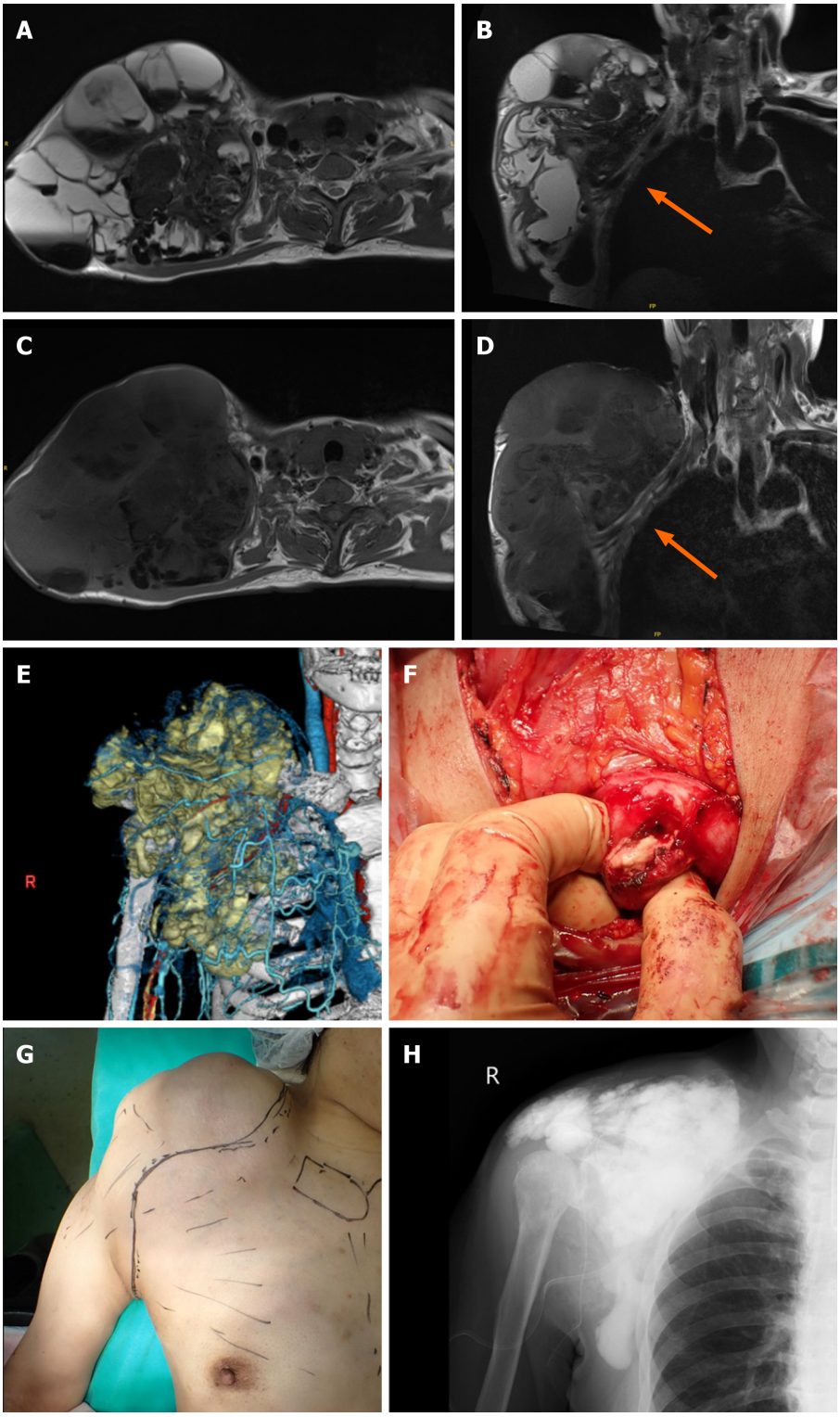

Figure 2 Magnetic resonance imaging and perioperative images. A-D: The magnetic resonance (MR) images reveal multi-cystic lesions with low-to-high signal intensity on T2- (A and B) and T1-weighted images (C and D); A: Axial T2-weighted image shows a fluid-fluid level with a high signal at the top and a low signal at the bottom; B and D: Coronal MR images show brachial plexus and subclavian vessels between the lesion and the chest wall (orange arrows); E: Three-dimension computed tomography shows the extension of the calcified lesion; F: The operation field shows solid calcified lesion trapped in the fibrous wall; G: A photograph shows swelling and planned incision line; H: After the resection, the plain radiograph shows residual calcified fluid and the materials over the operative field.

