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REVIEW

Conservative treatment of knee osteoarthritis: A review of the literature

Wei Boon Lim, Oday Al-Dadah

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Abstract

Knee osteoarthritis (KOA) is a common chronic debilitating disease with an estimated prevalence of 23.9% in the general adult population. The condition is characterised by joint pain, functional impairment and significant reduction in quality of life. Management for KOA can generally be divided into conservative (non-operative) and surgical (operative) measures. Conservative management broadly compromises pharmacological and non-pharmacological options and is conventionally the first line treatment to avoid or delay the need for surgical management. The aim of this study is to provide an overview of the current recommendations, efficacy and safety profile of different conservative treatments through a review of the literature.

Key Words: Osteoarthritis; Knee; Conservative; Non-surgical; Treatment; Management

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Core Tip: Conservative management is conventionally used as the first line treatment to avoid or delay the need for surgical management in knee osteoarthritis. However, it remains under-utilised and recommendations of different conservative management options can vary greatly among different international guidelines. Hence, this study aims to provide an overview of the current recommendations, efficacy and safety profile of different conservative management options so as to better understand the value of each treatment option.

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INTRODUCTION

Traditionally, osteoarthritis is considered a degenerative disease that leads to loss of articular cartilage, bone remodelling (osteophyte formation), subchondral sclerosis and subchondral cysts. Articular cartilage is a shock-absorbent connective tissue that provides a smooth surface to minimise friction upon joint movement. The above changes lead to joint dysfunction and hence pain worsened upon activity, stiffness and loss of function. However, more recent studies[1,2] have shown that the pathogenesis is much more complex with metabolic and inflammatory aspects to it.

TREATMENT OPTIONS

The main overarching aim of conservative treatment is to provide symptomatic relief of the disease and slow its progression to avoid or forestall end-stage surgical options (*i.e.* total knee placement). The various conservative treatment options include exercise, weight loss, pharmacological agents and orthotics.

EXERCISE

Exercise therapy is core treatment in knee osteoarthritis (KOA) with the benefits of exercise having been linked to muscle strengthening and hypertrophy, weight management and even potential disease-modifying effects. The 2007 Osteoarthritis Research Society International (OARSI) guidelines[3] for management of KOA stated that exercise was strongly endorsed with 21 items recommending aerobic and strengthening exercises and a further 8 items recommending water-based exercises. Currently, an exercise regime is strongly recommended as 1st line treatment by international guidelines with strong evidence supporting its effectiveness[4,5]. Uthman *et al*[6] concluded that it is unlikely further clinical trials comparing exercise *vs* non-exercise will ever contradict the clear benefit of the former. Consequently, this review will focus on the effectiveness of mind-body exercises, balance exercises and general recreational physical activity (*i.e.* walking) that are often under-reported.

Mind body exercises

Mind-body exercises, including Tai Chi and Yoga, combine physical activity, mental focus and controlled breathing. In a single-blinded randomised controlled trial (RCT) comparing Tai Chi with standard physical therapy for KOA, Wang *et al*[7] concluded that both interventions showed improvements in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and most secondary outcomes at the post-intervention period and 52 wk follow-up. Notably, the Tai Chi group demonstrated superiority in terms of depression and the physical component in quality of life. Secondary analysis of the same trial concluded that patients begin to notice the improvements after 2-5 wk[8]. Other studies have also supported the effectiveness of yoga in KOA. In a RCT of 113 patients older than 60 years with self-reported KOA, Cheung *et al*[9] reported that both yoga and the control aerobic/strengthening exercises resulted in improved pain relief and physical function. Moreover, perhaps due to the inclusion of meditation and standing-up exercises, the 8-wk yoga program was superior in terms of improving anxiety and fear of falling. As a result, the above studies show the potential of mind-body exercises over traditional standard physical therapy for a more holistic approach.

Balance training

Balance training has been shown to be effective for KOA in improving mobility and reduce pain and falls risk. Liao *et al*[10] in a RCT reported that addition of balance exercises to conventional training further improved function such as stair climbing and standing from a seated position. Balance training has also been shown to be as effective in pain reduction as strength training in a RCT by Chaipninyo *et al*[11]. Holistic exercise programmes that incorporate balance exercises have also been shown to reduce falls risk in a systemic review by Sherrington *et al*[12].

Non-strenuous activities

The benefits of recreational non-strenuous activity such as walking differ based on the pre-existing severity of KOA and length of activity. In a RCT by Wallis *et al*[13] of 46 patients with severe KOA, a 12-wk walking program of 70 min per week was not effective in decreasing knee pain as compared to the control group receiving standard care. They concluded that walking may have cardiovascular benefits without relieving knee pain. However, it must be noted that the patients recruited had grade III or IV osteoarthritis and hence walking might not have significant benefits at a severe stage. In addition, excessive recreational physical activity might lead to worsening outcomes. In a clinical study assessing the dose response of walking for patients with severe KOA (Grade III and IV), Wallis *et al*[14] found that there was a higher risk of adverse events leading to worsening knee pain beyond 70 min per week of supervised walking. However, in a RCT of patients with mild to moderate KOA, Alghadir *et al*[15] concluded that a 6-wk walking program of 30 min a week resulted in greater pain relief, physical function and quadriceps muscle strength. Farrokhi *et al*[16] recommended shorter interval bouts of walking over continuous and longer sessions due to reported knee pain and undesirable knee loading when patients walk continuously for 30 min or more. Therefore, increased general activity might be more effective in mild to moderate KOA at a lower dose to prevent adverse symptoms.

However, most research trials tend to recruit patients who are physically inactive and it is questionable whether patients who are already physically fit can expect to experience the same magnitude of benefits. In the data analysis of 12796 patients in the nationwide physical exercise program for patients with KOA in Denmark, Skou *et al*[17] concluded that all patients regardless of baseline physical activity level can expect to see similar pain reduction at both post-intervention and the 12 mo mark.

Exercise regimen prescription

Prescription of an exercise regime can also be further complicated by the large number of exercises available and variable dosage in terms of frequency, sets and repetition. In addition, there have been far less research done that directly compares different exercises due to the cost and sheer number of exercises available. In a recent systematic review and network meta-analysis, Goh *et al*[18] classified exercises into aerobic, mind-body, strengthening, flexibility/skill and mixed types. Overall, mixed exercises that targeted multiple physical domains were the least effective for unknown reasons whereas other exercises were superior in some target outcomes.

In a single-blinded RCT of 78 patients with grade II or III KOA, Kabiri *et al*[19] reported that a supervised exercise program including resistance training and aerobic training resulted in significant improvements in pain relief and physical function. However, the arm ergometer group demonstrated superior reduction in Visual Analogue Scale (VAS) and change of function in the Knee injury and Osteoarthritis Outcome Score dimension while the treadmill group was superior in the timed up and go test. Therefore, this reinforces the possibility of customising exercises to better target desired outcomes in patients. Moreover, in a RCT of elderly patients with pre-radiographic KOA, Suzuki *et al*[20] concluded that a well-rounded program that targeted overall muscle strength with flexibility was more effective than targeting certain groups.

Aquatic exercises

It has been proposed that aquatic exercises have certain advantages over land-based ones such as pain reduction and reduced joint loading due to the buoyancy of the water. However, in a single-blinded randomised trial comparing land based *vs* water based exercise, Wang *et al*[21] concluded that both types of exercises demonstrate benefits in pain relief, physical function and quality of life without significant differences between them. Instead, they recommended that choice should be based on the patient's preference and convenience.

Mode of delivery of exercises

Despite the proven benefits of exercise therapy in KOA, several studies have noted low compliance rates. An important factor affecting compliance is mode of delivery which can include supervised or internet or home based. In a randomised clinical trial comparing internet *vs* supervised based sessions, Allen *et al*[22] identified baseline body mass index (BMI) and symptom duration as factors that affected the effectiveness of the program. Data analysis from the study showed that patients with low BMI had greater improvements through internet-based exercise sessions while those with high BMI and longer history of symptoms benefitted more from physical therapy. In another RCT comparing a month of supervised exercise in the clinic *vs* unsupervised sessions at home for KOA, Deyle *et al*[23] reported that both were effective but the supervised sessions was twice as effective in terms of pain, stiffness and function. Therefore, it might be more appropriate to use supervised sessions when KOA is more severe or patient has greater co-morbidities or low compliance. Another mode to consider would be group *vs* individual therapy. In a single-blinded randomised clinical trial comparing group *vs* individual approach, Allen *et al*[24] found that 12 wk of both approaches were effective in improving WOMAC and physical performance without significant difference between them.

Integration of exercise and patient education

ESCAPE-knee pain rehabilitation program is a community-based exercise rehabilitation program that combines exercise and patient-education to encourage self-management of osteoarthritis and patient empowerment. The program is supported by National Health Service England and widely available across the United Kingdom. In a RCT by Hurley *et al*[25] concluded that the ESCAPE program was effective, cost-efficient and resulted in better functional outcomes over conventional primary care. The clinical and cost benefits persisted 30 mo after completion of the rehabilitation program. The program was also equally effective regardless of being implemented on an individual or collective group basis. An RCT by Jessep *et al*[26] also supported the economic efficiency of the program over outpatient physiotherapy. While both methods had similar clinical benefits, the ESCAPE program had a lower cost per person and healthcare utilisation cost. Qualitative interviews by Hurley *et al*[27] concluded that the ESCAPE program enables patients to have greater confidence in the safety, effectiveness and applicability of exercising to improve their condition. Hence, it is evident that a holistic exercise program is able to achieve both physiological improvements and psychosocial benefits that fosters health beliefs and behaviours.

WEIGHT LOSS IN KNEE OSTEOARTHRITIS

The OARSI guidelines[28] for KOA noted that 13 international guidelines recommended weight loss as a core treatment. High BMI is a risk factor for developing KOA and has been associated with worse outcomes following knee replacement surgery.

Many studies have shown the effectiveness of weight management. In a randomised trial of 80 obese patients with KOA, Christensen *et al*[29] found that a low energy diet was significantly superior over the control education group in improving physical function over 8 wk. In addition, they concluded that body fat reduction was significantly associated with increase in function and a 10% bodyweight reduction would result in a 28% increase in function. In another clinical study by Coriolano *et al*[30] they found that weight loss of 16.5% in bodyweight through a diet program resulted in significant pain and function improvement. The benefits of the diet program were sufficient for patients to postpone their need for total knee replacement surgery. In addition, in the long-term Osteoarthritis Initiative cohort study, Gersing *et al*[31] reported that weight loss was associated with slower cartilage deterioration especially in the medial compartment. It should be noted that the benefits for cartilage loss was only seen in groups that had lost weight through dieting as opposed to exercise. Hence, it is evident that weight loss is effective in treating KOA, both short-term and long-term.

The benefits of weight loss might be linked to reduce joint loading. In a secondary analysis of data from the CAROT trial, Aaboe *et al*[32] found that every kilogram lost in bodyweight resulted in 2.2 kg reduction in the peak knee joint loading. Weight loss has also been linked to inflammatory and interstitial turnover changes. Loeser *et al*[33] in a RCT of 429 patients with symptomatic KOA found that weight loss through diet decreased biomechanical markers of interstitial matrix inflammation and turnover (IL-6, C1M, C3M and CRPM). However, the limitation of this study was that the biochemical results do not show a relationship with change in physical function or radiographic progression of osteoarthritis.

Weight loss is often promoted in tandem with exercise therapy and the combination of both interventions has been shown to be more effective. In a single-blinded RCT of 316 patients with symptomatic KOA, Messier *et al*[34] compared the effectiveness of exercise and weight reduction measured in primary (WOMAC function index) and secondary (functional tests, pain and stiffness score, joint space width) outcomes. The clinical study concluded that a combination of both interventions was superior over either intervention alone in self-reported pain and function, and physical performance. The benefits were maintained for 12 additional months. Moreover, in the Osteoarthritis Initiative, it was noted that slower cartilage loss was seen in the diet and diet plus exercise group, but not in the exercise only group[31]. Therefore, this highlights the increased effectiveness in combining both weight loss and exercise intervention.

However, there have been doubts about the viability of weight loss programs in the long run due to the possibility of regaining weight or potentially negative side-effects of weight cycling. Weight cycling refers to periods of weight loss followed by weight gain which can lead to adverse events such as increased metabolic risk. However, in a randomised trial comparing intermittent weight cycling through low-energy diet *vs* steady weight loss through daily meal replacements over 3 years, Christensen *et al*[35] concluded that both strategies with dietary counselling were equally viable and effective with a good safety profile. Firstly, both structured diet programs were effective in maintaining weight loss without rebounding. In addition, the benefits of weight loss on symptom relief and cardiovascular disease risks were maintained over 3 years. Hence, this emphasises the effectiveness of weight loss as long as a structured program is in place to ensure patient compliance.

PHARMACOLOGICAL MANAGEMENT IN OSTEOARTHRITIS

Originally, the World Health Organisation (WHO) analgesic pain ladder was established for treatment of cancer pain in 1986. The WHO ladder consisted of the following steps: Step I with non-opioid analgesics [acetaminophen or nonsteroidal anti-inflammatory drug (NSAIDs)], Step II with weak opioids and step III with strong opioids. This approach has been extrapolated to pain management for osteoarthritis and involves going to the next step if the current step was inadequate for pain relief. However, such an approach has now been questioned due to the multiple pain modalities present in KOA.

Acetaminophen/paracetamol

Even though acetaminophen is often recommended as first-line analgesia, its effectiveness is questionable and it was not recommended in the most recent OARSI guidelines[4] for KOA. In a double-blinded RCT involving 779 patients with KOA, Miceli-Richard *et al*[36] concluded that acetaminophen at 4 g/day taken over 6 wk did not demonstrate statistically superior results over placebo in terms of knee pain intensity and assessment of their condition. The use of acetaminophen was well-tolerated with a good safety profile. In a separate double-blinded RCT by Case *et al*[37], acetaminophen similarly did not demonstrate statistically or clinically meaningful results over placebo as assessed by the WOMAC index. Although other trials by Prior *et al*[38] and Altman *et al*[39] do support the effectiveness of acetaminophen, the Cochrane systematic review for paracetamol in KOA concludes that the benefits for pain and physical function are small and are clinically unimportant[40]. Therefore, recommendation of acetaminophen as first-line analgesic medication should be reconsidered.

However, acetaminophen might be valuable for its advantageous synergistic effect when combined with other analgesics for pain relief. Pareek *et al*[41] in a randomised multicentre study demonstrated that the combination of aceclofenac and acetaminophen was superior over monotherapy in rapid pain relief for osteoarthritic flare-ups. However, Doherty *et al*[42] in a randomised double-blinded study concluded that while the combination of paracetamol and ibuprofen was superior for pain relief over paracetamol alone, it was not significantly superior over ibuprofen alone. In addition, patients taking two ibuprofen/paracetamol tablets were found to be at greater risk of reduction in haemoglobin levels due to gastrointestinal (GI) blood loss than either monotherapy alone. This suggests a synergistic interaction between paracetamol and ibuprofen in causing GI complications.

NSAIDs

NSAIDs work by inhibiting cyclo-oxygenase enzymes, and in turn reducing prostaglandin levels. Hence, this leads to a reduction in pain and inflammation. NSAIDs can be classified into non-selective or selective COX-2 inhibitors, as well as topical and oral formulations. The National Institute for Health and Care Excellence (NICE)[43] recommends topical NSAIDs before systemic analgesics (oral NSAIDs, COX-2 inhibitors and opioids) for KOA. The OARSI guidelines[44] also consider topical NSAIDs to be safer and better tolerated than oral NSAIDs.

Comparison of selective and non-selective NSAIDs

Head-to-head trials have shown both classes to have comparable effectiveness. In a 6-wk RCT comparing efficacy of celecoxib (COX-2 selective NSAID) *vs* ibuprofen (non-selective NSAID) for KOA, Gordo *et al*[45] concluded that both were similarly effective and well-tolerated. Pooled results from two placebo-controlled trials[46] showed that both Naproxen (non-selective NSAID) and Celecoxib (COX-2 selective NSAID) resulted in early significant pain relief based on WOMAC score by the second day of treatment and analgesic effect was maintained for 12 wk. However, while both treatments were statistically superior over placebo at week 6 based on the OMERACT-OARSI response, Naproxen remained superior at week 12 but Celecoxib was not.

Instead, the bigger difference would be tolerability and safety profile. COX-2 selective inhibitors have been thought to cause fewer GI side-effects as the inhibition of COX-1 is responsible for the associated GI toxicity. In the CONDOR randomised trial, Chan *et al*[47] reported that the risk of GI complications was lower in the patient group taking COX-2 selective NSAIDs than in patients taking non-selective NSAIDs with a proton pump inhibitor. There is an increased risk of GI complications with prolonged intake and in patients over 70 years of age.

In terms of cardiovascular risks, both classes appear to have similar risks. Two population-based analysis studies in Taiwan and Finland reported that use of all NSAIDs increase the risks of cardiovascular events[48,49]. A meta-analysis[50] concluded that naproxen, out of all the NSAIDs, is associated with the least vascular risks. Overall, NSAIDs have varying safety profiles and prescription of the most appropriate drug should be done based on the balance of benefits *vs* risks to the individual patient. In a network meta-analysis[51], Naproxen was ranked as the most effective conservative treatment of KOA, coupled with its good relative safety and low cost to improve pain and function.

Oral vs topical NSAIDs

Despite oral NSAIDs being a step-up in pharmacological pain management, oral NSAIDs are not shown

to be superior in studies. Tugwell *et al*[52] in a RCT reported that oral and topical preparations of diclofenac were equivalent in symptomatic relief of KOA. While the topical form resulted in minor local skin irritation, the oral form had significantly greater systemic side-effects and abnormal laboratory tests (liver function tests, haemoglobin and creatinine clearance). In the TOIB RCT comparing topical and oral ibuprofen for chronic knee pain, Underwood *et al*[53] reinforced that both formulations were similar in effectiveness but oral NSAIDs produced more instances of minor adverse side-effects. However, neither resulted in significant improvements in WOMAC scores from baseline to follow-up at one year, hence this shows that neither preparation is particularly effective in some patients.

Opioids: Evidence regarding the safety and effectiveness of opioids are still contradictory based on current literature with mixed recommendations from guidelines. The latest OARSI guidelines[4] strongly recommends against opioid use due to the risk of potential dependency, be it transdermal or oral form. However, the latest American College of Rheumatology guidelines[5] conditionally recommends Tramadol over non-Tramadol opioids if opioids are considered. Non-tramadol opioids are only recommended if alternatives are exhausted and should be used at the lowest possible dose for the shortest possible time.

Opioids can generally be classified as weak or strong (Table 1).

Weak opioids: Research has generally supported the effectiveness of weak and strong opioids over placebo for pain relief. Peloso *et al*[54] in a RCT reported that controlled release codeine was statistically superior over placebo in improving pain, stiffness and physical function based on the WOMAC subscales. Also, in a non-inferiority trial, Conaghan *et al*[55] concluded that buprenorphine patches with oral paracetamol and co-codamol tablets were effective in significantly reducing patients' pain over 7 d of treatment. However, over 80% of patients in both groups reported adverse events and the study was limited by its high withdrawal rate in both groups.

Tramadol: Tramadol's mechanism of action is unique as it is not only a weak opioid receptor agonist, but also modulates norepinephrine and serotonin levels. Current clinical trials have shown tramadol to have mixed effectiveness. In a RCT of 1020 adults with osteoarthritis of the knees or hips, Gana *et al*[56] reported that tramadol at 200-300 mg once daily was statistically superior over placebo for improvements on pain, physical functioning but did not reach significance for subject global assessment of disease activity. Post-hoc data analysis by Kosinski *et al*[57] revealed tramadol also improved sleep quality and decreased pain-related sleep disturbance. However, in another RCT by DeLemos *et al*[58], the 100 mg and 200 mg dosages were not superior over placebo in any of the primary end-points. As for the 300 mg dose, significant improvements were achieved in patient global assessment of disease activity but not in WOMAC pain and physical function scores. Addition of tramadol at 200 mg per day has also been shown to allow significant naproxen dose reduction in patients taking them based on a placebo-controlled study by Schnitzer *et al*[59].

Due to the mixed effectiveness shown, the paper looked towards systematic reviews to ascertain effectiveness of tramadol. In the latest Cochrane review for tramadol[60], tramadol alone or combined with acetaminophen is not likely to be clinically important in improving pain or function in patients, but an additional 5% of patients do report a clinically important improvement of 20% or more in pain relief compared to placebo.

Head to head trials have also shown tramadol to be comparable to other opioids. In a randomised parallel trial comparing tramadol and dihydrocodeine, Wilder-Smith *et al*[61] reported that strong osteoarthritic pain insufficiently controlled by NSAIDs alone was controlled by both medication by the second day. While tramadol was superior for analgesia at rest and interfered less with GI function, it resulted in greater sedation and drowsiness as compared to dihydrocodeine. Karlsson *et al*[62] in a randomised non-inferiority trial of patients with chronic osteoarthritis pain reported that tramadol tablets were comparable to buprenorphine patches.

Strong opioids: In a randomised controlled study by Matsumoto *et al*[63], oxymorphone resulted in superior pain relief and functional improvements over placebo in patients with osteoarthritic pain uncontrolled by other non-opioid analgesia. However, 83% of patients reported at least one adverse event which were mild to moderate and was the biggest reason for patient withdrawal. Conversely, Caldwell *et al*[64] in an RCT reported that morphine sulphate only resulted in statistically significant pain relief but not physical function. While opioids have been shown to maintain their analgesic effect in the long-term for open-label extension studies, Bialas *et al*[65] concluded that such studies are limited due to the low-quality evidence and high dropout rates.