was made at the lateral side of the sole. Muddy material with the same appearance as the shoulder lesion was removed. A cystic fibrous wall had formed, but was smaller than the shoulder lesion. The fibrous cystic wall was preserved, but calcified materials embedded in the cystic wall were removed as much as possible. Particles of calcified tissue at the fibrous wall were observed, even after resection of the calcified material (Figure 3). After filling with a total of 1000 mL of bicarbonate Ringer's solution, a significant decrease in calcareous deposits was observed by the naked eye and fluoroscopy during the operation (Figure 3). Intra- and post-operative examinations showed no abnormalities in pH or

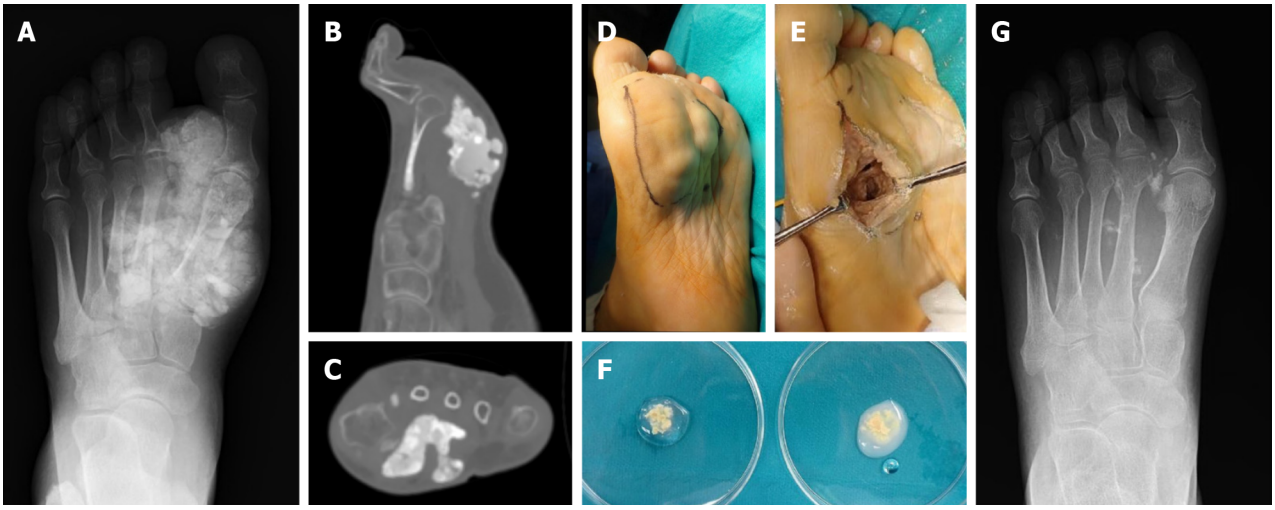

Figure 3 Tumoral calcinosis in the foot. A-C: A plain radiograph (A) and computed tomography (B and C) shows a calcified lesion of the foot; D: A photograph shows swelling and the planned incision line; E: Calcified lesion deposits at the wall after the calcified lesion were removed with suction and curettage; F: The resected calcified material had no reaction in saline (left), but became turbid and dissolved in bicarbonate Ringer's solution (right); G: The calcified lesion was almost removed and no additional deposition was noted 6 months postoperatively.

base excess values. The postoperative course was uneventful. No fluid collection was observed 6 months postoperatively.

OUTCOME AND FOLLOW-UP

The resected materials of tumoral calcinosis were soaked with saline or bicarbonate at the side of the operation theatre. The calcified materials soaked with saline did not change, while the calcified materials soaked with bicarbonate Ringer solution became turbid immediately.

DISCUSSION

The current case was a typical presentation of tumoral calcinosis associated with hemodialysis. According to the literature, the average time of appearance of the mass after the start of dialysis ranges from a few months to several years [10]. Clinically, the lesions present as masses of slow evolution, up to 20 or 30 cm in diameter[10]. The location of the tumoral calcinosis was also typical, and is most often located in the vicinity of the large joints (hips, shoulders, and elbows)[10].