Opioids in general: Despite opioids being recommended as a last pharmacological resort when all alternatives fail, their use has not been shown to be superior over non-opioid in non-inferiority trials. In the SPACE trial comparing non-opioids and opioids for moderate to severe chronic osteoarthritis, Krebs *et al*[66] concluded that opioid therapy should not be initiated as they were not superior for pain relief, function and quality of life. Instead, the opioid group had significantly more medication-related side-effects and higher pain intensity over 12 mo. Beaulieu *et al*[67] also reported that tramadol and diclofenac were equally effective in pain relief and functional improvement. In another systematic

Table 1 Strength of opioids

Weak opioids	Strong opioids
Codeine	Morphine
Dihydrocodeine	Methadone
Tramadol	Fentanyl
	Oxycodone
	Tapentadol
	Oxymorphone

review comparing pain reduction, Smith *et al*[68] reported that NSAIDs, strong and weak opioids all have similar analgesic. Therefore, the lack of a demonstrable difference between strong and weak opioids suggests the need for more comparative trials in chronic non-cancer pain. Elderly patients prescribed opioids as opposed to NSAIDs also have a significantly greater risk of falls and fractures by 4.1 times[69].

Despite lack of evidence for clinical superiority over placebo, meta-regression in systematic reviews [70,71] have shown them to have small or no clinical impact on pain relief and functional improvements. Their effectiveness is also compromised by their high incidence of adverse events and side-effects as demonstrated by the high withdrawal rates in clinical studies although this can be partially mitigated by titration as many clinical studies often start with a non-titrated dose. Side-effects include GI adverse events (constipation, nausea, vomiting); central nervous system events (sedation, dizziness); dermatological events (pruritus, rashes)[72].

Opioid use also leads to poor long-term outcomes and result in both peri-operative and post-operative complications. In terms of post-operative complications, pre-operative opioid use has been linked to a greater likelihood of chronic opioid use following surgery[73]; greater risk of adverse outcomes that includes peri-prosthetic joint infection[74], higher hospital readmission rates[75] and post-operative pain[76]. The higher risk of complications would further obfuscate management as patients would need to wean or reduce their opioid use for several months prior to the surgery[77]. In terms of peri-operative complications, long-term opioid use can result in hyperalgesia and tolerance [78]. This would make it more difficult to provide adequate peri-operative and post-operative analgesia in patients undergoing knee replacement (or any form of) surgery.

Intra-articular corticosteroids: Intra-articular corticosteroids (IACs) are frequently-used as an adjunctive treatment for pain control in KOA due to its anti-inflammatory effect. Recommendation for use of IACs in treatment of KOA is variable. While the American Academy of Orthopaedic Surgeons[79] found it inconclusive, other organisations such as NICE[43], OARSI[80] and American College of Rheumatology[5] have recommended or conditionally recommended its use.

Clinical studies have affirmed the effectiveness of IACs as an adjunctive therapy for short-term pain relief and the effectiveness of IACs in the literature has varied from 4 wk up to 26 wk. A network meta-analysis of conservative treatments[51] concluded that IACs provided the greatest short-term pain relief from 4 to 6 wk. In a RCT comparing a single intra-articular injection of hyaluronic acid and triamcinolone acetonide, Tammachote *et al*[81] concluded that IACs resulted in improved pain, function and knee range of motion without any serious adverse events that was present in the 1st week and lasted for 6 mo. However, Yavuz *et al*[82] reported in a prospective study that all three IACs (methylprednisolone, betamethasone and triamcinolone) were effective but their benefits declined at week 12. Regarding the choice of corticosteroid administered, the literature has been mixed. Lomonte *et al*[83] supported that both methylprednisolone and triamcinolone were equally effective for sustained improvement in pain and function up to 24 wk whereas Yavuz *et al*[82], reported that Methylprednisolone also provided better analgesia until the 6th week. The effectiveness of IACs is also independent of the injection site. In a RCT of 60 patients with KOA receiving IACs, Parrilla *et al*[84] concluded that corticosteroids resulted in a clinically significant pain improvement regardless of the injection site.

However, IACs have not shown synergistic benefits when combined with other conservative treatments. A RCT by Henrikson *et al*[85] concluded that addition of IACs to physical therapy provided no further benefits. Another RCT by Deyle *et al*[86] also showed that physical therapy was superior over IACs in the long-term with less pain and functional disability.

Furthermore, the effectiveness of repeated IACs has been shown to be variable. In a randomised placebo-controlled trial, McAlindon *et al*[87] concluded that repeated IACs every 3 mo did not result in superior knee pain control over saline injections. However, intra-articular injections of triamcinolone acetonide at the same dose resulted in significant improvement in knee pain and stiffness over 2 years in a RCT by Raynauld *et al*[88].

IACs have shown a good safety profile but long-term safety profile of IACs has been inconclusive. Raynauld *et al*[88] in a RCT comparing intra-articular injections of steroids against saline, concluded that long-term IACs was safe and did not negatively affect the knee joint. However, McAlindon *et al*[87] concluded that IACs resulted in significantly greater loss of cartilage volume compared to intra-articular injection of saline. In the recent Osteoarthritis Initiative observation study[89], IACs and especially repeated IACs may be associated with greater risk of radiographic KOA progression.

Intra-articular hyaluronic acid: Hyaluronic acid is a glycosaminoglycan naturally found within the knee joint that decreases with the progression of osteoarthritis. Its anti-arthritic effects have been hypothesised to be due to multiple mechanisms of action including chondroprotection, joint lubrication, shock absorption, anti-inflammation and immune cells modulation. Intra-articular hyaluronic acid (IAHA) is an alternative to IACs but recommendation among national and international guidelines for its use in KOA remains inconclusive. The OARSI guidelines[4] state that IAHA treatment is conditionally recommended for longer term treatment effects in patients with KOA whereas NICE guidelines[43] do not recommend it.

Research studies have shown IAHA and IACs to have comparable efficacy with IACs providing greater pain relief in the short-term while IAHA provide greater pain relief in the long-term. In a randomised non-inferiority study by Tammachote *et al*[81], they concluded that both groups had similar symptomatic improvement by the end of six months. However, IACs resulted in better pain relief in the first week and greater functional improvement in the second week. In a multi-centre prospective study, Leighton *et al*[90] reported that IACs and IAHA were comparable throughout the first 12 wk but IAHA was superior for pain, stiffness and function from the 12th to 26th week. Bannuru *et al*[80] in a systematic review concluded that current evidence suggests corticosteroids to be more effective in the short term up to 4 wk, whereas hyaluronic acid is more effective beyond the 4th week. Therefore, the differing therapeutic trajectory plays a key role in clinical prescription based on the patients' symptoms and expectations. A randomised study by Ozturk *et al*[91] reported that the combination of IAHA and IACs was superior over hyaluronic acid alone, resulting in more rapid pain relief and to a lower level. This shows the potential of synergistic effects of combining both therapies. However, it should also be noted that available research trials have been criticised for publication bias and risk of selective reporting of outcomes in an analysis of randomised trials[92].

Repeated use of hyaluronic acid has also been shown to be effective with a good safety profile. In the AMELIA randomised controlled study, Navarro-Sarabia *et al*[93] found that patient responsiveness increased throughout the 40-mo study with repeated injections. In terms of symptom improvement, IAHA not only improve symptoms in-between injections but also had a carry-over effect that lasted for at least 1 year after the last injection. As for safety, incidence of adverse events did not differ from that of placebo's and there were no serious adverse events. Neustadt *et al*[94] also reported that five injections of hyaluronic acid at weekly intervals up to 26 wk was associated with an excellent safety profile and only had minor local adverse reactions. Follow-up at 24 mo still supported the excellent safety profile of the injection.

Overall, the current literature suggests that hyaluronic is an effective alternative to corticosteroid injections with an excellent safety profile.

Topical capsaicin: Capsaicin has been recommended by NICE[43] for adjunctive pain management in KOA. Its mechanism of action is *via* selective depression of type-C nociceptive fibres.

Initial research regarding its effectiveness dates back to 1991 where Deal *et al*[95] reported that topical application four times daily resulted in significant pain relief compared to placebo. This was supported by subsequent research trials. In a double-blinded RCT, Kosuwon *et al*[96] further reported that 0.0125% capsaicin gel was effective for improving stiffness and function in patients with grade II and III Kellgren-Lawrence KOA. In a long-term extension trial of a RCT by Schnitzer *et al*[97] concluded that capsaicin cream was effective in all three primary end-points for patients with mild to moderate KOA who were already taking NSAID or COX-2 inhibitors. The efficacy was also maintained up to a year of continuous use. McCleane *et al*[98] has also highlighted the potential of combining capsaicin with glyceryl nitrate which resulted in reduced localised burning sensation and superior analgesic effects even in patients with osteoarthritis uncontrolled by other pharmacological treatments. However, the study did include patients with osteoarthritis in other joints besides knees which would affect the generalisability of its results.

Capsaicin also has a good safety profile due to its lack of systemic absorption. The main side-effect is a localised burning sensation but withdrawals due to this has been low in the afore mentioned research trials.

As a result, topical capsaicin is effective for mild to moderate KOA. More research would need to be done for patients with severe KOA or other co-morbidities as they are excluded in afore mentioned trials.

Flexiseq gel: Flexiseq gel is marketed as an adjunctive analgesia that contains phospholipid vesicles that passes into the knee synovial joint where it provides lubrication to minimise friction between cartilage and hence reduces pain. In a RCT of 1395 patients with osteoarthritic knee pain, Conaghan *et al*[99] reported that Flexiseq gel was superior to oral placebo with comparable efficacy to oral celecoxib in pain

reduction and functional improvement. There have also been an additional three clinical studies that used Flexiseq gel as a treatment arm[99-102]. However, these clinical studies have shown low quality of evidence. All three of these clinical studies also involve Flexiseq gel as the topical placebo arm and there has been no comparison of Flexiseq gel against a true inactive topical gel to date to account for placebo effects. Furthermore, all the trials have the potential to introduce funding bias as they are sponsored by pharmaceutical companies. There is also limited evidence base for the analgesic mode of action as stated in NICE guidelines[103].

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

Transcutaneous electrical nerve stimulation (TENS) therapy involves passing of electrical currents through electrodes placed on the targeted area to stimulate peripheral nerves for pain control. Delivery of the electrical currents can be of varying frequencies and intensity. Clinical studies examining the effectiveness of TENS therapy have shown that it is mostly ineffective with little clinical benefits for patients.

In a double-blinded RCT of 203 patients with KOA by Atamaz *et al*[104], application of TENS therapy did not result in a statistically significant or superior results in pain intensity or physical functioning over placebo treatments. While it was suggested that the lower intake of paracetamol in treatment groups suggested pain relief, lower intake was only present in the first 3 mo for the TENS group and did not persist to the end of the study. In addition, it would be difficult to attribute the improvements in assessment parameters to application of physical agents as every group also had a structured exercise and education program. In another RCT by Cheing *et al*[105], the combination of TENS and exercise training resulted in the best overall improvements in physical outcomes but this was not significantly superior over placebo stimulation. Another randomised placebo-controlled study by Fary *et al*[106] similarly showed that 26 wk of pulsed electrical stimulation was not more effective than placebo. Hence, the current literature does show that TENS therapy at best has small benefits that are not likely to be clinically meaningful.

KNEE BRACING

Knee bracing is often recommended as an adjunctive treatment in KOA. Proposed mechanisms of action for knee bracing include unloading of the medial compartment, or through general biomechanical and neuromuscular effects that lead to improved proprioception and joint stability.

However, clinical studies do not support the theoretical benefit of knee braces. In a RCT of 117 patients with unicompartmental KOA, Brouwer *et al*[107] found that benefits in using the brace was small and compliance was low due to ineffectiveness and skin irritation. In a separate 52 wk observation study of 204 patients with KOA, Yu *et al*[108] found that that neither patellofemoral or tibiofemoral customised bracing resulted in a significant difference in overall pain and functional improvements compared to the control unbraced group. Rather, a multidisciplinary program with a multidisciplinary approach was effective and sufficient for symptomatic improvements. However, limitations of this study included high dropout rate with less than 60% participating in the final assessment and potential recall bias. Survey results by Squyer *et al*[109] also indicated low compliance use of knee brace in patients which is 28% after the first year and 25% after the second year. No patient or radiographic factors were identified in the survey to predict usage or discontinuation of the knee brace.

Due to the lack of research supporting its efficacy and poor-quality evidence, the OARSI guidelines[4] now recommended against knee bracing.

FOOT ORTHOSES

Laterally-wedged insoles have also been recommended in the treatment of medial KOA because of their potential to reduce the knee adduction moment (KAM) (medial-to-lateral knee loading). Research has shown that an increased external knee adduction moment (EKAM) causes an increase in risk of structural deterioration over time of the medial knee compartment. Therefore, insoles might have the potential to minimise the rate of deterioration and help relieve symptoms.

However, several clinical studies have shown that laterally-wedged insoles might not confer any beneficial biomechanical effect and symptom relief. In a secondary analysis of data from a RCT study, Duivenvoorden *et al*[110] concluded that neither valgus brace nor laterally wedged insoles resulted in clinically relevant biomechanical alterations. Unloading of the medial compartment was only present in laterally wedged insoles at baseline and did not persist beyond six weeks. However, the unloading effect at baseline was small and might not be clinically relevant. Another randomised study assessing

the relationship between KAM and knee pain in 70 patients with medial KOA by Jones *et al*[111] concluded that lateral wedges did reduce the average EKAM but changes in EKAM had no clear-cut relationship with knee pain reduction. Instead, some subjects experience paradoxical pain reduction even though EKAM increased. This finding was further supported by a three-month RCT by Lewinson *et al*[112] Their study concluded that the magnitude of KAM reduction was not associated with the same magnitude of change in pain.

Several studies have shown little difference between laterally wedged insoles and neutral insoles. In a 6 mo prospective RCT of 156 patients with symptomatic medial KOA, Pham *et al*[113] concluded that lateral wedged insoles was not superior over neutral insoles in terms of pain, stiffness and physical functioning with the exception of decrease NSAIDs consumption. Neither neutral nor lateral wedged insoles demonstrated disease-modifying effects. Bennell *et al*[114] double-blinded RCT of 200 subjects with mild to moderately severe medial KOA also similarly reported that lateral wedge insoles demonstrated no additional benefit over flat insoles in symptom improvement or disease modifying effect.

Effectiveness of insoles also depends on patient factors. Shimda *et al*[115] in a prospective study analyzing the gait of 42 patients reported that laterally wedged insoles were most effective in reducing KAM in patients with early and mild osteoarthritis. Toda *et al*[116] concluded that insoles are more effective for younger patients and those with higher lean body mass. Conversely, use of insoles are less effective for older patients with sarcopenia.

Overall, insoles and knee bracing have similar effectiveness. However, insoles do have an advantage because of higher compliance, lower cost and ease of use. Therefore, clinicians and allied health professionals should take this into consideration if they wish to recommend foot orthoses as an adjunctive treatment.

THERMOTHERAPY

Thermotherapy involves superficial application of heat or cold to improve symptoms. Cryotherapy is thought to help in pain management by vasoconstriction of blood vessels and blocking of nerve impulses in the joint. This would be useful in reduction of inflammation, oedema of the joint and pain. Alternatively, heat therapy has been proposed to help by relaxing muscles and increasing blood circulation to the applied area. This would then result in pain and stiffness reduction, as well as improving mobility.

Evidence to support use of thermotherapy has been inconclusive. An early RCT by Clarke *et al*[117] in 1974 reported that use of ice packs for three weeks did not result in statistically significant or clinically important pain relief compared to the control group. Subsequently, Hecht *et al*[118] found that ten treatment sessions of cold pack application resulted in oedema reduction while hot packs did not. However, the clinical importance of oedema reduction was unclear. Yurtkuran *et al*[119] reported that ice massage for 20 min at 5 sessions per week was clinically superior over control in increasing quadriceps strength. No difference was seen for function, joint range of motion or knee oedema. In a recent RCT, Aciksoz *et al*[120] concluded that both hot and cold applications in addition to standard treatment resulted in mild improvements for pain, function and quality of life. However, the improvement was not sufficient to be statistically superior over the control group.

Overall, the current literature has been inconclusive with contradicting results. However, given that the thermotherapy is easily implemented and relatively safe, there is no harm in its recommendation as an adjunctive therapy. The decision on heat or cold application would heavily depend on patient's preference as Denegar *et al*[121] in a randomised trial reported greater improvements in pain and function when patients used their preferred treatment.

ORAL SUPPLEMENTS

Glucosamine and chondroitin are two of the most popular dietary supplements marketed for effective management of symptoms of osteoarthritis and improvement of joint health.

Clegg *et al*[122] in a large RCT of 1583 patients concluded that neither glucosamine nor chondroitin sulfate taken alone or together reduced pain effectively and was not significantly better than placebo. Part of the centres of the above GAIT trial also participated in an ancillary study whereby Swaitzke *et al*[123] reported that neither glucosamine nor chondroitin sulfate alone or in combination had a predefined clinically important difference on progress of joint width space narrowing. However, they did note that patients with Kellgren-Lawrencegrade II KOA showed the greatest potential for disease-modifying effect by these treatments. In a more recent RCT by Fransen *et al*[124] the study similarly reinforced the ineffectiveness of glucosamine and chondroitin for symptomatic benefit over placebo. However, patients taking the glucosamine-chondroitin combination had a statistically significant reduction in progress of joint space narrowing at 24 mo. This could be due to the lower percentage of patients with moderate to severe KOA compared to the GAIT trial.

However, the preparation of the supplements does impact the effectiveness. In the CONCEPT trial, Reginster *et al*[125] concluded that pharmaceutical-grade chondroitin at 800 mg/day over 6 mo was superior to placebo and similar to celecoxib in pain reduction and improvement in function. Similarly, Hochberg *et al*[126] in a randomised double-blinded study reported that a combination of prescription-grade chondroitin and glucosamine had comparable efficacy to oral celecoxib in symptomatic relief for KOA after six months of use. However, this study does have several limitations. The study compared the supplementation against oral celecoxib which did not demonstrate superior results over placebo in the GAIT trial. Furthermore, sponsorship of this study by a pharmaceutical company could have introduced bias.

In terms of safety profile, the above research trials show both glucosamine and chondroitin to have a good safety profile. In fact, a recent prospective cohort study across the United Kingdom reported that glucosamine supplements might even be beneficial and associated with lower cardiovascular disease risks[127]. However, follow-up analysis of the osteoarthritis initiative reported that long-term data showed that chondroitin sulfate and glucosamine supplementation could be associated with higher risks of radiographic osteoarthritis and subsequent knee replacements[128].

Overall, glucosamine and chondroitin have shown promise for potential of disease progression and symptomatic relief. However, efficacy would depend on the preparation of the supplements and severity of the disease. More research would also need to be done regarding the long-term safety profile of the supplements. Several meta-analysis and systematic reviews have also criticised that trials supporting large symptomatic benefits often have poor quality, publication bias and small samples while more robust methodologically sound studies have found small to no benefits.

DRY NEEDLING

Dry needling involves the use of fine needles to penetrate the skin and deactivate myofascial trigger points. The mechanism of action has been linked to activation of descending pain pathways that inhibit nociceptive processing[129].

Studies by Ceballos-Laita *et al*[130] and Itoh *et al*[131] have shown dry needling to be effective in improving function and pain intensity for osteoarthritis in the short term when compared to patients receiving control sham treatment. However, limitations of the above studies include low number of dry needling treatments and lack of long-term follow ups to examine the long-term benefits.

Moreover, the effectiveness of dry needling as part of a multidisciplinary approach remains questionable. Romero *et al*[132,133] examined the benefits of adding dry needling to a structured exercise program in KOA in two separate RCTs from a short-term and long-term perspective. However, dry needling failed to show improvements in function and pain intensity in the treatment group for both studies at the 3-mo and one-year mark respectively. The correlation between trigger points and intensity of KOA pain has also shown to be poor based on a secondary analysis by Romero *et al*[134]. Overall, more studies, especially with longer term results, are required to support the effectiveness of dry needling as part of a multidisciplinary approach.

CONCLUSION

Based on the current literature available to date, a multidisciplinary and a multimodal approach with a key focus on exercise, weight loss and pharmacological pain management would be the most appropriate. Out of the multiple pharmacological options available, chronic pain management through topical NSAIDs with intermittent intra-articular injections of corticosteroids or hyaluronic acid provides a reasonable balance between benefit and risk. Topical capsaicin can also be effective in mild to moderate KOA. Acetaminophen has not been shown to be an effective analgesic. Opioids, preferably tramadol, would have to be evaluated on a case-by-case basis due to their potent side-effects which are sufficiently detrimental to negate their benefits. While the post-operative negative impact is clear, more research is needed around the optimal adjunctive peri-operative analgesia and the effect of opioid tolerance on patients undergoing surgery.

There are numerous types of effective exercise therapy available, including a well-structured physical therapy program. Alternate interventions such as thermotherapy, leg orthoses or TENS have shown conflicting results and perhaps only conditionally recommended on an individual basis. Further research is required regarding the effectiveness of chondroitin and glucosamine.

FOOTNOTES

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important intellectual content. All of the authors reviewed and approved the final manuscript as submitted.

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MINIREVIEWS

Patient-specific instrumentation in total ankle arthroplasty

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Abstract

The recent increase in the adoption of total ankle arthroplasty (TAA) reflects the improvements in implant designs and surgical techniques, including the use of preoperative navigation system and patient-specific instrumentation (PSI), such as custom-made cutting guides. Cutting guides are customized with respect to each patient's anatomy based on preoperative ankle computed tomography scans, and they drive the saw intra-operatively to improve the accuracy of bone resection and implant positioning. Despite some promising results, the main queries in the literature are whether PSI improves the reliability of achieving neutral ankle alignment and more accurate implant sizing, whether it is actually superior over standard techniques, and whether it is cost effective. Moreover, the advantages of PSI in clinical outcomes are still theoretical because the current literature does not allow to confirm its superiority. The purpose of this review article is therefore to assess the current literature on PSI in TAA with regard to current implants with PSI, templating and preoperative planning strategies, alignment and sizing, clinical outcomes, cost analysis, and comparison with standard techniques.

Key Words: Total ankle arthroplasty; Total ankle replacement; Patient-specific instrumentation; Ankle computer navigation system; Preoperative navigation; Prophecy; Infinity; INBONE II

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Core Tip: The recent increase in the adoption of total ankle arthroplasty (TAA) reflects the improvements in implant designs and surgical techniques, including the use of preoperative navigation system and patient-specific instrumentation (PSI). The outcomes of TAA have generally been less satisfactory compared to those of other arthroplasties. Preoperative planning using PSI theoretically improves implant positioning and alignment. This review article assess the current literature regarding PSI in TAA.

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INTRODUCTION

The recent increase in the adoption of total ankle arthroplasty (TAA) reflects the improvements in implant designs and surgical techniques. Nonetheless, the outcomes of TAA have commonly been less satisfactory compared to those of other arthroplasties[1]. Thus, the search for successful TAA continues, and in fact, the interest in implementing this new technology is growing.

The literature on the subject has shown that proper implant positioning and alignment are necessary for achieving good results in TAA. Even the mispositioning of a small implant component has a relevant impact on motion and contact pressure, which may lead to failure[2,3].

As a matter of fact, most of the current TAA instrumentations do not really address patient's variable anatomical features. When using a traditional system, the main parameter considered for tibial cutting block is represented by the tibial tuberosity as proximal reference and the middle of the anterior border of the tibiotalar joint as distal reference. The talar resection is performed with the foot in a visual neutral position[2,3]. This technique allows an experienced surgeon to adopt a good implant positioning; however, many other factors should be considered in order to fully re-establish gait symmetry and natural ankle motion.

Much as with hip and knee arthroplasty, large efforts have been devoted to improving TAA surgical techniques, including the use of preoperative plans based on computer software, and patient-specific instrumentation (PSI), such as custom-made cutting guides. Cutting guides are customized with respect to each patient's anatomy based on preoperative ankle computed tomography (CT) scans, and they drive the saw intra-operatively to improve the accuracy of bone resection and implant posi-tioning.

Nevertheless, there is no unanimous agreement regarding the indication and efficacy of PSI in TAA [4]. The purpose of this review article is therefore to assess the current literature on PSI in TAA. In particular, we will discuss the following topics: (1) Current implants with PSI; (2) Templating and preoperative planning strategies; (3) Alignment and sizing; (4) Clinical outcomes; (5) Cost analysis; and (6) Comparison with standard techniques.

TYPES OF IMPLANTS

Only three implants with PSI for TAA are currently available (Table 1): The INFINITY TAA (Wright Medical Technology Inc, Arlington, TN, United States). The INBONE II Total Ankle System (Wright Medical Technology Inc), and a custom-made version of the BOX TAA (MatOrtho, Ltd., Leatherhead, United Kingdom).

The INFINITY TAA

This implant has a 2-component fixed bearing design, with a low-profile tibia and talar resurfacing, and requires minimal bone resection. The tibial resurfacing component is made of titanium alloy and presents three angled pegs, whilst the talar component has two pegs and is made of cobalt chrome alloy. The INFINITY TAA can be implanted using a CT scan-derived PSI through the PROPHECY Preoperative Navigation System (Wright Medical Technology Inc)[5,6].

The INBONE II total ankle system

This implant is an evolution of the original INBONE design and consists of an intramedullary fixed-bearing two-component design with a polyethylene bearing surface locked into the tibial baseplate. The system retains some main features of the INBONE I design and instrumentations, including the modular tibial stems, thicker polyethylene bearings, and intramedullary guidance. In addition, the INBONE II total ankle system has certain enhancements, including sulcus articulation, additional talar fixation, anteroposterior long tibial trays, trial reduction placement of the talar component, and bone

Table 1 Summary of all actual studies about patient-specific instrumentation in total ankle arthroplasty

Author	Implant type	Study type	No patients	Navigation system	Tibial implant size predicted	Talar implant size predicted	Implant positioning accuracy	Neutral alignment	Comparison with standard technique
Berlet *et al* [10] (2014)	INBONE	Cadaveric study	15 lower limb	PROPHECY			Within 3 degree and translational within 2 mm		
Hsu *et al* [11] (2015)	INBONE II *vs* INFINITY	Retrospective case series	42	PROPHECY	100% INBONEII *vs* 92% INFINITY	76% INBONEII *vs* 46% INFINITY	± 3° coronal and sagittal	100%	
Hanselman *et al*[12] (2015)	INBONE II	Case report	1	PROPHECY				Yes	
Daigre *et al* [13] (2017)	INBONE II	Retrospective multicenter study	44	PROPHECY	98%	80%	< 3° (79.5%), < 4° (88.6%), < 5° (100%)	93.2%	
Saito *et al*[1] (2019)	INFINITY	Retrospective study	99 (75 PSI - 24 SRG)	PROPHECY	73%	51%	Coronal: SRG: 88% < 3°, 8% from 3° to 5°, 4% > 5°; PSI: 85.3% < 3°, 3.3% from 3° to 5°, 1.3% > 5°. Sagittal: SRG: 88% < 3°, 8% from 3° to 5°, 4% > 5°; PSI: 85% < 3° of deviation, 11% from 3° to 5°, 4 % > 5°	100% in PSI *vs* 96% in SRG	$P = 0.884$ not statistically different
Faldini *et al* [8] (2020)	BOX	Case report	1	GEOMAGIC CONTROL	-	-	-	Yes	-

PSI: Patient-specific instrumentation; SRG: Standard Referencing Guide.

removal instrumentation. This new sulcus design has twice as much coronal plane stability as the saddle design of the INBONE I TAA; moreover, it has two 4-mm anterior pegs in addition to the single talar stem design of the INBONE I component, resulting in increased rotational stability[7]. The INBONE II total ankle system can be implanted using a CT scan-derived PSI through the PROPHECY Preoperative Navigation System (Wright Medical Technology Inc).

Custom-made version of the BOX TAA

A three-component implant, with cast cobalt-chrome-molybdenum alloy components fixed to the body of the talus and the distal portion of the tibia, along with an interposed mobile biconcave meniscal bearing, designed to be compatible with the movements of isometric fibers within the calcaneofibular and tibiocalcaneal ankle ligaments[8,9]. The custom-made BOX TAA can be implanted using a CT scan-derived PSI with GeoMagic Control (3D Systems, Inc).

Considering the low number of implants available on the market, there are also few studies in the pertaining literature regarding PSI for TAA, as reported in Table 1.

TEMPLATING AND PREOPERATIVE PLANNING STRATEGIES

Templating in joint prosthetic surgery facilitates alignment optimization, helps in the selection of the correct implant size, and leads to more reliable and consistent prosthesis placement, theoretically lowering the risk of intra-operative complications.

While pre-operative templating is of great importance in planning hip and knee arthroplasty, its role in TAA is less clear.

Traditional preoperative planning methods for TAA are based on antero-posterior (AP) and lateral weight-bearing radiographs. Standard technique uses the tibial tuberosity as a point of reference and is based on the principle that the mechanical axis of the tibia (MAT) should equal the anatomical axis of the tibia (AAT)[14].

Differently from standard techniques, preoperative planning using PSI for TAA is initiated by obtaining preoperative ankle CT imaging, according to manufacturer established protocols, in order to create the patient-specific 3D model. Although with some differences, all computer navigation systems require preoperative CT scans from the knee through the mid-foot.

CT scans allow us to assess preoperative coronal plane deformity, sagittal plane deformity, and rotational deformity, as well as permitting an evaluation of MAT, and AAT alignments.

On the coronal plane, varus or valgus deformity should be determined (neutral alignment is considered as less than 5 degrees of varus or valgus[4]). The tibial slope must be measured in the sagittal plane considering the anterior distal tibial angle, the angle between the AAT, and the line connecting the distal points on the anterior and posterior tibial articular surface (normal values: 83.0 ± 3.6 degrees)[15].

All these measurements can deviate significantly depending on several factors, such as congenital or post-traumatic femoral or/and tibial deformities[16]. More frequently, in the presence of coronal deformity, AAT deviation from the MAT is accentuated.

In the past, ankle coronal and sagittal plane deformities represented a contraindication to TAA[17]. The recent literature shows a trend toward extending the indication of TAA even in the case of severe deformities. During the templating, deformity correction must be evaluated and addressed. Realignment procedures can be performed before TAA surgery or simultaneously to the prosthesis implantation, acting on bone or soft tissue structures depending on patho-anatomy[18,19].

In addition, during pre-operative planning, the prosthesis size and corresponding bone cuts to prepare implant accommodation and its best possible position should always be considered[8].

Very few reports have evaluated the reliability of templating with PSI. In 2007, Adams *et al*[20] were the first to apply computer-assisted surgery for TAA in a cadaver study. Seven matched-pair lower extremities were used. One leg from each pair was randomized for the conventional tibial preparation arm of the study, using the external alignment guide and tibial cutting block from the Scandinavian Total Ankle Replacement system (STAR, Waldemar Link GmbH & Co., Hamburg, Germany). Since dedicated TAA software did not exist at the time of the study, the other leg from each matched pair underwent computer-assisted tibial cut preparation using the VectorVision navigation system (BrainLAB, Munich, Germany) with total knee arthroplasty software. Pre-operative CT data was used to assess the tibial mechanical axis. In both groups, the accuracy of the tibial plafond preparation relative to the tibial shaft axis in both the coronal and sagittal planes was determined by fluoroscopic, radiographic, and CT analysis. Although the conventional and the computer-assisted measurements were not statistically different when compared to one another, the development of computer-navigation software specific to TAA continued.

The first PSI system for TAA that was able to provide a preoperative plan is the PROPHECY INBONE II and PROPHECY INFINITY Preoperative Navigation System. As in other forms of navigation-assisted surgery, the software generates a highly accurate rendering of the patient's bony anatomy. This technology allows the surgeon to interact with the computer model and develop the surgical strategy through stepwise considerations. This process identifies loose bodies, the osteophytes' location, size, and shape, the presence of bone deficits, the 3-plane nature of any preexisting deformity, and the desired features, position, and size of the final implants.

The PROPHECY template calculates the preoperative deformity and the MAT *vs* the AAT based on anatomic landmarks. Anatomic landmarks are established in order to determine tibia/talus alignment achieving neutral axes. According to Berlet *et al*[10], the tibia landmarks are: The proximal tibia, the distal tibia, the proximal anatomic canal, and the distal medial and lateral gutter. The talus landmarks are: The talar neck, and the proximal medial and lateral gutter. These landmarks are used to combine the 3D bone model with 3D computer-assisted design (CAD) models of the implants and instrumentation to perform a virtual TAA implantation. Implant positioning is usually based on the AAT[13], but the choice is at the discretion of the surgeon[17]. Once templating and preoperative planning are approved, patient-specific guides that reference bony anatomy are built through selective laser sintering.

The first study using the PROPHECY system was conducted by Berlet *et al*[10] in 2014 in order to evaluate the reproducibility of tibia and talus patient-specific guide placement and variation between the pre-operative plan and real component position. Fifteen cadaveric lower extremities were scanned and imported into a CAD environment which created the 3D models based on the ankle CT scan. The 3D bone models were combined with the 3D CAD models of the implants and instrumentation to perform a virtual TAA after choosing the appropriate implant size and position. Patient-specific guides were then manufactured to define the resection planes, and the final implant position was recorded. Mean deviation among pre- and post-operative implant position was less than 2° and 1.4 mm[10].

This preoperative planning strategy has been proposed in other clinical studies, demonstrating overall positive accuracy and reproducibility[1,11,13].

More recently, a new and complete TAA customization process was introduced by Faldini *et al*[8], consisting of patient-specific 3D-printed implants and instrumentation. Images obtained from a CT scan were processed for a 3D customized model of the ankle and the BOX ankle prosthesis (MatOrtho, United Kingdom). Using GeoMagic Control (3D Systems, SC), TAA was performed virtually by selecting the most suitable size for each implant according to the dimensions of the joint about to be replaced. Through the use of GeoMagic Control, it was possible to retrieve the corresponding bone resections and the corresponding PSI, designed to perfectly fit the frontal bone of the ankle and embed all required guides for bone preparation. The obtained models were printed in Acrylonitrile Butadiene Styrene by additive manufacturing for a final check. Upon approval of the planning procedure, the

models were sent for final state-of-the-art additive manufacturing (the metal components using cobalt-chromium-molybdenum powders, and the guides using polyamide).

Overall, preoperative three-dimensional bone imaging, and MAT and AAT axis determination are important aspects of planning and templating for PSI.

Several issues regarding PSI templating and preoperative planning strategies must still be addressed. First, different PSI image acquisition methodologies may influence the results. As a matter of fact, cutting guides are usually produced from a non-weightbearing preoperative CT scan. A weight-bearing CT scan, such as cone beam CT, may produce changes to the plan.

Other factors should also be considered: Dissimilar CT image resolutions and planning software, differences in the production methods used for the cutting blocks and their types, margin of error on the part of the manufacturer, and surgeon learning curve may affect the PSI outcomes, and influence the results.

Full-length weight-bearing lower limb imaging is rarely considered, though a complete lower limb alignment evaluation seems to be crucial in order to provide the most appropriate ankle alignment[14].

Lastly, it would be interesting to clarify whether pre-operative templating is more accurately performed using an AP radiograph or 3D imaging using CT scans, and to investigate if preoperative weight-bearing radiographs correlate with the PSI guide measurements.

ALIGNMENT AND SIZING

PSI was introduced as an innovative approach to also improve ankle alignment, and the accuracy and reproducibility of implant placement and sizing.

The literature has already shown that adequate TAA implant alignment and positioning are essential for achieving good clinical results[15,21]. Even a small implant component malpositioning could result in a significant impact on motion and contact pressure, which may determine its failure[2].

Kakkar *et al*[22] described how an implant misalignment could result in eccentric overloads. Traditionally, every arthroplasty system purpose is to reach a neutral axis[23]. According to certain authors[24,25], neutral coronal ankle alignment is defined as less than 5 degrees of valgus to less than 5 degrees of varus.

There is still a good amount of controversial debate in the literature regarding whether PSI improves the reliability of achieving neutral ankle alignment and more accurate implant sizing.

In the cadaver-based study performed by Berlet *et al*[10], PSI led to a reliable and reproducible position of TAA component and ankle alignment. The mean prosthesis alignment variations between pre-operative plans and final location were all within ± 3 degrees.

Hsu *et al*[11] reported similar results in a retrospective case series of 42 consecutive TAAs using preoperative CT scan-derived patient-specific plans and guides (PROPHECY). Of the 42 TAAs, 29 intramedullary referencing implants (INBONE II) and 13 low-profile tibia and talar resurfacing implants (INFINITY) were used. The study revealed that postoperative weight-bearing alignments were in a range of ± 3° from the expected coronal and sagittal alignments reported in the surgical plans following CT scans. Moreover, neutral alignments were gained for all TAAs, independently of preoperative coronal deformity.

Surgical plans have forecasted the real tibial component size utilized in 29 of 29 (100%) INBONE II cases and in 12 of 13 (92%) INFINITY cases. Conversely, plans were more inaccurate for talar component and predicted the real talar component size utilized in 22 of 29 (76%) INBONE II cases and 6 of 13 (46%) INFINITY cases. In all cases of predicted tibia or talar size mismatch, surgical plans estimated one implant size larger than the one that was actually used.

In 2015, Hanselman *et al*[12] reported the case of a 54-year-old man with a 29° varus hindfoot deformity treated by TAA using an INBONE II implant with PROPHECY PSI. Three months post operation, a neutral alignment was achieved, with a coronal plane angle of 1.8°.

In 2017, Daigre *et al*[13] reported on a retrospective multicenter study of 44 TAAs (INBONE II) using PROPHECY PSI. In 79.5% of cases, the postoperative tibial implant position corresponded to the preoperative plan within 3° of the planned aim, within 4° in 88.6% and 5° in 100% of cases. The preoperative navigation system aided to reach a postoperative neutral alignment in 93.2% of cases. The tibial component coronal size was properly predicted in 98% of cases, whereas the talar component was correctly predicted in 80% of cases.

When comparing PSI with the Standard Referencing Guide (SRG) on a retrospective analysis of 99 INFINITY TAAs, Saito *et al*[1] reported that the absolute variation of the tibial component from the intended alignment was 1.6 ± 1.2 degrees in the coronal plane, and 1.9 ± 1.5 degrees in the sagittal plane.

The PSI preoperative plan correctly predicted the implant size in 73% of cases for the tibial component, and in 51% for the talar component, whereas among the mismatched cases, the plan tended to predict an implant size larger than what was actually utilized for both implants.

Considering the reported data, imprecision of the computerized navigation system in predicting the talar implant size still exists. Some authors propose to justify the talar component mismatch with the matter of gutter debridement: An aggressive debri-dement may affect the sizing of the talar component,

leading to smaller talar sizes[1,11,13].

CLINICAL OUTCOMES

Theoretically, the advantages that PSI confers on TAA should translate into impro-vements in clinical outcomes. However, given that PSI is still a novel technique, the current literature is lacking in long-term studies that can assess the differences in instrumentation techniques.

A single case report deals with clinical outcomes. Hanselman *et al*[12] reported good clinical results at 8 mo in a 54-year-old man using the INBONE II Prophecy TAA system. The patient was ambulating without assistance and the ankle range of motion was 40°.

The advantages of PSI in clinical outcomes are still theoretical and need to be confirmed. Conversely to primary arthritis of the hip and knee, end-stage ankle arthritis was frequently post-traumatic and generally involves younger patients. For this reason, looking at the joint replacement, ankle patients are reported to produce greater common physical demands than hip and knee ones; hence, the duration of implants for ankle patients needs to be increased by roughly 10 years. Therefore, obtaining a more accurate anatomic alignment with PSI may reduce the incidence of eccentric wear, component loosening, subsidence, and failure, and indirectly improve longevity and clinical outcomes[10].

COMPARISON WITH STANDARD TECHNIQUES

Advocates for PSI in TAA argue that the advantages conferred by patient-specific cutting block also translate to subsequent improvements in implant positioning, reduced surgical time, and clinical outcomes.

Adams *et al*[20] compared computer-assisted tibia preparation with standard techniques in a cadaveric study. Results showed that the conventional and computer-navigated tibial measurements were not different in the 95% confidence interval for CT, fluoroscopy, or radiographic assessments.

In 2019, Saito *et al*[1] performed a retrospective analysis of 99 patients comparing the utilization of PSI with the SRG. The accuracy of the tibial component placement was similar between the two groups. Neutral ankle alignment was obtained postoperatively for all cases in the PSI group, and for all but one patient in the SRG group, who had 5.7° of varus deviation post operation. The use of PSI had to be abandoned intraoperatively in three cases (3.8%). Operative time (167 *vs* 190 min, $P = 0.040$) and fluoroscopy time (85 *vs* 158 s, $P < 0.001$) were significantly decreased in the PSI group.

COST ANALYSIS

Any new technology, in addition to demonstrating clinical improvements, must undergo an economic analysis to reveal the added cost to the healthcare system in relation to its expected benefits.

Promoters of PSI suggest that PSI will reduce the overall costs of TAA. Although this technology has added associated costs, mostly because of preoperative CT imaging and the creation of custom-made cutting guides, the reduced operative time, the lower processing costs due to fewer sterile trays, the decrease in radiation exposure[4], the reduction in perioperative complications[26], and the better alignment leading to fewer revision surgeries represent the main advantages that can translate to reduced healthcare costs.

Only one study analyzed the costs of PSI in TAA. Hamid *et al*[1] identified a cost-savings threshold of $863 below which PSI was less costly than SR instrumentation. However, only the objective reduction of costs resulting from a decrease in operative time was considered.

CONCLUSION

PSI for TAA may represent an additional tool for surgeons and patients. However, the current literature does not allow us to confirm the superiority of PSI over standard techniques, and there are still several questions to be answered.

Surgical experience is always necessary in order to consider all the factors influencing lower limb alignment, and bone, soft tissue, or ligament balancing. Moreover, blindly trusting PSI can potentially lead to mistakes in implant placement and sizing. For this reason, a surgeon should always know the SR and select a different implant size or abandon PSI when necessary.

Based on the current data from the pertaining literature, the main strengths of PSI for TAA are represented by good reproducibility and accuracy of implant positioning, good neutral alignment and correction of pre-existing deformities[27], shorter operative and fluoroscopy exposure time, and

therefore, a potential decreased risk of complications as well as cost reductions[1].

The insufficiency of corroborating literature and scarcity of studies (in two cases financed by the manufacturer)[10,13] represent the current and main limitations of PSI. Moreover, it is not clear whether PSI may be more useful in order to restore ankle neutral alignment when dealing with complex deformities involving the whole lower limb.

Further prospective, randomized, and multicenter studies are therefore necessary to better evaluate PSI and confirm its routine use in TAA.

FOOTNOTES

Author contributions: Mazzotti A and Arceri A conceived the presented idea; Mazzotti A made substantial contributions to study conception and design, and data acquisition, analysis, and interpretation, drafted the manuscript, and revised it critically; Arceri A coordinated and supervised manuscript preparation; Zielli S provided documentation, and helped shape the research, analysis, and manuscript; Bonelli S provided documentation and critical feedback; Viglione V contributed to the design and implementation of the research; Faldini C revised the manuscript critically and gave final approval of the version to be published; and all authors read and approved the final manuscript.