Histologically, tumoral calcinosis has a nodular architecture with fibrous septa coursing between nodules. The fibrous wall shows calcification surrounded by macrophages, osteoclast-like multinucleated giant cells, fibroblasts, and chronic inflammatory cells. Calcified materials are entrapped into the fibrous wall[24,25]. Surgical resection of the lesions is not considered in accordance with the recommendations in the literature. The unsatisfactory results of surgical resection are due to these trapped calcified lesions in the fibrous wall. Calcium phosphate deposits in tumoral calcinosis have been shown to be $Ca_{10}(PO_4)_6(OH)_2$[21]. We have developed a method to dissolve hydroxyapatite as an adjuvant therapy in surgical resection.

Hydroxyapatite has very low solubility. Hydroxyapatite is easily dissolved by blowing CO_2 into the hydroxyapatite suspension. The dissolution amount was 200 times that found without CO_2 blowing[22,23]. $Ca_{10}(PO_4)_6(OH)_2$ reacts with CO_2 as soluble $Ca(HCO_3)_2$ and liquid phosphoric acid (H_3PO_4) [$Ca_{10}(PO_4)_6(OH)_2 + 20CO_2 + 18H_2O \rightarrow 10Ca(HCO_3)_2 + 6H_3PO_4$][26]. CO_2 reacts with H_2O to form carbonic acid (H_2CO_3). Then, H_2CO_3 further dissociates into HCO_3^- and a H^+. Therefore, CO_2 and HCO_3^- have the same chemical reaction in solution. $CaCO_3$ is a calcium salt with the same insolubility, but dissolves easily in solutions containing CO_2. Hydroxyapatite co-existing with CO_2 or $CaCO_3$ changes into the highly soluble $Ca(HCO_3)_2$[22,23]. The bicarbonate Ringer's solution had HCO_3- 28 mEq/L. The bicarbonate Ringer's solution was used in emergency cases as well as in liver transplantation for compensation of extracellular fluid and correct metabolic acidosis. A bicarbonate Ringer's solution is used in the current new method to dissolve hydroxyapatite in tumoral calcinosis.

Use of bicarbonate of Ringer's solution was shown to be safe. The value of HCO_3- (28 mEq/L) was within normal limits *in vivo*, the solution had a pH of 7.0, and the osmotic pressure was approximately 1.0. In a previous report, critical alkalosis occurred in a patient who was irrigated with 1000 mL of 7% sodium bicarbonate solution intraperitoneally as adjuvant therapy for pseudomyxoma peritonei. The peritoneal capillary vessels easily absorb sodium bicarbonate in the abdominal cavity by diffusion, such as in peritoneal dialysis, and the peritoneal surface area is equal to the body surface area. The predicted amount of absorbed sodium bicarbonate was estimated to be approximately 30% of the entire

irrigation volume[27]. The 7% sodium bicarbonate solution was 833 mEq/L, which is much greater than the 28 mEq/L in the solution used in our case. Alkalosis was not reported in a patient who was twice-irrigated with 200 mL of 7% sodium bicarbonate solution for 2 min (total volume = 400 mL; estimated absorbed volume = 85 mL), even for intraperitoneal irrigation for adjuvant therapy for pseudomyxoma peritonei[27].

CONCLUSION

In conclusion, bicarbonate Ringer's solution was used as an adjuvant therapy for tumoral calcinosis, which is a common complication in hemodialysis patients. Bicarbonate Ringer's solution has a role in dissolving $Ca_{10}(PO_4)_6(OH)_2$. The bicarbonate dissolution method is a new, simple, and effective treatment for tumoral calcinosis in hemodialysis patients. The dissolution mechanism needs to be chemically verified in a corollary study.

FOOTNOTES

Co-corresponding authors: Takashi Noguchi and Akio Sakamoto.

Author contributions: Noguchi T, Sakamoto A, Kakehi K and Matsuda S were participated in the treatment; Sakamoto A drafted the manuscript; All authors reviewed the manuscript and approved the final version of the manuscript. Noguchi T and Sakamoto A contributed equally to this work as co-corresponding authors. This invention was achieved through the cooperation of Noguchi T and Sakamoto A, they contributed efforts of equal substance throughout the research process, the designation of co-corresponding authorship accurately reflects our team's collaborative spirit and equal contributions.

Informed consent statement: The analysis used anonymous clinical data that were obtained after each patient had been notified at the Kyoto University home page that the data could be used for a clinical study.

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