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MINIREVIEWS

Diagnosis, treatment and complications of radial head and neck fractures in the pediatric patient

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Abstract

Radial head and neck fractures represent up to 14% of all pediatric elbow fractures and can be a difficult challenge in the pediatric patient. In up to 39% of proximal radius fractures, there is a concomitant fracture, which can easily be overlooked on the initial standard radiographs. The treatment options for proximal radius fractures in children range from non-surgical treatment, such as immobilization alone and closed reduction followed by immobilization, to more invasive options, including closed reduction with percutaneous pinning and open reduction with internal fixation. The choice of treatment depends on the degree of angulation and displacement of the fracture and the age of the patient; an angulation of less than 30 degrees and translation of less than 50% is generally accepted, whereas a higher degree of displacement is considered an indication for surgical intervention. Fractures with limited displacement and non-surgical treatment generally result in superior outcomes in terms of patient-reported outcome measures, range of motion and complications compared to severely displaced fractures requiring surgical intervention. With proper management, good to excellent results are achieved in most cases, and long-term sequelae are rare. However, severe complications do occur, including radio-ulnar synostosis, osteonecrosis, rotational impairment, and premature physeal closure with a malformation of the radial head as a result, especially after more invasive procedures. Adequate follow-up is therefore warranted.

Key Words: Radial head; Proximal radius; Fracture; Pediatrics; Closed fracture reduction; Open reduction fracture; Fracture fixation; Synostosis; Osteonecrosis

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Core Tip: This article presents the latest evidence-based insights in pediatric proximal radius fractures. A stepwise progression of treatment is warranted, starting with closed reduction and immobilization, and progressing to more invasive measures in case of unsuccessful reduction. Open reduction with internal fixation is left as the last option due to the high risk of complications and inferior functional results.

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INTRODUCTION

Radial head or neck fractures can be a difficult challenge in the pediatric patient. Limited data are published on the subject, and there is controversy surrounding the optimal treatment and expected results[1,2]. This article aims to provide an overview of the currently available literature on the diagnosis, classification, treatment, outcomes and complications of proximal radius fractures in the pediatric patient.

Development and anatomy of the radial head and neck

Ossification of the radial head occurs between the ages of 3 years and 5 years, and the radial head fuses with the radial shaft between the ages of 14 years and 17 years[2,3]. The epiphysis of the radial head is covered by the annular ligament, which lies in continuity with the joint capsule. The capsule extends to the proximal metaphysis. Therefore, part of the radial neck is localized outside of the joint capsule. The blood supply to the radial head enters through the metaphysis to retrogradely perfuse the radial head. The posterior interosseous nerve, which provides innervation to the digital extensor muscles, runs directly over the radial neck. The anatomic angle of the radial neck relative to the radial shaft is up to 15 degrees valgus and 10 degrees apex posterior[2]. Knowledge of this anatomy is essential when evaluating a fracture and indicating the appropriate treatment.

Epidemiology of proximal radius fractures

Elbow fractures represent 10% of all fractures occurring in the pediatric population[4]. Unlike in adults, proximal radius fractures are relatively rare, representing up to 14% of all pediatric elbow fractures[4,5]. Radial head and neck fractures occur most frequently in children aged 7 years to 12 years[3,6]. The majority of proximal radius fractures are radial neck fractures (89%), and these fractures occur more frequently in younger patients compared to radial head fractures[7]. A concomitant fracture occurs in up to 39% of radial head or neck fractures, and can easily be missed on the initial interpretation of the radiographs[5,7].

Trauma mechanism

The most common trauma mechanism for radial head and neck fractures is valgus loading with the elbow in extension, such as a fall on an outstretched hand. The force through the lateral capitellum compresses the radial head, causing it to break at the weakest point, which is often the radial neck at the metaphysis. A second injury mechanism is a radial head dislocation, which is most commonly seen in relation to radial head fractures[4].

CLINICAL PRESENTATION

Children with a proximal radius fracture present with symptoms of pain and limited range of motion after a fall or other type of trauma. Patients generally refuse to move the affected elbow. In some cases, pain may be referred to the wrist. Physical examination shows swelling, and pain exacerbated by motion, particularly with attempted pronation and supination. There is tenderness on palpation of the proximal radius[2,8,9]. Neurovascular examination should be performed, with specific consideration to the posterior interosseous nerve[10,11]. Attention should also be paid to soft-tissue swelling to assess the rare risk of forearm compartment syndrome[12].

Concomitant injuries

A concomitant fracture is seen in up to 39% of cases[5,7]. A retrospective study of 494 proximal radius fractures showed that 25% of the concomitant fractures were missed on the initial analysis of radiographs. In retrospect, 56% were visible, and 44% radiographically occult[7]. A high index of

suspicion of additional fractures is therefore required.

The most common concomitant injury is a fracture of the olecranon. Less common are ulnar metadiaphyseal fractures, ulnar fractures as part of a Monteggia fracture-dislocation and medial epicondyle fractures. Risk factors for concomitant fractures include joint effusion, young children, and complete or displaced proximal radius fractures[5,7]. In addition to concomitant fractures, other injury patterns can accompany a proximal radius fracture, such as elbow dislocation or acute longitudinal radioulnar disruption (ALRUD or Essex-Lopresti injury). In general, fractures in the pediatric patient can be easily missed due to the unique characteristics of the pediatric bone and varying clinical presentation, with patients not always being able to clearly communicate their symptoms[13]. Therefore, when assessing a child with a suspected fracture of the proximal radius, thorough examination of the wrist, shoulder and contralateral arm should be performed to exclude associated injuries.

IMAGING

Conventional radiographs are used for the diagnosis and grading of radial head and neck fractures in the pediatric patient. Anteroposterior and lateral views are made. In case of a high clinical suspicion of a fracture, such as a positive fat pad sign, but no fracture on standard radiographical views, an additional radial head-capitellum (Greenspan) view can be made to allow for easier visualization of the radial head [14]. Some studies have shown the effectiveness of the Greenspan view in identifying fractures which were occult on regular views, providing additional information in up to 21% of patients[14,15]. However, other studies dispute the added value of this view reporting only one additionally identified fracture in 32 and 125 patients[16,17].

A bilateral radiograph of the wrist can be made to exclude additional injuries such as an ALRUD injury. Nondisplaced radial neck fractures can be difficult to detect and are often occult on the initial radiograph. Fat pad signs may aid in diagnosing a nondisplaced fracture in combination with high clinical suspicion (Figure 1)[18]. However, since a part of the radial neck lies outside the joint capsule, joint effusion and fat pad signs may be absent in radial neck fractures. In these cases, a nondisplaced radial neck fracture is easily missed[7].

Imaging modalities other than plain radiographs play a less prominent role in the assessment of proximal radius fractures in children. Magnetic resonance imaging may be used to visualize the preossified elbow in young children but is not routinely indicated. In addition, magnetic resonance imaging may be useful in assessment of ligamentous integrity in case of elbow instability, dislocation, or secondary instability after successful treatment of the fracture[2,19]. Computed tomography may be used in planning operative fixation, specifically in cases of comminuted radial head fractures in older children and adolescents[2]. However, in the majority of cases plain radiographs are sufficient.

Determining fracture displacement

Angulation and translation of the proximal radius fracture are essential in the choice of treatment. There are several ways to determine these two measures. A simple way to determine angulation is to draw a line perpendicular to the articular surface of the radial head and a line through the center of the radial shaft, the angle is measured at the intersection of the lines (Figure 2A). Angulation should be measured using the radiograph that shows the greatest abnormality[2]. For the translation of the fracture, the percentage of the uncovered radial metaphysis is divided by the total width of the metaphysis. Alternatively, the distance in millimeters from the center of the proximal part to the center of the distal part of the radius can be measured (Figure 2B)[2].

Classification

Several classification systems of proximal radius fractures using conventional radiographs are available. Commonly used are the Judet classification, Metaizeau's modification of the Judet classification, and the O'Brien classification (Table 1, Figure 3)[20-22]. These classifications are useful for the choice of treatment.

TREATMENT AND OUTCOME

The treatment options for proximal radius fractures in the pediatric patient range from conservative measures, such as immobilization alone and closed reduction followed by immobilization, to more invasive options, including closed reduction and percutaneous pinning and open reduction with internal fixation. The choice of treatment depends on the degree of angulation and displacement of the fracture. Generally, an angulation of fewer than 30 degrees (O'Brien type I or Judet grade I or II) and translation of less than 50% or 3 millimeters (Metaizeau grade I or II) is accepted[2,3,23]. A higher degree of displacement is usually an indication for surgical treatment[3,23,24]. Studies comparing immobilization with percutaneous intervention and percutaneous with open treatment have shown that

Table 1 Classification systems

	Angulation, degrees	Translation
Judet		
I	Nondisplaced or horizontal shift	
II	< 30	
III	30-60	
IVa	60-80	
IVb	> 80	
Metaizeau's modification		
I	Non-displaced or horizontal shift	< 3 mm
II	< 30	< 50%
III	30-60	> 50%
IVa	60-80	> 100%
IVb	> 80	
V	Epiphyseal separation	
O'Brien		
Type I	< 30	
Type II	30-60	
Type III	> 60	

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Figure 1 Fat pad sign. Lateral radiograph of a 13-year-old boy, showing an anterior and posterior fat pad sign without visible fracture. A proximal radius fracture was identified using computed tomography.

a conservative approach leads to better outcomes in terms of patient-reported outcome scores, range of motion and fewer complications[3,4,25]. However, these results may be confounded by the fact that more severely displaced fractures are often treated more aggressively. Nonetheless, it is advised to initially attempt a conservative approach and follow a stepwise progression to more invasive options if the former fails to achieve an adequate and stable reduction (Figure 4).

Immobilization

The indication for non-surgical treatment is an isolated fracture with less than 30 degrees angulation and less than 50% translation, on the initial presentation or after closed reduction. In addition, some studies have shown superior results of non-surgical treatment in children younger than 10 years of age, suggesting that non-surgical treatment should be more liberally indicated for younger children[22,26-28]. The affected arm is splinted in a long-arm cast or pressure bandage for 1 wk, followed by range of motion exercises without loading. If reduction is required, the arm is immobilized for 2 wk to 4 wk

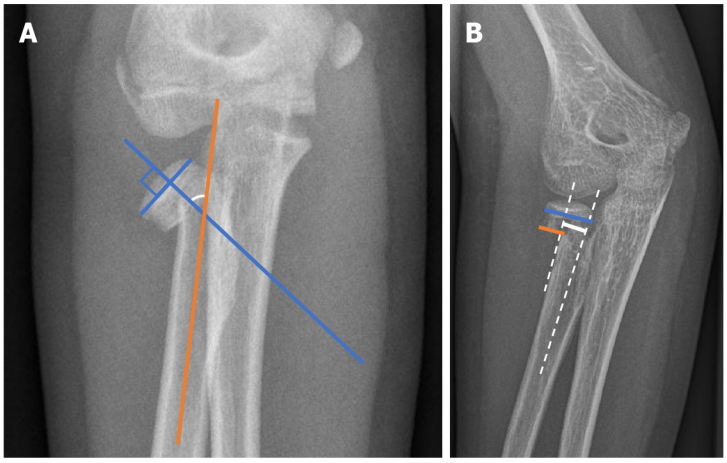

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Figure 2 Measurement of angulation and translation of the proximal radius fracture. A: Angulation measurement. Angulation of a proximal radius fracture is measured by drawing a line perpendicular to the surface of the radial head (blue line) and a line through the middle of the radial shaft (orange line). The angle is measured at the intersection of the two lines (white arc); B: Translation measurement. Translation of a proximal radius fracture is calculated by dividing the length the uncovered part of the metaphysis (orange line) by the total width of the proximal radius (blue line), multiplying by one hundred provides the percentage of translation. Alternatively, the distance from the middle of the proximal part to the middle of the distal part can be measured in millimeters (continuous white line).

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Figure 3 Anteroposterior radiograph of proximal radius fracture. A: Grade I fracture. Anteroposterior radiograph of a 5-year-old boy with a proximal radius fracture that is (nearly) nondisplaced. Judet grade I; Metaizeau grade I; O'Brien type I; B: Grade II fracture. Radiograph of a 9-year-old girl with a proximal radius fracture in 27 degrees of angulation and 17% translation. Judet grade II; Metaizeau grade II; O'Brien type I; C: Grade III fracture. Anteroposterior radiograph of a 10-year-old girl with a proximal radius fracture in 58 degrees of angulation and 55% translation. Judet grade III; Metaizeau grade III; O'Brien type II; D: Grade IV fracture. Anteroposterior radiograph of a 7-year-old girl with a proximal radius fracture in 87 degrees of angulation and 80% translation. Judet grade IVb; Metaizeau grade IVb; O'Brien type III.

depending on patient age and injury severity[29,30]. If there is no concomitant injury, the patient may return to full usage of the elbow after 4 wk[2,3]. Immobilization, with or without closed reduction, results in good to excellent outcomes in terms of range of motion and Mayo Elbow Performance Index in the majority of patients[3].

Closed reduction

In case fractures do not meet the criteria for direct immobilization, closed reduction under anesthesia is attempted. Various techniques have been described to reduce the proximal radius fracture[29,30]. (1) Patterson maneuver: With the elbow in extension and the forearm supinated, distal traction and varus force is applied while pressing directly over the radial head; (2) Israeli technique: With the elbow in flexion and the forearm supinated, pressure is applied directly over the radial head while pronating the forearm; (3) Neher-Torch technique: With the elbow in extension and the forearm supinated, two thumbs stabilize the radial head while distal traction, varus force and lateral pressure are applied. This technique requires at least two persons; and (4) Elastic bandage technique: An elastic bandage is tightly wrapped around the forearm starting at the wrist progressing proximally over the elbow. This may lead to a spontaneous reduction.

Overall success rate of closed reduction is approximately 25%, with higher success rates in lower Judet grade fractures[31]. A recent retrospective study of 70 children found that a longer time from injury to presentation and larger degree of angulation was associated with unsuccessful closed reduction; in only one of the 14 patients presenting more than 24 h after injury and none of the 10

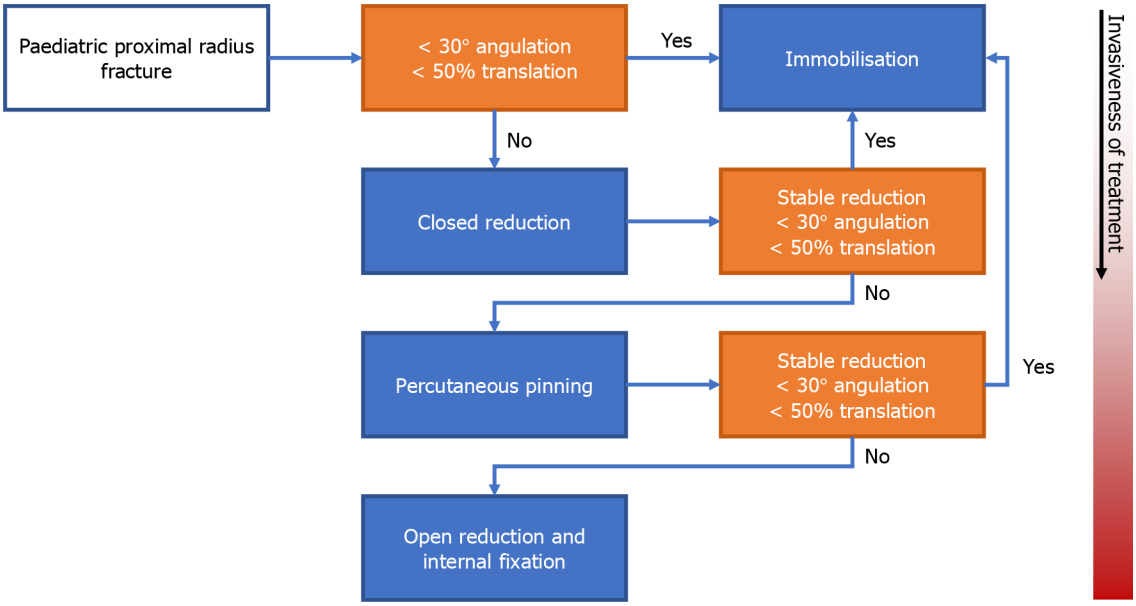

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Figure 4 Treatment flowchart. Treatment flowchart that plots the stepwise progression from conservative to increasingly invasive treatment of pediatric proximal radius fractures. Starting from the left, orange boxes represent points of decision-making and blue boxes represent treatment options. Boxes placed lower in the chart represent more invasive procedures than those placed above.

patients with an angulation larger than 60 degrees the fracture could be successfully reduced[31].

If the fracture is successfully reduced, non-surgical treatment is sufficient. Otherwise, percutaneous pinning is the next step in the treatment ladder.

Percutaneous pinning

Besides the above-mentioned reduction maneuvers, the fracture can be reduced percutaneously in several ways. Kirschner wires can be used to position the fragment, either by placing the wire into the fragment and levering it into position (joystick technique) or by pushing the fragment with the blunt end of the wire. Kirschner wires can then be used to fixate the fragment (Figure 5A and B).

Alternatively, an elastic, flexible intramedullary nail can be used (Metaizeau technique). The nail is pre-bent and inserted at the distal radius through a standard radial styloid approach or a dorsal approach over Lister's tubercle. The nail is advanced in a retrograde fashion across the fracture site into the proximal fragment. The nail can be rotated to reduce the fragment and is left in place for permanent fixation (Figure 5C)[32]. Previous studies found no difference in functional and radiographic results between the two percutaneous techniques[28,33,34]. However, fluoroscopy and operating times are greater when using the Metaizeau technique[34].

Percutaneous fixation is generally performed under guidance of radiographic fluoroscopy. However, a recent retrospective study of 50 children showed the feasibility of percutaneous pinning under ultrasound guidance, reporting comparable outcomes between the two types of imaging guidance[35]. Using ultrasound may reduce the amount of radiation exposure in children with proximal radius fractures.

Following percutaneous fixation of a proximal radius fracture, the patient is placed into a long-arm cast for 4 wk, after which the Kirschner wires are removed and elbow range of motion exercises can be started. In case an intramedullary nail is used, it is removed after 3 mo to 6 mo[2,3,24]. If initial percutaneous fixation fails, there is controversy surrounding the choice for a second attempt at percutaneous fixation before continuing onto internal fixation. It is thought that multiple attempts may damage the blood supply to the radial head and increase the risk of complications. However, only one study has assessed this problem and found no association between multiple attempts and worse outcomes[28]. It is generally accepted to continue to the next step in the treatment ladder if a single attempt at percutaneous fixation is unsuccessful.

Open reduction and internal fixation

The indication for open reduction and internal fixation is a fracture with more than 30 degrees angulation or more than 50% translation, which is unstable and cannot be reduced adequately with the previously mentioned methods. In addition, in case of concomitant injuries that may result in instability, internal fixation can be indicated. A lateral approach through the Kocher or Kaplan interval is used. The forearm should be pronated to avoid the posterior interosseous nerve. The method of fixation varies greatly. Kirschner wires can be placed through the fracture to fixate the proximal fragment; titanium

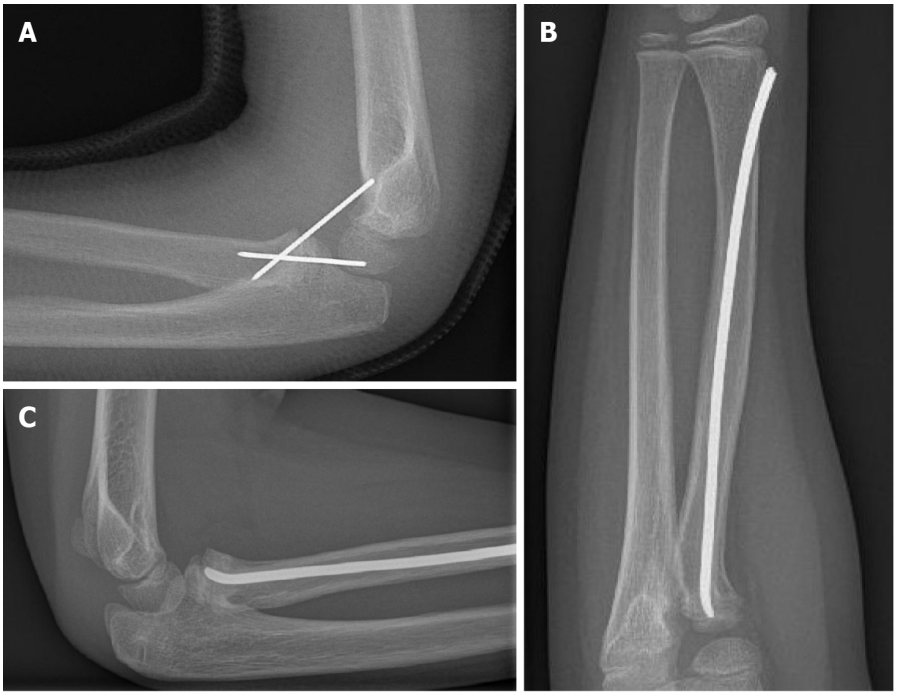

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Figure 5 A fracture can be reduced percutaneously in several ways. A: Percutaneous Kirschner wire fixation. Lateral radiograph of a 7-year-old boy with a proximal radius fracture after percutaneous reduction and fixation using two Kirschner wires; B and C: Intramedullary nail: Anteroposterior radiograph of a 10-year-old girl with a proximal radius fracture that was reduced and fixated using a flexible intramedullary nail (Metaizeau technique) (B), Lateral radiograph of a 10-year-old girl with a proximal radius fracture that was reduced and fixated using a flexible intramedullary nail (Metaizeau technique) (C).

elastic nails can be placed in the radial shaft; or in some cases, screws are used to reattach the radial head[3,24]. If deemed necessary, the annular ligament can be repaired. Transcapitellar pin fixation has been used in the past but is no longer advised due to the tendency of these pins to break inside the joint, which may result in chondral damage of the capitellum. Fixation may not always be necessary after open reduction, and in rare cases, a stable situation is achieved with open reduction leaving the joint capsule intact. However, two studies have reported cases of non-union, synostosis and avascular necrosis after open reduction without fixation, arguing that open reduction should always be accompanied by adequate fixation[3,19].

Open reduction and internal fixation have been associated with a greater loss in range of motion and increased rates of osteonecrosis and synostosis compared to closed reduction techniques[3,25,36]. However, these results are controversial due to open reduction being more frequently used in fractures with a higher degree of displacement and more concomitant injuries. Worse outcomes have also been reported with increasing age, and better outcomes are achieved in children of 10 years or younger[3,8,27,28]. However, older children have been reported to sustain more severe fractures. Nonetheless, two studies have shown worse outcomes with increasing age while statistically correcting for the degree of fracture displacement[8,28]. Long-term results of pediatric proximal radius fractures are positive; a study of 24 patients treated conservatively or with open reduction and internal fixation with a mean follow-up of 19 years reported no complaints in 86% of patients, a mean decrease in flexion arc of 3 degrees compared to the uninjured population, and no osteoarthritis[37].

Intra-articular fractures

Intra-articular fractures are less common in skeletally immature children compared to skeletally mature adolescents (52 *vs* 7 per cent) and may be missed on radiographic imaging[38]. Recent case series have reported rapid radiocapitellar degeneration and progressive radial head subluxation in pediatric patients with an intra-articular radial head fracture[39,40]. This type of fracture should not be underestimated and should, in contrast to extra-articular fractures, be treated more aggressively.

COMPLICATIONS

Various complications have been reported after radial head or neck fractures in children. Overall, the complication rate increases with increasingly invasive treatment and is highest after open articular surgery[3]. General complications related to surgery or anesthesia, such as infection or postoperative bleeding, are not mentioned here. Common complications or complications with severe consequences

that are specific to radial head or neck fractures are discussed in descending order of severity.

Radio-ulnar synostosis

Radio-ulnar synostosis is a complication involving a bony or soft-tissue connection that is formed between the proximal radius and ulna during post-traumatic remodeling. It has a reported incidence of approximately 1% after radial head or neck fractures in children and occurs predominantly after open reduction or delayed treatment[3]. Synostosis is the most severe complication in terms of functional results and typically presents as an inability to rotate the forearm with an intact flexion arc. The diagnosis is confirmed on conventional radiographs or computed tomography. Treatment is surgical and involves excision of the synostosis. A common problem is the recurrence of the synostosis after excision, and a wide variety of additional techniques have been proposed to prevent this problem, including rotation osteotomy, the interposition of a silicone spacer, interposition of a free fat graft, interposition of a pedicled or free muscle flap, or nonsteroidal anti-inflammatory drugs. Due to the low incidence of post-traumatic radio-ulnar synostosis, the available evidence for all techniques is based on a handful of cases[41-47]. No conclusion can be drawn as to which technique is superior. Although pronation and supination motion is partly restored in most cases, the functional results of these procedures vary greatly, and a large proportion of patients have poor long-term outcomes[41-47]. Radio-ulnar synostosis is associated with open treatment of proximal radius fractures. Therefore, the incidence of synostosis is most effectively reduced by using minimally invasive techniques when possible[3,25,36]. Furthermore, it is the senior authors' practice to remove bone dust using gel or water and avoid interfering with the radio-ulnar space.

Avascular necrosis

Due to the main blood supply to the radial head entering through the metaphysis and running retrogradely to the radial head, it is vulnerable to disruption in the case of a radial neck fracture. This may result in osteonecrosis of the radial head. The reported incidence of avascular necrosis after proximal radius fractures in children is approximately 1%[3]. The occurrence of avascular necrosis is associated with a higher degree of fracture displacement and open treatment[3,48]. Patients with avascular necrosis present with a new and increasing pain at the elbow and restriction of movement. In addition, swelling is seen in some cases. Symptoms of post-traumatic necrosis can first occur several years after the initial injury[49]. The diagnosis is confirmed using conventional radiographs. Initial treatment is conservative with range of motion exercises and may provide relief in some cases. If severe symptoms persist, avascular necrosis can be treated surgically using bone grafting or radial head resection[3,49]. However, these interventions often do not provide sufficient pain relief or restore range of motion entirely and are associated with poor outcomes in the pediatric population[3,49]. Overall, the presence of avascular necrosis is associated with worse functional outcomes and restricted elbow motion at long-term follow-up[48,49].

Posterior interosseous nerve injury

The posterior interosseous nerve may be injured during the initial trauma or during surgery, resulting in transient or permanent nerve palsy. Iatrogenic injury of the posterior interosseous nerve is rare; a recent systematic review including 751 cases reported no cases of permanent iatrogenic nerve injury[3]. Risk of injury to the posterior interosseous nerve can be reduced by pronating the forearm during the (lateral) surgical approach. Transient neurological deficits in both the radial and ulnar nerves after treatment of proximal radius fractures are reported in approximately 1% of pediatric patients[3]. The typical clinical presentation of posterior interosseous nerve palsy includes limitations in finger and thumb extension together with radial deviation when extending the wrist, due to preserved function of the extensor carpi radialis longus and brevis. The posterior interosseous nerve does not have cutaneous branches, and there will be no loss of sensory function. Available follow-up data of proximal radius fracture-related posterior interosseous nerve palsies in children are limited. Case reports of adults generally show spontaneous recovery between 2 mo and 6 mo after injury, and operative intervention is rarely required[10,11,50,51].

Non-union

After treatment of a proximal radius fracture, non-union can occur. However, the incidence of non-union is low, with two studies reporting 0% and 0.7% non-union in children with a proximal radius fracture, respectively[27,28]. Patients may present with a decreased range of motion, mostly affecting supination. In addition, intermittent pain or functional complaints are reported in some cases, as well as valgus deformity[52]. The diagnosis is confirmed using conventional radiographs. The time between fracture and presentation for non-union varies greatly and is reported up to 8.5 years in rare cases[19]. Depending on the severity of the symptoms, a non-union can be treated conservatively with range of motion exercises. In case of severe symptoms, a non-union can be treated surgically with open reduction and internal fixation, with the option of bone grafting. In some cases, radial head resection is required [52]. Results of both conservative and operative treatment vary greatly. In general, improvement in complaints and range of motion is seen, but various remaining abnormalities are seen on follow-up

radiographs[19,52]. In case of radial head resection, improvement in range of motion often comes with complaints of instability[52]. However, the available evidence is limited and relies on a small case series.

Mal-union

If the fracture consolidates in a non-anatomical position, it is considered a mal-union. The reported incidence of mal-union is equally low, ranging from 0% to 4%[3,27,28]. Patients may present with elbow pain and restricted motion, which can occur up to decades after the initial injury in rare cases[53,54]. The diagnosis is made using conventional radiographs. Depending on the severity of the symptoms, a mal-union of the radial neck or head can be treated with corrective osteotomy or radial head resection [55]. Limited data are available on the results of surgical interventions in these patients. Case series have shown overall pain reduction after osteotomy, but contrasting results with regards to restoring range of motion[53,54,56]. Mal-union of the proximal radius should be distinguished from partial growth arrest or injury of the growth plate of the radius, resulting in a posttraumatic malformation of the radial head, most commonly an enlargement of the radial head and an incongruent proximal radioulnar joint[8,26].

Heterotopic ossification

Heterotopic ossification may occur in the soft-tissue surrounding the elbow after a proximal radius fracture. The incidence is approximately 2% after a proximal radius fracture in children[3]. Patients with heterotopic ossification may present with restricted motion, swelling of the joint, joint and muscle pain, or in some cases fever[57-59]. The severity of heterotopic ossification ranges from mild symptoms that resolve spontaneously to complete ankylosis. The presence of heterotopic ossification is confirmed on radiographs or computed tomography. The use of medications such as vitamin-K antagonists or nonsteroidal anti-inflammatory drugs have been suggested to prevent heterotopic ossification but are not routinely advised in children[60,61]. Treatment options for heterotopic ossification include range of motion exercises and excision of the ossification through arthroscopic or open surgery[57-59]. Limited data on the results of surgical excision of heterotopic ossification around the elbow in children are available, but the few reported cases show good results and no recurrence[57-59].

Physeal arrest or premature physeal closure

The damage caused to the growth plate by the fracture or consequential treatment may result in an arrest or premature closure of the physis, but it may also be the result of avascular necrosis. The incidence of premature physeal closure after a proximal radius fracture in children is approximately 1.5% but is not always reported, and a physeal arrest may be missed in the absence of symptoms[3]. Symptoms can include mild restriction of motion, pain, a clicking sensation, or a visible deformity such as cubitus valgus, but growth arrest can also be asymptomatic[62]. Closure of the physis or physeal arrest, with malformation of the radial head as a result, may be seen on conventional radiographs. Approximately 25% of growth in the radius occurs in the proximal physis[63]. Therefore, there is less remodeling potential than distally, but a lower chance of symptoms due to longitudinal deficiency. In most cases, physeal arrest or premature closure can be treated conservatively, with range of motion exercises. In case of severe symptoms, surgical treatment can be attempted using corrective osteotomy or bone lengthening procedures[64]. Limited data are available on the results of these interventions, and conflicting results are reported, with most treated children showing an improved range of motion, but worsened outcomes in a selection of cases[64].

Decreased range of motion

Elbow stiffness is the most common complication, reported in up to 31% of patients[27]. It is often caused by soft-tissue contraction and fibrous tissue formation, but can also be caused by bone overgrowth. It has been associated with injury severity, concomitant fractures and multiple attempts at closed and open reduction and has been correlated with a worse functional outcome[48]. Elbow stiffness is best prevented by early mobilization and adequate guidance during rehabilitation, preferably by a physiotherapist. If conservative treatment, including static progressive splinting, is unsuccessful and elbow motion is severely limited, the stiff elbow can be released arthroscopically or with open surgery. This generally results in improved range of motion, but rarely to the extent that it matches the unaffected side[65].

Radial head overgrowth

Post-traumatic osseous overgrowth of the radial head or neck is a common radiographic finding after fracture of the pediatric proximal radius, reported to occur in 18% to 37% of patients[66]. It is often asymptomatic but may result in restricted motion.

CONCLUSION

Radial head and neck fractures remain challenging injuries in the pediatric patient. Fractures are

classified based on the initial angulation and translation, which determine the type of treatment. With proper management, generally good to excellent results are achieved, and long-term sequelae are rare. However, severe complications such as synostosis, osteonecrosis or (partial) growth arrest do occur, especially after more invasive procedures. Complications such as stiffness and radial head overgrowth are more common but can generally be treated successfully with conservative measures. There is controversy in the literature regarding the treatment of older pediatric patients nearing skeletal maturity and whether they should be approached in a similar fashion as adult patients. Furthermore, apart from striving to use the least invasive treatment options, there is limited data available on prevention of specific complications. In addition, the rate of missed fractures and missed concomitant injuries is relatively high. Future research should focus on more accurate diagnosis, expanding the closed and percutaneous treatment options, and prevention of complications.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Functional and radiological outcomes of different pin configuration for displaced pediatric supracondylar humeral fracture: A retrospective cohort study

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Abstract

BACKGROUND

The most widely accepted treatment for pediatric supracondylar humeral fracture is closed reduction and percutaneous pinning (CRPP). However, there is debate regarding the technique that is utilized, whether crossed or lateral pinning, and the number of pins used.

AIM

To compare the functional and radiological outcomes of lateral and cross pinning in the management of humeral supracondylar fracture.

METHODS

A retrospective analysis was performed on 101 patients who were surgically managed by either one of the CRPP techniques from 2015 to 2019. Several clinical parameters were taken into account, including pre- and post-intervention Baumann angle, as well as scores for pain, range of motion, function, and stability. Statistical analysis was performed to study the outcomes of the utilized techniques.

RESULTS

Amongst our study sample, which included 63 males and 38 females with a mean age of 5.87 years, about one-third of the patients underwent crossed pinning fixation configuration and the remaining two-thirds were managed by lateral pinning configuration. Similar results were obtained in the two groups with no

statistical difference regarding Mayo elbow performance scores (MEPS) and Baumann angle. The mean MEPS in the lateral and crossed pinning groups were 93.68 + 8.59 and 93.62 + 9.05, respectively. The mean Baumann angle was 72.5° + 6.46 in the lateral group and 72.3° + 4.70 in the crossed-pinning group (P = 0.878).

CONCLUSION

Both lateral pinning and crossed pinning fixation configuration for displaced pediatric supracondylar humeral fractures provide similar functional and radiological outcomes.

Key Words: Supracondylar fracture; Gartland; Pinning; Functional; Radiological

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Core Tip: Closed reduction and percutaneous pinning is the mainstay in the management of pediatric supracondylar fracture. It is still controversial what pin configuration should be used (lateral *vs* cross pinning), and how many pins should be used. Both lateral and cross pinning techniques provide adequate stability for the fracture with nearly similar radiological and functional outcomes.

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INTRODUCTION

A supracondylar humeral fracture happens through the thin part of the distal humerus above the growth plate level. These fractures are typical pediatric injuries, accounting for 60% of upper limb fractures and 13% of pediatric fractures. They are most commonly seen in children 5-7 years of age with no gender predilection[1-3].

These fractures may be complete or incomplete with varying degrees of severity. The Gartland classification system is a popular system for the evaluation and treatment of these fractures. It classifies them as type 1 - nondisplaced or minimally displaced, type 2 - displaced with intact posterior cortex, and type 3 - completely displaced without contact between fragments[3]. In addition, the modified Gartland classification is frequently used, describing one more type, type 4 - complete multidirectional displacement of fragments with periosteal disruption[4].

As for the management of these fractures, a trial of conservative management may be undertaken with type 1 fractures and minimally displaced type 2 fractures. This involves long arm casting with less than 90 degrees of elbow flexion[5].

Operative management is almost always required in more severe types, including closed reduction and percutaneous pinning (CRPP). Pinning is performed retrogradely, using two pins for type 2 fractures and three pins for type 3 fractures. Rarely, open reduction with percutaneous pinning is needed in open fractures and in cases of failed closed reduction[6]. The most commonly reported postoperative complication is pin migration[7].

Despite reported complications of neurovascular injuries[8], it has been well documented in the previous literature that pediatric supracondylar humerus fractures generally have good outcomes. Elbow range of motion (ROM) and function are usually preserved, provided that adequate reduction is achieved through surgical intervention or casts application[9].

CRPP has two techniques: Lateral pinning technique (Figure 1A) and cross pinning technique (Figure 1B). Controversy persists between the two perspectives regarding which is better in terms of fixation stability and risk of developing complications.

Theoretically, crossed pinning is superior in providing biomechanical stability, yet this construct increases the risk of iatrogenic ulnar nerve injury due to the medial pin position. Conversely, lateral pinning may be less stable biomechanically but avoids ulnar nerve injury[10-12].

Therefore, this study aimed to study the difference in stability and functional outcomes between patients managed by lateral pinning and those managed by crossed pinning for displaced supracondylar fracture of the humerus. The null hypothesis was that there is no difference between the treatment groups.

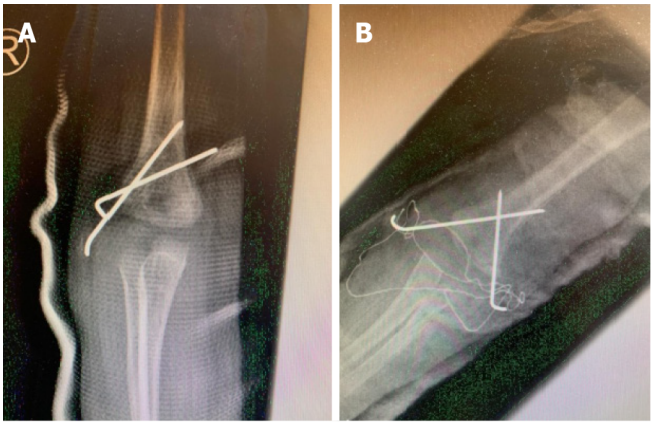

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Figure 1 Postoperative AP view radiographs. A: Lateral pinning; B: Cross pinning.

In order to compare the two techniques, the well-validated Mayo elbow performance score (MEPS) was used as a standardized functional outcome measure[13,14]. Other measures with clinical-radiological value may be considered as well. These may include measurement of Baumann angle (Figure 2), carrying angle, the development of complications, and the necessity to re-operate.

MATERIALS AND METHODS

We conducted a single-blinded retrospective cohort study at the Department of Orthopedics of King Abdullah University Hospital (KAUH). Before conducting this study, ethical approval was obtained from the Institutional Review Board (IRB) committee of KAUH. This study reviewed a total of 101 cases of children with supracondylar humeral fractures that were presented to the emergency department of KAUH between 2015 and 2019. Multiple parameters were reviewed, including gender, age, and surgical intervention, as well as scores for pain, ROM, function, and stability. A convenience sampling method was used to obtain our sample.

Our inclusion criteria for the study involved any patient up to the age of 13 years who had a supracondylar humeral fracture and underwent closed reduction with percutaneous pinning within 24 h of the insult and with no neurological or vascular injury prior to the operation. The pinning was either lateral or crossed configuration with medial and lateral wires. Our exclusion criteria included patients who did not respond to our call, patients with bilateral fractures, patients with multiple surgeries in the same limb, and those who ever had a previous elbow fracture. This was to avoid the confounding effects of previous fractures and surgeries on our results. However, unknown confounders might still be present.

An orthopedic specialist reviewed the patients' radiographic images (Figure 3) and categorized them using the Gartland classification system. Then, surgery was performed and techniques were standardized in regards to pin location, pin size, stability, and positioning of the elbow. They were performed by a well-trained orthopedic surgeon.

Patients were scheduled for follow-up visits; the follow-up period was customized according to patient cases individually, with a timeframe ranging from 1 mo postoperatively to 1 year. They underwent pin removal and cast change and were inspected for symptoms and ROM. Radiographs were taken to guarantee proper healing and reduction (Figure 4).

All fractures were also assessed by altering their Baumann angle, which was measured both postoperatively and during the last follow-up in January-March 2020. Baumann angle refers to the angle between the long axis of the humeral shaft and the growth plate of the lateral condyle. A difference in the angle of more than 5 degrees between the two limbs was considered abnormal. All measurements were performed by a single calibrated examiner. The interclass correlation coefficient for the angle measurement was above 90%.

MEPS was used to assess functional limitations of the elbow on daily activities and administered during January-March 2020 *via* patient interviewing and physical examination in the clinic. Elbow function was measured across four domains: Pain (45 points), ROM (20 points), stability (10 points), and daily function (25 points). Clinical information from these four subscales was rated on a 100-point scale and categorized as follows: < 60, poor; 60-74, fair; 75-89, good; and 90-100, excellent[13,14].

All of our patients were eligible to participate in our study. Matching by age and gender was not performed due to the small number of patients in the crossed pinning group and the portability of introducing bias. Case selection bias was minimal because we applied strict inclusion and exclusion criteria, and the outcome of interest was clear for all categories. In addition, information bias was

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Figure 2 Lateral radiograph demonstrating Baumann's angle (angle between the long axis of humeral shaft and growth plate of lateral humeral condyle).

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Figure 3 Pre-operative AP view radiograph.

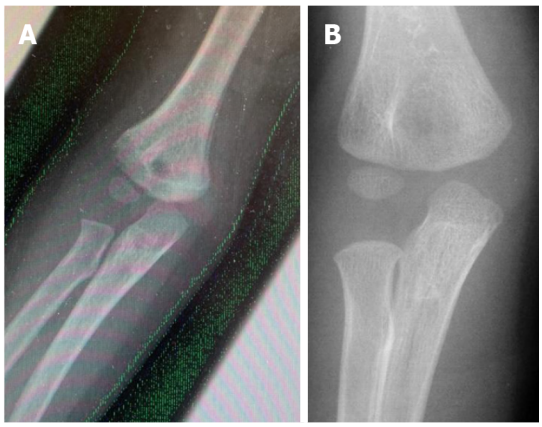

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Figure 4 AP radiographs post pin removal. A: Lateral pinning B: Crossed pinning.

controlled by excluding all patients with missing information.

Data was entered and analyzed using IBM SPSS statistics version 23. We looked at MEPS, Gartland type, type of fixation, and Baumann angle. We classified the patients according to the technique used (crossed pinning *vs* lateral pinning); the lateral pinning group was further sub-classified into 2 pins *vs* 3 pins. Patients were also categorized according to Gartland type, MEPS score, and gender. Using the *t*-test, we measured if there was a difference in Baumann angle according to the type of fixation, and whether it was lateral pinning or crossed pinning. Using multiple linear regression, we measured the

factors that affect Baumann angle and MEPS. Using ANOVA, we measured if there was a difference between two lateral pins, three lateral pins, and crossed pinning groups in their effect on Baumann angle and MEPS. Results were considered significant at $P < 0.05$.

RESULTS

A total of 101 patients with supracondylar fractures were qualified to join our study. All patients responded and were included in the analysis. Of these patients, 63 (62.4%) were male, and 38 (37.6%) were female. The mean age of patients was 5.87 ± 1.5 years, with the youngest patient being 35 d of age and the eldest being 13.0 years of age.

We subdivided them by type of fixation into a cross pinning group with 28 patients (28.7%) and a lateral group with 72 patients (71.3%). Patients were further subdivided by Gartland type and MEPS (Table 1). As for Gartland type distribution, none had type I, 21 (20.8%) had type II, 43 (42.6%) had type III fractures, 28(27.7%) had type IV, and 9 (8.9%) had flexion type supracondylar fracture. The mean time for the last follow-up was 24.65 and 20.55 mo in the lateral pinning and cross pinning groups, respectively.

Regarding outcomes in the lateral pinning group, 62.5% of the patients had excellent outcomes, 36.1% had good outcomes, and 1.4% had fair outcomes. There were no reports of poor outcomes. Meanwhile, in the crossed pinning group, 62.1% of patients had excellent outcomes, 34.5% had good outcomes, and 3.4% had fair outcomes with no reports of poor outcomes.

There was no statistical difference in functional outcome according to MEPS ($P = 0.06$). The mean MEPS in the lateral pinning and crossed-pinning groups were 93.68 ± 8.6 and 93.62 ± 9.0, respectively. Multiple linear regression analysis was performed to determine the relationship between MEPS and different clinical parameters for functional outcomes. However, there was no statistical difference found in functional outcome regardless of gender ($P = 0.220$), fracture type ($P = 0.647$), and type of fixation ($P = 0.888$).

There was no statistical difference between the groups according to Baumann angle ($P = 0.878$). The means in the lateral pinning and crossed pinning groups were 72.5° ± 6.5 and 72.3° ± 4.7, respectively. Multiple linear regression analysis was also performed with Baumann angle with no result of statistical difference regardless of gender ($P = 0.115$), fracture type ($P = 0.949$), and type of fixation ($P = 0.995$).

We further subdivided the lateral group into 2 wires lateral (36 patients) and 3 wires lateral (36 patient) groups; there was no statistically significant difference between the three groups using one-way ANOVA according to MEPS ($P = 0.694$) and Baumann angle ($P = 0.115$).

DISCUSSION

The management of pediatric supracondylar humeral fractures includes non-operative and operative treatments. Fractures are further individualized based on the presentation (open or closed fracture), Gartland classification, the degree of the displacement, and the physician preference[5,7,10]. Regarding operative treatments, CRPP is the mainstay of treatment for displaced extension type supracondylar fracture. However, controversy regarding the optimal technique, whether lateral pinning or crossed pinning, remains under discussion[7,15,16].

In this study, we retrospectively evaluated 101 patients; some managed by crossed pinning (27.8%) and others by lateral pinning (72.1% [2 pins in 50% and 3 pins in the remaining 50%]). Supracondylar fracture incidence was higher in males, nearly 2 times more than in females. The mean age was 5.87, ranging from 35 d to 13 years, with a peak incidence of 5-7 years. This result is comparable to the series done by Patel *et al*[17], where they reported a peak incidence in the 6-8-year-age group with an average age of 7.48 years. Also, male predominance was noted in Patel *et al*[17], Wilkins *et al*[18], and Solak *et al*[19] series. Most clinical and radiological studies used Baumann angle, Flynn grade, and fracture complications to assess clinical outcomes[20]. In our study, we used the MEPS and Baumann angle for this purpose. There was no statistically significant difference between the treatment groups.

The loss of reduction in our study was 0%. In a recent meta-analysis done by Dekker *et al*[20] comparing the two techniques, the loss of reduction occurred in 11.6% of patients treated by crossed pinning and 12.4% of patients treated with lateral pins. Yet, there was no statistically significant difference between the two groups. In addition, there was no significant difference according to the Flynn criteria, ROM, and measures of radiographic outcome.

Patel *et al*[17] also used MEPS for comparing lateral and crossed pinning technique outcomes. For the crossed pinning group, they reported that 90% of the patients had excellent outcomes, 10% had good outcomes, and 0% had poor outcomes. Lateral pinning showed 83.33% excellent and 16.66% good outcomes with no reports of poor outcome. While in our study, 62.5% of the patients in the lateral pinning group had excellent outcomes, 36.1% had good outcomes, and 1.4% had fair outcomes with no poor outcomes. Crossed pinning showed 62.1% excellent outcomes, 34.5% good outcomes, and 3.4% fair outcomes. Both studies showed no statistically significant difference between the two treatment groups.

Table 1 Demographic characteristics

		Lateral group	Cross pin group
Male		43 (59.7%)	20 (69%)
Female		29 (40.3%)	9 (31%)
Extension type 2		15 (20.8%)	6 (20.7%)
Extension type 3		36 (50%)	7 (24.1%)
Extension type 4		15 (20.8%)	13 (44.8%)
Flexion type		6 (8.3%)	3 (10.3%)
Age mean		5.7920	6.0693
Age SD		3.17336	3.0422
MEPS mean		93.6806	93.6207
MEPS SD		8.59877	9.05307
MEPS	Poor	0 (0%)	0 (0%)
	Fair	1 (1.4%)	1 (3.4%)
	Good	26 (36.1%)	10 (34.5%)
	Excellent	45 (62.5%)	18 (62.1%)
Bumann angle mean		72.5139	72.3103
Bumann angle SD		6.46114	4.70640

SD: Standard deviation.

It could be that the difference in the percentages is due to the difference in the interpretation of the MEPS, as 15 points were considered a clinically negligible difference.

Several biomechanical studies demonstrated that crossed pinning is more stable than lateral pinning, especially on rotational testing and valgus and varus loading[21-23]. On the other hand, other studies reported no statistically significant differences radiologically and clinically between the two groups[15, 16]. Although crossed pins seem to provide more stabilization, their major disadvantage is the iatrogenic ulnar nerve injury. The studies estimated it to occur 3 to 5 times more than lateral pins alone [15,16,20]. Conversely, Chen *et al*[24] reported no significant difference in the biomechanical stability between divergent lateral pins and crossed pins in terms of resisting varus, internal rotation, and extension forces. Also, Hamdi *et al*[25] suggested that two or three divergent lateral pins provide optimal fracture stability. These studies support the concept that properly placed lateral pins provide adequate biomechanical stability.

The limitations of our study include it being a retrospective study, not a randomized prospective clinical trial. Another major limitation was the uneven number of cases in each group in addition to them only being followed for short intervals. Furthermore, we included patients with flexion type supracondylar fractures, and these patients may constitute a different population from those with the extension type. Moreover, we did not analyze or report complications. Thus, a randomized controlled trial involving larger samples and evenly distributed cases with long-term follow-up is warranted in future studies.

CONCLUSION

Within the limitations of our study, the two techniques for displaced pediatric supracondylar humeral fractures promote similar postoperative results. There is no significant difference between lateral and crossed pinning techniques regarding the functional and radiological outcomes.

ARTICLE HIGHLIGHTS

Research background

The most widely accepted treatment for pediatric supracondylar humeral fracture is closed reduction

and percutaneous pinning. However, there is debate regarding the technique that is utilized, whether crossed or lateral pinning, and the number of pins used.

Research motivation

To compare the functional and radiological outcomes of lateral and cross pinning in the management of humeral supracondylar fracture.

Research objectives

To compare the functional and radiological outcomes of lateral and cross pinning in the management of humeral supracondylar fracture.

Research methods

A retrospective analysis was performed on 101 patients who were surgically managed by either one of the CRPP techniques from 2015 to 2019. Several clinical parameters were taken into account, including pre- and post-intervention Baumann's angle, as well as scores for pain, range of motion, function, and stability. Statistical analyses were performed to study the outcomes of the utilized techniques.

Research results

Amongst our study sample, which included 63 males and 38 females with a mean age of 5.87 years, about one-third of the patients underwent crossed pinning fixation configuration and the remaining two-thirds were managed by lateral pinning configuration. Similar results were obtained in the two groups with no statistical difference regarding Mayo elbow performance scores (MEPS) and Baumann's angle. The mean MEPS in the lateral and crossed pinning groups were 93.68 + 8.59 and 93.62 + 9.05, respectively. The mean Baumann's angle was 72.5 + 6.46 in the lateral group and 72.3 + 4.70 in the cross-pinning group (P = 0.878).

Research conclusions

Both lateral pinning and crossed pinning fixation configuration for displaced pediatric supracondylar humeral fractures provide similar functional and radiological outcomes.

Research perspectives

A randomized controlled trial involving larger samples and evenly distributed cases with long-term follow-up is warranted in future studies.

FOOTNOTES

Author contributions: Radaideh AM, Rusan M, Mohaidat ZM, Sunallah AW, and Obeidat O designed the research; Radaideh AM, Rusan M, Mohaidat ZM, Sunallah AW, Obeidat O, Al-Nusair J, and Albustami IS performed the research; Obeidat O analyzed the data; Obeidat O, Al-Nusair J, and Albustami IS wrote the paper.

Institutional review board statement: This work was approved by the institutional review board (IRB) committee of King Abdullah University Hospital (KAUH).

Conflict-of-interest statement: Radaideh, Rusan, Obeidat, AL-Nusair, Albustami, Mohaidat and Sunallah declare that they have no conflict of interest.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at ahmadmr1970@yahoo.com.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Retrospective Study

Accuracy of shoulder joint injections with ultrasound guidance: Confirmed by magnetic resonance arthrography

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Abstract

BACKGROUND

Intra-articular glenohumeral joint injections are essential procedures for treating various shoulder disorders. Fluoroscopy-guided injections have been extensively used; however, they pose a risk of radiation exposure and are expensive and time-consuming. Recently, it has been suggested that ultrasound-guided injections are accurate and cost effective procedures.

AIM

To evaluate the accuracy of ultrasound-guided glenohumeral injections using a posterior approach that is confirmed using magnetic resonance arthrography (MRA).

METHODS

The study included 179 shoulders of patients with recurrent anterior instability (150 patients; 103 and 76 right and left shoulders, respectively; 160 males and 19 females; average age = 20.5 years; age range: 14-63 years) who underwent MRA for preoperative diagnosis. They were injected with 12 mL lidocaine (1%) using the ultrasound-guided posterior approach and then underwent magnetic resonance imaging. Two shoulder surgeons, except for the injector, evaluated the transverse relaxation (T2)-weighted images of axial planes and classified the intra-articular condition of injected contrast into three groups based on one of the three

following scenarios: no leakage, injection into the glenohumeral joint without leakage; minor leakage, practical intra-articular injection with some leakage outside the posterior rotator cuffs; and major leakage, inaccurate injection with mass leakage without any contrast into the joint. The inter-rater reliability between two assessors was also evaluated by calculating Cohen's kappa coefficient. The learning curve was assessed regarding the inaccurate injection rate by analyzing Spearman's rank correlation coefficient.

RESULTS

Of the 179 injections, 163 shoulders (91.0%) had no leakage, 10 shoulders (5.6%) had minor leakage, and six shoulders (3.4%) had major leakage. In total, 173 shoulders (96.6%) were intra-articularly injected; thus, we could detect anterior labrum and capsular pathologies. Regarding the inter-rater reliability, the kappa coefficient was 0.925, indicating consistency in the evaluations by both examiners. Regression analysis of the inaccurate injection rate for assessingtechnical learning showed a logarithmic curve with a downward trend ($R^2 = 0.887$, $P < 0.001$). Three (50%) of the six inaccurate injections classified into "major leakage" were observed in the first 30 injections, indicating that the accurate injection showed a leaning effect.

CONCLUSION

Ultrasound-guided intra-articular glenohumeral injections using a posterior approach had high accuracy; however, injection accuracy depends on clinical experience.

Key Words: Shoulder injections; Glenohumeral injections; Ultrasound guidance; Magnetic resonance arthrography

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Core Tip: This is a retrospective study that has evaluated the accuracy of ultrasound-guided glenohumeral injection confirmed using magnetic resonance arthrography. In this study, 163 shoulders (91.0%) were accurately injected without leakage outside the glenohumeral joint. Ten shoulders (5.6%) had minor leakage. In total, 173 shoulders (96.6%) were intra-articularly injected. Ultrasound-guided intra-articular glenohumeral injection using a posterior approach is an accurate injection procedure.

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INTRODUCTION

Intra-articular glenohumeral joint injections are essential procedures for treating various shoulder disorders at clinical settings, such as frozen shoulder, osteoarthritis, and rheumatoid arthritis[1]. These injections are distinguished from subacromial injections commonly used for treating subacromial bursitis, rotator cuff tears, and impingement syndrome. Accurate intra-articular injections of drugs can provide good clinical outcomes and enhance patients' satisfaction with treatment. Furthermore, accurate intra-articular injections of lidocaine, commonly referred to as the lidocaine test, help develop accurate clinical diagnoses. Conversely, injections at erroneous locations may cause damage to nerves, vessels, muscles, or ligaments around the shoulder, and inaccurate injections of lidocaine may mislead the clinical assessment.

Various shoulder injection techniques have been used by orthopedic surgeons or radiologists in their efforts to perform arthrograms. These injection techniques include: (1) blind injections with structures that can be palpated from the body surface, such as the acromion and coracoid process; and (2) image-guided injections with fluoroscopic or ultrasonic guidance, using the anterior, posterior, or supraclavicular approach[2-5].

Conversely, magnetic resonance arthrography (MRA) is a valuable tool used for detecting rotator cuff tears or anterior shoulder instabilities associated with anterior labrum and capsular pathologies. Some studies have reported that MRA is superior to magnetic resonance imaging (MRI) and computed tomography arthrography (CTA) in detecting lesions associated with anterior shoulder instabilities[6, 7]. Precise imaging of these shoulder abnormalities can help plan operative procedures.

A fluoroscopy-guided shoulder injection has been extensively used in conjunction with MRA. This technique was first reported by Baert *et al* in 1933[8], while other studies have reported that the accuracy of fluoroscopy-guided shoulder injections is in the range of 62%-100%[9-11]. However, fluoroscopy-guided injections expose both the examiners and patients to radiation. When MRA is considered helpful for diagnosis, outsourcing the MRA examinations to special institutions is common. However, in Japan, only a few institutions offer MRA examinations because of the lack of dedicated radiologists who can conduct arthrograms. Accordingly, orthopedic surgeons themselves are often needed to perform intra-articular injections before MRI examinations. In these cases, fluoroscopy and MRI reservations are required that is cost-demanding and time-consuming. Therefore, at our institution, we typically perform ultrasonography-guided shoulder injections in conjunction with MRA. The ultrasonographic examinations can be performed before MRI. These procedures are not as time-consuming as the injections performed with fluoroscopy. Recently, ultrasonography has become a widely used diagnostic tool in the field of orthopedics because of its availability, safety, and high diagnostic potential. Particularly, the shoulder joint is one of the bodily areas for which ultrasonography is most useful. Ultrasonography can detect tendons, fluid around the biceps or subacromial bursa, and the contours of the glenohumeral joint clearly that it enables early detection of rotator cuff or intra-articular pathologies, such as tears and fractures[12]. Moreover, ultrasound-guided injections have been gaining attention due to their accessibilities and safety withoutradiation exposure and direct observation of the needle[13]. Although some reports have described the convenience of ultrasound-guided injections, no reports have evaluated its accuracy.

This study was designed to evaluate the accuracy of ultrasound-guided glenohumeral joint injections using a posterior approach confirmed using MRA.

MATERIALS AND METHODS

We retrospectively reviewed the MRA images of patients with recurrent anterior shoulder instability. This study has been approved by the Internal Review Board of the corresponding author's affiliated institution. We excluded patients with rotator cuff tears and posterior shoulder instabilities and those who underwent surgeries. In total, 179 shoulders of 150 patients (including 103 right and 76 Left shoulders; 160 males and 19 females; average age of 20.5 years; age range, 14–63 years) were included in this study. Injections were performed with ultrasound guidance using the posterior approach, followed by MRI examinations (Magnetom Spectra 3T; Siemens Japan, Tokyo, Japan). Two shoulder surgeons, except for the injector, evaluated the transverse relaxation (T2)-weighted images of axial planes and classified the intra-articular condition of the injected contrast into three groups based on one of the three following scenarios. "No leakage" indicates injection into the glenohumeral joint without evidence of leakage. "Minor leakage" indicates intra-articular injections with some leakage outside the posterior rotator cuffs. "Major leakage" indicates inaccurate injection with severe/mass leakage without any contrast into the glenohumeral joint. Diagnosing joint pathologies in the last case was impossible (Figure 1). The chi-square test was used to compare the injection accuracy of the right and left shoulders. The inter-rater reliability between two assessors was evaluated by calculating Cohen's kappa coefficient. Moreover, the learning curve was assessed by determining the inaccuracy rate relative to the total cases. We defined inaccurate injection rate as the total number of "major leakage" divided by the total number of cases that was recorded every 10 cases and examined the correlation between the inaccurate injection rate and number of cases. This was analyzed using Spearman's rank correlation coefficient. All statistical analyses were performed using Statistical Package for the Social Sciences (version 26; IBM, NY, United States), and P values of less than 0.05 were used to denote statistical significance.

Injection technique

All injections were performed by an experienced surgeon (M.T.). The procedures were performed with the patients in the upright sitting position with their shoulders at the neutral rotation position. Ultrasound examinations were performed using a portable equipment (HI VISION Avius, HITACHI, Japan). The linear ultrasonic probe was operated within a variable frequency range (*i.e.*, 6–14 Hz) and was held horizontally and placed over the posterior aspect of the shoulder (Figure 2), allowing the detection of the glenohumeral joint space (Figure 3A). A 23-gage cathelin needle was inserted using an out-of-plane technique toward the gap between the humeral head and glenoid rim, and 12 mL lidocaine (1%) was administered. In the out-of-plane technique, observing the needle tip at all times during injection is difficult; however, the movement of the needle tip can be detected through the movement of soft tissues. Furthermore, as long as the needle does not deviate from the center of the ultrasound probe, the needle tip theoretically reaches the target in the glenohumeral joint. When the needle tip reaches the joint, the drug can be smoothly injected, and simultaneously, the flow of the fluid can be confirmed in the joint on the ultrasound image (Figure 3B and C).

MRI scans were obtained within 60 min after the injections.

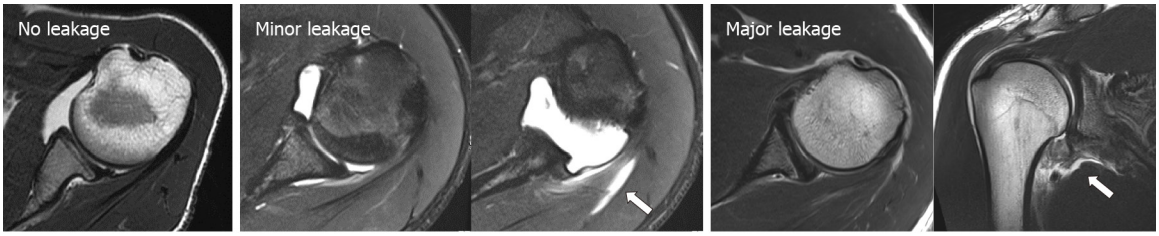

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Figure 1 Classification of the transverse relaxation (T2)-weighted images of magnetic resonance arthrography into three groups. No leakage: Right shoulder injection into the glenohumeral joint without leakage; Minor leakage: Practical intra-articular right shoulder injection; however, another magnetic resonance arthrography image shows the presence of some leakage (white arrow) outside the posterior cuff; Major leakage: Inaccurate injection into the glenohumeral joint of the right shoulder with a noted severe/mass leakage (white arrow) surrounding the axillary area.

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Figure 2 The setting of the injection procedure. Glenohumeral injection performed by a shoulder surgeon using ultrasonic guidance. The patient sits upright with the shoulder at a neutral rotation position, and the ultrasonic probe is placed over the posterior part of the right shoulder.

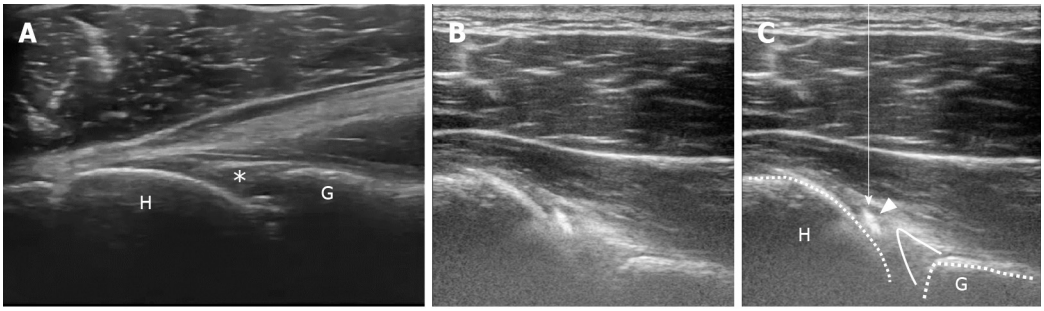

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Figure 3 Identification of the glenohumeral joint and needle insertion point on a captured ultrasound image. A: The gap between the humeral head (H) and glenoid rim (G) is the target of this injection. The needle insertion point (asterisk) should be visualized more clearly; B: Ultrasonographic image during injection; C: Arrowhead shows the high echoic flow of the injection and arrow line indicates the assumed needle path.

RESULTS

No patient complained of poor physical conditions after the injections. Additionally, no neurological disturbances were observed. From the 179 injections, 163 (91.0%) were completely administered in the glenohumeral joint and were classified as "no leakage." Furthermore, intra-articular injection with some leakage out of the rotator cuffs was detected in 10 shoulders (5.6%), and these were classified as "minor leakage" (Table 1). We could detect anterior labrum and capsular pathologies in 96.6% (173/179 shoulders) of the tested cases. Six shoulders were classified as "major leakage." In these cases, the leakages were mostly observed around the axillary area. No significant differences in the accuracy were observed between the right and left shoulders. Regarding the inter-rater reliability, the kappa coefficient was 0.925, indicating consistency in the evaluations by both examiners. Regression analysis of the inaccurate injection rate showed that the curve was logarithmic with a downward trend ($R^2 = 0.887$; $P <$

Table 1 The accuracy of the injections

	No leakage	Minor leakage	Major leakage	Total
Right	94 (91.3%)	7 (6.8%)	2 (1.9%)	103
Left	69 (90.1%)	3 (3.9%)	4 (5.3%)	76
Total	163 (91.0%)	10 (5.6%)	6 (3.4%)	179

No leakage: Injection into the glenohumeral joint without any leakage; Minor leakage: Practical intra-articular right shoulder injection; however, another magnetic resonance arthrography image shows the presence of some leakage outside the posterior cuff; Major leakage: Inaccurate injection into the glenohumeral joint with a noted mass leakage. Right: Right shoulders; Left: Left shoulders.

0.001) (Figure 4). Three (50%) of the six inaccurate injections that were classified into "major leakage" were observed in the first 30 injections. This indicated that the accurate injection showed a leaning effect.

DISCUSSION

An intra-articular shoulder injection is an important technique for diagnosing and treating various shoulder disorders. However, it is reported: (1) that these injections are more difficult to perform than other joint injection types; and (2) that theaccuracy of injection into the glenohumeral joint is poor when performed without image guidance.

Some studies have reported about the accuracy and techniques of shoulder injection. Cunnington *et al* [2] have compared the accuracy of ultrasound-guided injections conducted by research fellows with that of blind (clinical examination-guided) injections conducted by rheumatology consultants for the shoulders, elbows, knees, and ankles and found that ultrasound-guided injections were significantly more accurate than blind injections. Moreover, they have reported that the accuracy of blind injections to the glenohumeral joint was only 40% (8/20 shoulders), which tended to be more difficult than other joint injections. Tobola *et al*[14] have reported on the technique and accuracy of blind injections using theanterior, posterior, and supraclavicular approaches implemented by different providers. As indicated, the anterior approach was the most accurate (22/34 shoulders, 64.7%) in shoulder cases, regardless of the experience of the clinicians who performed them. Patel *et al*[4] have evaluated the accuracy of the ultrasound-guided posterior approach on fresh cadaver shoulders and reported that the accuracy was 92.5% (37/40 shoulders) and showed no significant differences owing to the clinical experiences of the injectors. Most injection accuracy reports have been associated with the use of fluoroscopic images (acquired after the injection procedures) to confirm the intra-articular contrast. Sethi *et al* [15] performed injections using the blind approach with an accuracy of 26.8% with fluoroscopic confirmation. In this study, we evaluated the accuracy of intra-articular shoulder injections using the ultrasound-guided posterior approach in conjunction with MRA images acquired from 179 shoulders (150 patients) for the preoperative diagnosis of anterior shoulder instabilities.

There have been various reports of the accuracy of shoulder injections. However, no reports have neither evaluated injections into the shoulders of living patients nor assessed these using MRA images. In this study, intra-articular shoulder injections that can provide helpful information on labrum and capsular pathologies were performed on 173/179 shoulders (96.6%). The accuracy was equally good or better than those reported in previous cadaveric studies[4].

In current clinical settings, a fluoroscopy-guided injection technique is still extensively used when CTA or MRA is available. Dépelteau *et al*[9] have reported the accuracy of fluoroscopy-guided injections. In these, 59/65 shoulders (90.8%) were successfully injected on the first attempt, four shoulders (6.2%) on the second attempt, and one (1.5%) shoulder on the third attempt. A fluoroscopy-guided technique allows multiple punctures until accurate injection is achieved given that judging whether the contrast material has been injected into the joint during the injection is possible. Conversely, in an ultrasound-guided technique, only indirect information, such as the patient's pain or injector's sensation (*e.g.*, injection pressure), can determine whether the injection is accurate or not. Another disadvantage of an ultrasound-guided injection technique is that detecting the glenohumeral joint space in obese patients it could be difficult because of deep attenuation of ultrasound, unlike the fluoroscopy-guided injection. In such cases, passive movement of the upper arm during ultrasound examination could make detecting the joint space easier. Eventually, we could perform intra-articular injections into the glenohumeral joint with the same or higher accuracy than that reported previously in fluoroscopy-guided injections.

Ultrasound-guided injections have some benefits. They allow more accurate intra-articular injections based on the visualization of the needle's position. Additionally, the portability of the ultrasound equipment could allow the execution of the injections quickly in the examination room; thus, reserving a

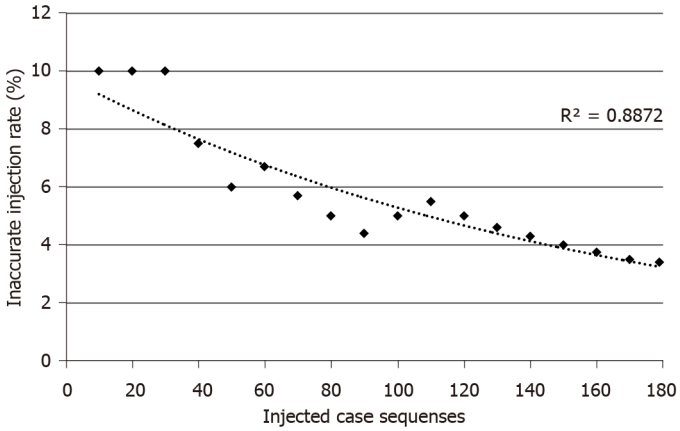

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Figure 4 Learning curve. The inaccurate injection rate is the total number of "major leakage" divided by the total number of injected cases that was recorded every 10 cases. The learning curve is represented by the dotted curve. Spearman's rank correlation coefficient was analyzed ($R^2 = 0.887$, $P < 0.001$).

fluoroscopy room is not needed, and there is no risk of radiation exposure for both doctors and patients. Additionally, the ultrasound-guided injection technique is a simple procedure and is considered superior to fluoroscopy-guided injection techniques in terms of time and cost-effectiveness[16].

In this study, we performed injections using the ultrasound-guided out-of-plane technique; however, observing the needle path continually from the insertion point was more difficult than that using the in-plane technique. Therefore, fulfilling the aim of this injection is necessary, that is, the clear detection and visualization of the gap between the glenoid rim and humeral head achieved by holding the probe in a stable manner at the target position. Conversely, unlike the in-plane technique, in the out-of-plane technique, the injector does not need to change the hand sides that hold the ultrasound probe or the syringe, depending on the side the patient's shoulder. Correspondingly, we can always perform injections using the same procedure. In a blind injection technique, an anterior approach was reported to be the most accurate. In previous reports, fluoroscopy-guided injections had been performed using the anterior approach. This is because landmarks around the shoulder palpated from the anterior body surface, such as the acromion and coracoid process, can provide helpful indications for the injection. However, in an ultrasound-guided injection technique, a posterior approach may allow easier detection of the joint space, given that there are no structures on the posterior shoulder.

The study strengths are the patient size and the technique used to accurately evaluate the accuracy of intra-articular shoulder injections. This study represents the largest patient size among all available reports that targeted the accuracy of injection techniques. In previous reports, fluoroscopy images were used to evaluate the condition of the joint and the accuracy of the injection; however, MRA images could allow us to clearly evaluate intra-articular contrast and leakage outside the joint because identifying the location of the contrast material in a three-dimensional view is possible.

This study has some limitations. First, this study evaluated the accuracy of ultrasound-guided injections performed by a single shoulder surgeon. Whether inexperienced physicians, surgeons who do not specialize in shoulder surgeries, or trainee surgeons who specialize in shoulder surgeries could equally achieve accurate injection outcomes is unclear. Additional studies, including the participation of injectors with different experiences and comparisons with other image-guided techniques or approaches are needed. Second, this study has no control group with blind injections. MRA is an essential test for patients with anterior shoulder instability to detect capsular and labral pathologies. A control group could not be established because of the potential disadvantage to the patients if ultrasound guidance is not used.

Third, the subjects of this study were patients with anterior shoulder instabilities in a relatively young age. We have not assessed the accuracy of intra-articular injections for other shoulder disorders, such as osteoarthritis, rheumatoid arthritis, and frozen shoulders. An ultrasound-guided intra-articular injection could be more difficult for older patients owing to capsular contractures or the presence of osteophytes.

CONCLUSION

Ultrasound-guided intra-articular glenohumeral injections using the posterior approach were an accurate procedure. Of the 179 shoulders, 163 (91.0%) were accurately injected, and 173/179 injections were conducted intra-articularly and provided useful MRA images to detect abnormalities in the glenohumeral joint. We encourage using ultrasonic guidance during shoulder injections because it is a simple and cost effective procedure with acceptable accuracy.

ARTICLE HIGHLIGHTS

Research background

Intra-articular glenohumeral joint injections are essential procedures in a clinical setting of shoulder surgery. In general, a fluoroscopy-guided shoulder injection has been extensively used.

Research motivation

At our institution, we typically perform ultrasound-guided shoulder injections for magnetic resonance arthrography (MRA). The accuracy of ultrasound guided shoulder injection has not been reported.

Research objectives

To evaluate the accuracy of ultrasound-guided shoulder injections with MRA images.

Research methods

We reviewed the shoulder MRA images of patients with anterior shoulder instability and classified the intra-articular condition in three groups and calculated the injection accuracy.

Research results

From the total of 179 injections, 163 (91.0%) were completely administered in the glenohumeral joint. In addition, intra-articular injection with some leakage was detected in 10 shoulders (5.6%).

Research conclusions

The ultrasound-guided shoulder injection was shown to be a very accurate procedure.

Research perspectives

Further, it is necessary to evaluate whether this technique is effective even for inexperienced examiners.

FOOTNOTES

Author contributions: Kuratani K performed the research, contributed to the analysis and wrote the paper; Tanaka M designed and performed the research and supervised the report; Hanai H supervised the statistical analysis; Hayashida K designed the research and supervised the report.

Institutional review board statement: This research has been approved by the IRB of the corresponding author's affiliated institution.

Informed consent statement: Patients were not required to give informed consent to this study because the analysis used clinical data that were obtained after each patient agreed to treatment by written consent.

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

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Comparative study of intertrochanteric fracture fixation using proximal femoral nail with and without distal interlocking screws

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Abstract

BACKGROUND

Intertrochanteric (IT) fracture is one of the most common fractures seen in an orthopaedic practice. Proximal femoral nailing (PFN) is a common modality of fixing IT femur fracture. We retrospectively studied whether a PFN with two proximal lag screws can be done without distal interlocking screws in the 31-A1 and 31-A2 fracture patterns according to the Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA) guidelines for IT femur fractures.

AIM

To compare the outcomes of IT fractures (AO/OTA 31-A1 and 31-A2) treated by PFN with and without distal interlocking screws.

METHODS

We carried out a retrospective study of 140 patients in a tertiary care centre who had AO/OTA type 31-A1 and 31-A2 IT fractures. We divided the patients into two groups, in which one of the groups received distal interlocking screws (group 1) and the other group did not (group 2). The subjects were followed up for a mean period of 14 mo and assessed for radiological union time, fracture site collapse, mechanical stability of implant, and complications associated with the PFN with distal interlocking and without distal interlocking. Then, the results were compared.

RESULTS

PFN without distal interlocking screws has several advantages and gives better results over PFN with distal interlocking screws in the AO/OTA 31-A2 fracture pattern. However, similar results were observed in both groups with the fracture pattern AO/OTA 31-A1. In patients with fracture pattern AO/OTA 31-A2 treated by PFN without distal interlocking screws, there were minimal proximal lock-related complications and no risk of distal interlock-related complications. The operative time, IITV radiation time and time to radiological union were reduced.

These patients also had better rotational alignment of the proximal femur, and the anatomy of the proximal femur was well maintained. It was also noted that in the cases where distal interlocking was performed, there was a gradual decrease in neck shaft angle, which led to varus collapse and failure of bone-implant construct in 21.40%.

CONCLUSION

In fracture pattern AO/OTA 31-A2, PFN without distal interlocking had better results and less complications than PFN with distal interlocking.

Key Words: Intertrochanteric fracture; Arbeitsgemeinschaft für Osteosynthesefra-gen/Orthopaedic Trauma Association 31-A1 and 31-A2; Proximal femoral nail; Distal interlocking screws; Without distal interlocking screws; Outcome

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Core Tip: There are few studies comparing clinical and radiological results of proximal femoral nail (PFN) with and without distal interlocking in fracture pattern 31-A1 and 31-A2 according to the Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association guidelines. From this retrospective study, we conclude that in type 31-A1 intertrochanteric fractures use of long anatomical PFN with or without distal interlocking screws have similar results in terms of radiological union, postoperative proximal femur anatomy, and rotational alignment. In type 31-A2, the use of long anatomical PFN without distal interlocking screws gives better results and less proximal lock-related complications than PFN with distal interlocking screws.

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INTRODUCTION

The incidence of fractures in the trochanteric area has risen with the increasing numbers of elderly persons with osteoporosis[1]. Intertrochanteric (IT) fracture is one of the most common fractures seen in orthopaedic practices, and proximal femoral nailing (PFN) has become a popular modality for its treatment. As per the Orthopaedic Trauma Association (OTA) classification system, these fractures are classified as Arbeitsgemeinschaft für Osteosynthesefragen (AO)/OTA 31-A and are further subdivided into groups A1, A2 and A3 (Figure 1). A1 fractures consist of two-part fractures, A2 fractures have multiple fragments, and A3 fractures include reverse oblique and transverse fracture patterns[2,3].

In 1996, for the treatment of unstable per-, intra- and subtrochanteric femur fractures the AO/Association for the Study of Internal Fixation designed the PFN as an intramedullary (IM) device [4]. It is routine practice to perform distal interlocking for fracture fixation while using PFN. Distal interlocking screws of the IM nail were made to avoid longitudinal or rotational instability as well as movement of distal tip of nail in cases of a broad canal for the IT fracture[5]. Nonetheless, drawback of the distal interlocking screw, like loosening, breaking and subsequent peripheral injures, and secondary femur fractures could not be ignored due to the minimal advantages gained[6].

The purpose of this study was to compare the outcomes of IT fractures (AO/OTA 31-A1 and 31-A2) treated by PFN with and without distal interlocking. We hypothesized that PFN without distal interlocking could be a dependable and acceptable option for IT fractures (AO/OTA 31-A1 and 31-A2).

MATERIALS AND METHODS

We conducted a retrospective study among 140 patients with AO/OTA 31-A1 and 31-A2 fractures treated with PFN at our institute from November 2016 to November 2019. The patients were divided into two equal groups, as follows: 70 patients treated with PFN with distal interlocking screws (group 1); and 70 patients treated without distal interlocking screws (group 2). The same chief surgeon performed the operations of all of the patients.

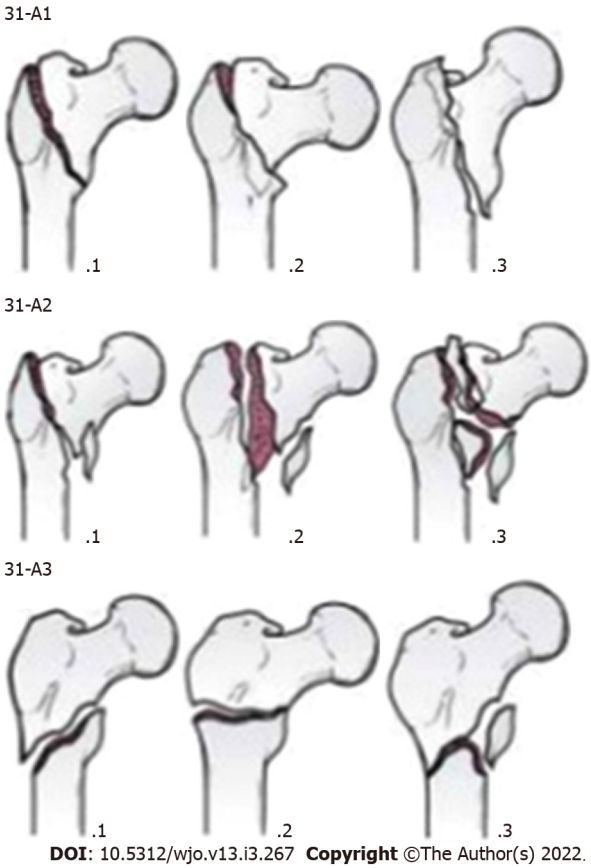

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Figure 1 Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association classification of 31-A fractures. Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association classification as follows: (1) A1: Simple two part, lateral cortex remains intact; (2) A2: Comminuted withpostero-medial fragment,lateral cortex remains intact; and (3) A3: line extend acrossboth medial and lateralcortices,include reverseobliques.

Inclusion criteria included AO/OTA 31-A1 and AO/OTA 31-A2 fracture pattern, age more than 20 years, no other injury or fracture, and those treated with long anatomical design PFN. Exclusion criteria included AO/OTA 31-A3 fracture pattern, age less than 20 years, patients lost to follow-up, patients having surgical site infection, and those treated with short PFN.

In our institute, standard preoperative workup included radiographic evaluation of the fracture type along with blood, medical and anaesthetic assessments. Postoperative protocol included intravenous antibiotics given for 48 h followed by oral antibiotics. On postoperative day 1 of surgery, bedside knee bending, static quadriceps exercises and ankle toe mobilisation exercises were started under supervision of a physical therapist. Regular stitch dressings were completed every third day, and stitches were removed between 12-14 d postoperatively. All patients were sent to the same rehabilitation program. Patients were followed up weekly for the first month after surgery. After that, they received follow-up care every 15 d for the next 2 mo and then monthly follow-up for 14 mo.

The patients were evaluated based on the following clinical and radiological parameters: (1) Fracture patterns according to the AO/OTA classification; (2) Duration of surgery (starting from skin incision to skin closure); (3) Time of IITV radiation exposure; (4) Time to radiological union; (5) Implant-related complications like backing-out of proximal screws from the lateral cortex of the femur, 'Z' effect, screw breakage, cut-through of implant from femoral head, breakage of distal interlocking screw, and breakage of nail; (6) Anatomy of the proximal femur (neck shaft angle of femur); (7) Level of the distal lock screw in relation to the nail in the anterior posterior (AP) view of the postoperative radiograph and radiograph after union were compared in group 1 and the downward migration of the nail in the IM canal in the AP view of the postoperative radiograph and radiograph after union were compared in group 2; and (8) Length and rotation of the limb after healing.

RESULTS

Out of 140 patients, the 70 patients in group 1 were treated with PFN with distal interlocking screws. Among these, 24 were male and 46 were female, and 32 patients had AO/OTA 31-A1 fracture pattern and 38 patients had AO/OTA 31-A2 fracture pattern. In group 2, 70 patients were treated with PFN without distal interlocking screws. Among these, 29 were male and 41 were female, and 28 patients had

Table 1 Distribution of participants according to groups, gender and fracture pattern according Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association classification

	Group-1 (with distal locking)	Group-2 (without distal locking)
Male	24	29
Female	46	41
Total patients	70	70
31-A1	32	28
31-A2	38	42

Table 2 Comparison of operative time and IITV radiation time amongst both groups

	Group-1	Group-2	*P* value
Average operative time	42 min	28 min	< 0.001
Average IITV radiation time	59 s	45 s	< 0.001

Table 3 Incidence of proximal lock related complications

	Group-1 (*n* = 70)		Group-2 (*n* = 70)	
	31A1 (*n* = 32)	31A2 (*n* = 38)	31A1 (*n* = 28)	31A1 (*n* = 42)
Proximal screw backout	01	08	00	04
Proximal screw breakage	00	01	00	00
Proximal screw cut out	00	02	00	00
Z effect	00	03	00	00

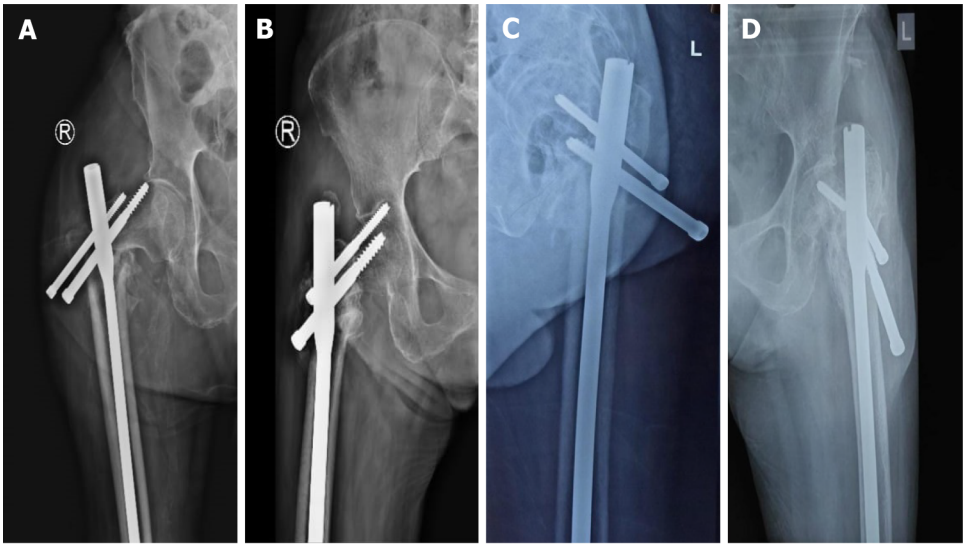

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Figure 2 Proximal lock-related complications. A: Proximal screw cut-out; B: Z-effect; C: Proximal screw back-out; D: Proximal screw breakage.

AO/OTA 31-A1 fracture pattern and 42 patients had AO/OTA 31-A2 fracture pattern. (Table 1)

Operative time and IITV radiation time

The average operation time in group 1 was 42 min, and IITV radiation time was 59 s. In group 2, the average operative time was 28 min ($P < 0.001$) and IITV radiation time was 45 s ($P < 0.001$). This suggests that there was a significant reduction in operative time and IITV radiation time in group 2. (Table 2)

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Figure 3 Distal screw breakage.

Proximal lock-related complications

As shown in Table 3, In group 1, 2 out of 70 (2.85%) patients had screw cut-out (Figure 2A), 3 out of 70 (4.28%) patients had Z-effect (Figure 2B), 9 out of 70 (12.85%) patients had a proximal screw back-out (average back-out = 14 mm) (also Figure 2C), and 1 out of 70 (1.42%) patients had proximal screw breakage (also Figure 2D). In group 2, 4 out of 70 (5.71%) patients had a proximal screw back-out (average back-out = 7 mm). There was no Z-effect, screw breakage or proximal screw cut-out.

Time for radiological union

Average time of union was 14-16 wk in both groups for patients having fracture pattern AO/OTA 31-A1. However, in fracture pattern AO/OTA 31-A2, the average union time was 16-18 wk in group 1 and 15-16 wk in group 2 ($P < 0.001$). There were 3 cases of non-union in group 1 and no cases of non-union in group 2.

Rotational alignment of the proximal femur

Compared to the opposite limb, there was an average of 5 degree external rotation difference in fracture pattern AO/OTA 31-A1 in both groups ($P = 0.66$). There was an average of 6 degrees more external rotation in group 1 with AO/OTA 31-A2 fracture pattern, and there was an average of 7 degrees more external rotation in group 2 with fracture pattern AO/OTA 31-A2 ($P = 0.08$). Malrotation of the operated limb was less than 10 degrees in all patients in both groups. This suggests that there was a negligible effect of distal interlocking on the rotational alignment of the limb for fracture patterns AO/OTA 31-A1 and AO/OTA 31-A2.

Anatomy of proximal femur

Varus rotation of the proximal femur was less than 5 degrees in both groups for all patients with AO/OTA 31-A1 ($P = 0.81$). In AO/OTA 31-A2, the mean neck shaft angle in group 1 was 117 degrees (114-125 degree), and the mean neck shaft angle in group 2 was 126 degrees (124-135 degree) ($P < 0.001$). This suggests that there was better control of the neck shaft angle where distal interlocking was not performed.

Downward migration of nail

We consider downward migration of the nail as a decrease in distance between the tip of the nail and the upper border of the intercondylar notch of the femur on the AP view of the radiograph. In group 2, 6 out of 70 patients had downward migration of the nail due to controlled collapse of the fracture site,

which averaged 5 ± 2 mm. Moreover, in 3 out of 70 patients in group 1, we observed that there was a change in position of the nail in relation to the distal dynamic interlocking screw. There was no downward migration of the nail in the patients in group 1 with static distal locking.

Distal lock-related complications

In group 1, we noted thigh pain over the distal locking site in 19 out of 70 (27.14%) patients, and 1 out of 70 patients had breakage of the distal lock due to downward migration of the nail resulting in auto-dynamization (Figure 3). No thigh pain was reported for any patient in group 2. In the postoperative period, 5 out of 70 patients in group 1 had knee joint effusion, and no patient had knee joint effusion in group 2.

Clinical evaluation

In group 1, 6 out of 70 patients had limb length discrepancy with mean shortening of 12 mm (6-18 mm), 10 out of 70 patients had implant impingement, and 5 out 70 patients had decreased range of movement. In group 2, there was an average of 10 mm of limb shortening (5-15 mm), 1 patient had implant impingement, and all patients had near to normal range of movement as compared to the opposite site.

DISCUSSION

IT femur fractures amount to almost half of total hip fractures caused by a low-energy injury, like a fall from standing height. These fragility hip fractures occur in a population with risk factors including elderly age, female sex, osteoporosis, history of trauma and gait problems[7]. IT fractures are not common in young age patients and require investigation; in this population, IT fractures are caused by high-energy injuries or from a pathological process. Thus, secondary injuries or malignancies must be ruled out[8]. Surgery is typically the recommended treatment as the morbidity and mortality associated with non-operative treatment has been high historically. Patients often have pre-existing comorbidities that dictate the ultimate outcome.

Diagnosis is confirmed by plain radiographs in the AP and lateral views. Traction with internal rotation radiograph view is helpful in assessing significant fracture displacement if the patient is able to tolerate. The antero-posterior and lateral X-ray views of the whole femur are required for long anatomical PFN fixation.

The treatment of proximal femoral fractures with sliding hip screw implants involving an extramedullary or an IM device is a universally accepted method of fixation[4]. In IM fixation there is minimal soft tissue dissection, less blood loss, a lower chance of infection, and fewer wound complications than extramedullary fixation, which has popularized PFN in IT fractures.

At present, PFN is a favourable minimally invasive technique for treating proximal femur fractures, especially where closed reduction is achievable. Nonetheless, proximal lag screw cut-out, Z-effect, reverse Z-effect, femur fracture at the tip of nail or at the site of distal screw insertion, thigh pain as a result of iliotibial tract irritation or cortical hypertrophy and difficulty in insertion of distal interlocking screw are among the probable complications that can occur[1].

There was no pre-established treatment protocol for choosing a long nail or short nail for femoral IT fractures. However, many surgeons are reluctant to use short nails based on the historic literature showing high fracture rates. They also believe that long nails will avoid diaphyseal stress risers and make peri-prosthetic fracture rates acceptable[9]. Short PFNs do not follow the anatomical curvature and the tip may impinge the endosteum of the anterior femoral cortex giving rise to anterior thigh pain. Long PFNs follow the anatomical shape of the femur and would not cause such a problem. At our institute, we have been using long anatomical PFNs. We routinely use long PFN with two proximal interlocks that maintain IT fracture reduction in good valgus position and provide excellent rotational control of the proximal fragment.

Hardware or fixation failure is not related to the type of nail, implant material or AO/OTA classification, but a neck shaft angle of < 125 degrees leads to a significant increase in fixation failure[10]. The influence of varusmal reduction for femur neck fractures and trochanteric fractures was described previously[11]. An increased varus reduction is associated with a higher cut-out rate after sliding hip screw fixation. An increased valgus reduction is beneficial for screw positioning resulting in stable fixation of the femoral head and neck[12]. Kashigar *et al*[13] showed a significant association between an increased varus reduction and cut-out for cephalo-medullary nailing. In addition to nail design, surgical method is also an important factor in determining the incidence of the above-mentioned complications.

Some personnel have supported the IM nailing without distal locking through their biomechanical studies. A biomechanical study done by Lacroix *et al*[14] comprised of 10 paired human cadaveric femurs and gave significant support that an added hole in the distal part of the IM nail could reduce the mean failure load in torsion by 36% because a stress raiser is a factor for peri-implant fracture.

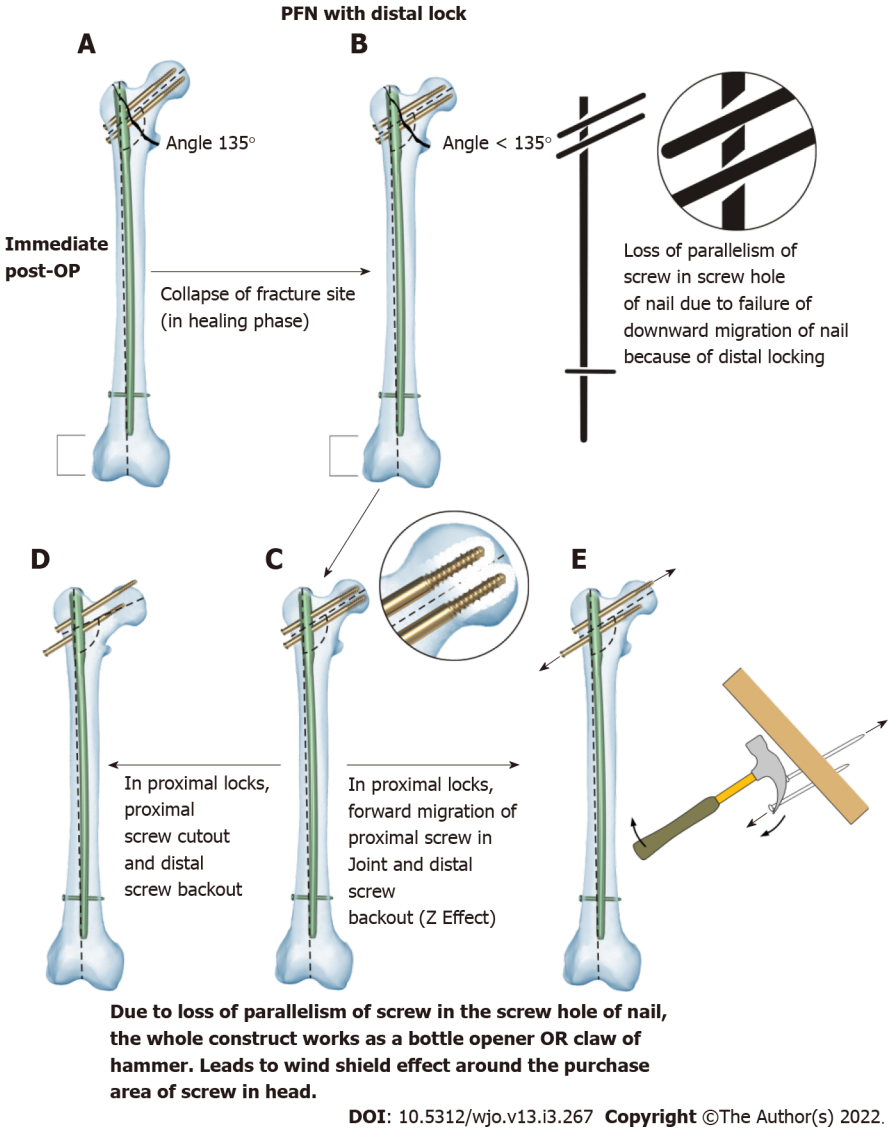

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Figure 4 Typical case presentation of a patient treated with proximal femoral nail with distal interlocking screw. A: Immediate postoperative period; B: Downward migration of the nail because of distal locking; C: Windshield wiper effect around the purchase area of the screw in the head; D: Screw cut-through from the femoral head; E: Z-effect. PFN: Proximal femoral nailing; Post-OP: Postoperative period.

The pattern of the fracture had a significant effect on the distal interlocking of the nail. In stable IT fractures (31-A1 and 31-A2), the lateral cortex of the femur is unaffected. After anatomical reduction when the proximal locks are inserted from the lateral wall of the distal fracture part into the femoral head and the IM nail is matched well to the medullary canal, then varus deformity of the hip joint and rotational instability are controlled by the nail-proximal lock structure. In stable IT fractures, good cortical connection is established after acceptable reduction, and most of the compressive forces on the fracture site are borne by the bony cortex along the axis of neck of femur after surgery. Thus, performing distal interlocking of the nail was found to be unnecessary.

In unstable IT fractures (31-A3), the lateral cortex of the femur is fractured. This includes reverse oblique and transverse fracture patterns with particular anatomical and mechanical properties. Weight bearing on the affected limb gives rise to shearing movement at the fracture site that results in telescoping of the implant[15]. When IM nailing of this unstable fracture pattern was done without distal interlocking screws, neither longitudinal nor rotational stability was attained. Thus, this fracture is not fixed firmly without a distal interlocking screw. However, we concluded that distal interlocking screws are needed for unstable IT fractures (31-A3), particularly those with subtrochanteric extension of the fracture or those with wide IM canals.

Hardy *et al*[16] stated that use of two static locking screws during IM fixation of IT fractures is correlated with a higher rate of cortical hypertrophy, while the use of a dynamically locked nail significantly decreases the rate of this complication. On the basis of these findings, we discontinued the use of distal interlocking screws in AO/OTA 31-A1 and 31-A2 IT femur fractures.

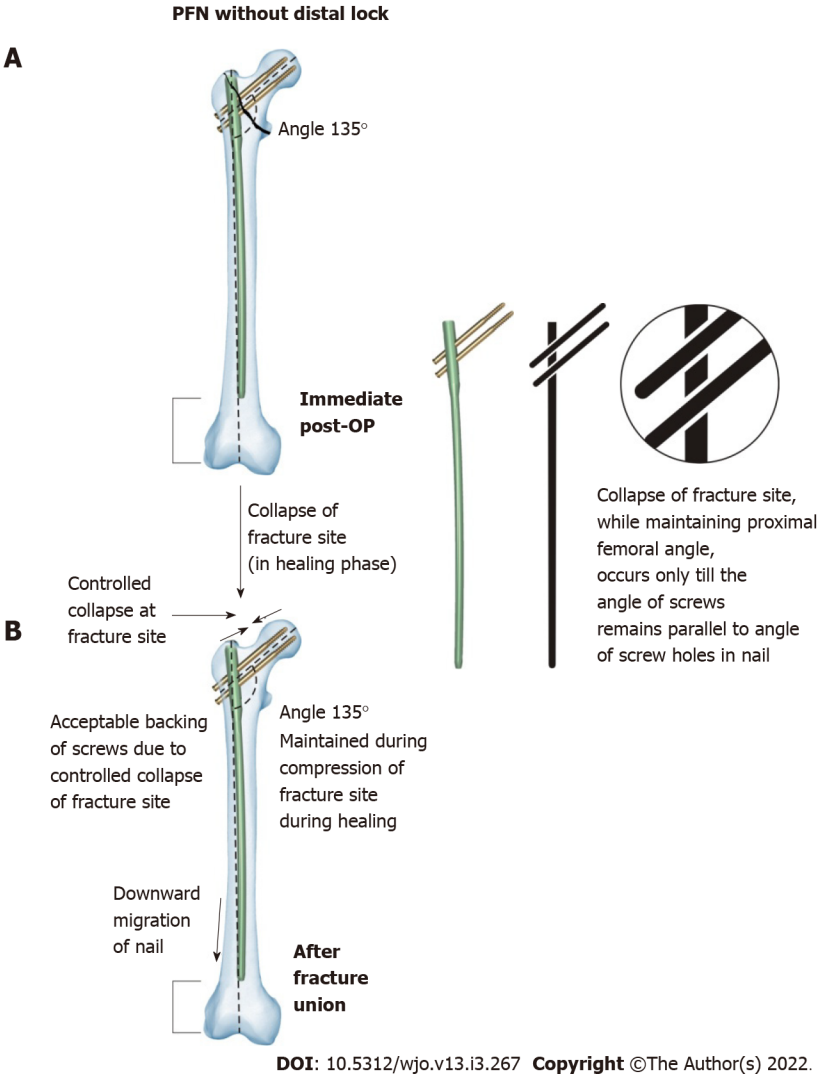

Figure 5 Typical case presentation of a patient treated with proximal femoral nail without distal interlocking screw. A: Immediate post-OP; B: After fracture union. PFN: Proximal femoral nailing; Post-OP: Postoperative period.

Figure 4 shows a typical case where PFN with distal locking was performed. In the immediate postoperative period (Figure 4A), the proximal femoral neck shaft angle was maintained. In the healing phase, there was collapse of the fracture site, but the proximal femoral neck shaft angle was not maintained. There was loss of parallelism of the screw in the screw hole of the nail due to failure of downward migration of the nail because of distal locking (Figure 4B). The whole construct works as a bottle opener or hammer claw, that leads to a windshield wiper effect around the purchase area of the screw in the head (Figure 4C) resulting in forward migration of the proximal lag screw and back-out of the distal lag screw. Due to this loss of parallelism, there can be screw back-out, screw cut-through from the femoral head (Figure 4D), Z-effect (Figure 4E), reverse Z-effect, and screw breakage.

Figure 5 shows a scenario where PFN with distal locking was not performed. It was observed during the postoperative period that the proximal femoral neck shaft angle was maintained. In the healing phase, controlled collapse of the fracture site occurred. During controlled collapse of the fracture site, the proximal neck shaft angle was maintained until the angle of the screws remained parallel to the screw holes in the nail. Parallelism of the screws in the screw holes was maintained due to downward migration of the nail in the canal during the healing phase. Also, there was acceptable backing-out of screws due to collapse of the fracture site.

Metaphyseal fractures heal by direct bone contact and creeping substitution. In comminuted IT femur fracture, controlled collapse at the fracture site is desirable for fracture union because of resorption and comminution at the fracture site. Therefore, in such situations, if there is a static implant bone construct, then there would be an increase in friction at the junction of the nail and screws (Figure 4). This would increase probability of Z-effect, reverse Z-effect, implant breakage, cut-through of screws and back-out of lag screws in the proximal femur. Whereas in cases where distal locking was not performed, the parallelism between the screw hole and screw will be maintained, and the controlled desired collapse with a maintained neck shaft angle would occur, which would increase the chances of fracture union

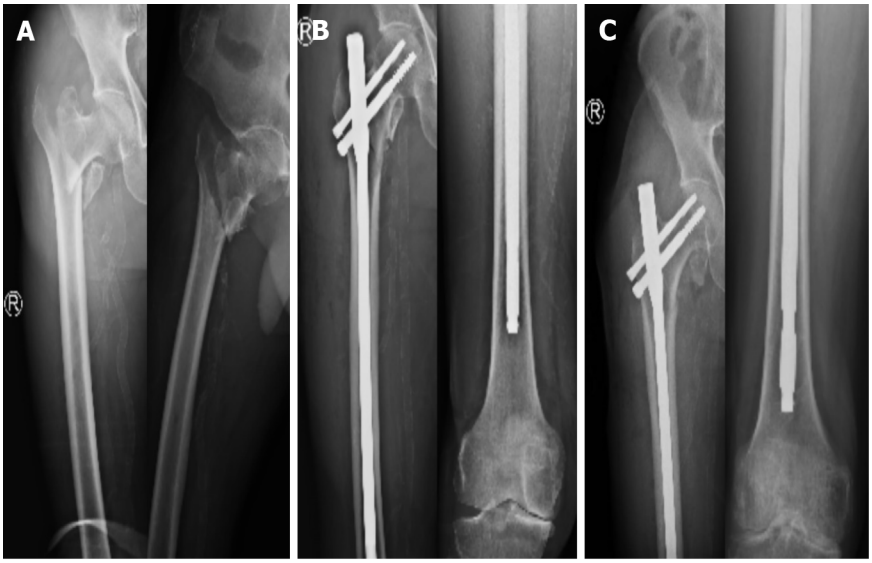

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Figure 6 Case of a 68-year-old female with right intertrochanteric fracture pattern Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association 31-A2. A: Preoperative X-ray; B: Immediate postoperative X-ray; C: After union.

(Figure 5).

In PFN that is done without distal locking, it is desirable to keep the nail length up to the superior border of the patella. A nail with a length up to the intercondylar notch of the femur will not allow downward migration. Therefore, it is desirable to keep a nail short to allow downward migration of the nail with controlled collapse of the fracture.

In our study, it was noted that in the cases for which distal interlocking was performed, there was a gradual decrease in the neck shaft angle, which led to varus collapse and failure of bone implant construct in 21.40% of patients.

There was no significant difference in radiological union, postoperative rotational alignment and proximal femur anatomy between both groups with fracture pattern AO/OTA 31-A1, but the incidence of proximal lock-related complications was increased in group 1 patients with fracture pattern AO/OTA 31-A2 than in group 2 patients with fracture pattern AO/OTA 31-A2 (Table 3).

The limitations of our study were a short follow-up period and a small sample size. We also used only one type of long anatomically designed PFN with two proximal locks.

Case 1

A 68-year-old female patient sustained an IT femur fracture (AO/OTA 31-A2) on the right side (Figure 6A). A long anatomical PFN with two proximal screws without distal interlocking were used for the operation, as shown in immediate postoperative X-ray (Figure 6B). The X-ray image in Figure 6C showed a complete union at 12 mo with maintained neck shaft angle and distal downward migration of the nail, as compared to that in Figure 6B.

CONCLUSION

From this study, we concluded that in IT fractures AO/OTA type 31-A1, use of long anatomical PFN with or without distal interlocking screws gives similar results in terms of radiological union, postoperative proximal femur anatomy, and rotational alignment. However, in AO/OTA type 31-A2, use of long anatomical PFN without distal interlocking screws gave better results and less proximal lock-related complications than PFN with distal interlocking screws.

ARTICLE HIGHLIGHTS

Research background

There are few studies comparing clinical and radiological outcomes between proximal femoral nail (PFN) with or without distal interlocking screws in fracture pattern Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA) 31-A1 and 31-A2.

Research motivation

The motivation of this study was to assess the clinical and radiological outcomes of PFN with or without distal interlocking screws in fracture pattern AO/OTA 31-A1 and 31-A2, which were performed by the same chief surgeon.

Research objectives

The objective of this study was to compare the outcomes of intertrochanteric (IT) fractures (AO/OTA 31-A1 and 31-A2) treated by PFN with and without distal interlocking screws.

Research methods

We conducted a retrospective study of 140 patients having fracture pattern AO/OTA 31-A1 and 31-A2. We divided the patients into two groups based on distal interlocking. We evaluated patients based on clinical and radiological parameters like fracture type, duration of surgery and IITV radiation time, time for radiological union, proximal lock and distal lock-related complications, femoral neck shaft angle and length and rotation of limb after surgery.

Research results

There was no significant difference in radiological union, postoperative radiological alignment and proximal femur anatomy between patients with fracture pattern AO/OTA 31-A1 treated by PFN with or without distal interlocking. However, the incidence of proximal lock-related complications was higher in patients with fracture pattern AO/OTA 31-A2 treated by PFN with distal interlocking than in patients treated by PFN without distal interlocking.

Research conclusions

PFN without distal interlocking is a reliable and acceptable option for IT fracture types AO/OTA 31-A1 and 31-A2.

Research perspectives

A prospective study with long-term follow-up and a larger number of patients is necessary to draw a definitive conclusion.

FOOTNOTES

Author contributions: Lil NA, Makwana VR, Patel TD and Patel AR made substantial contributions to the study conception and design, to the acquisition, analysis and interpretation of data, and to the drafting of the article and making critical revisions related to important intellectual content of the manuscript; and all authors provided final approval of the version of the article to be published.

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ORIGINAL ARTICLE

Retrospective Study

Ilizarov bone transport combined with the Masquelet technique for bone defects of various etiologies (preliminary results)

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Abstract

BACKGROUND

The Ilizarov bone transport (IBT) and the Masquelet induced membrane technique (IMT) have specific merits and shortcomings, but numerous studies have shown their efficacy in the management of extensive long-bone defects of various etiologies, including congenital deficiencies. Combining their strong benefits seems a promising strategy to enhance bone regeneration and reduce the risk of refractures in the management of post-traumatic and congenital defects and nonunion that failed to respond to other treatments.

AIM

To combine IBT and IMT for the management of severe tibial defects and pseudarthrosis, and present preliminary results of this technological solution.

METHODS

Seven adults with post-traumatic tibial defects (subgroup A) and nine children (subgroup B) with congenital pseudarthrosis of the tibia (CPT) were treated with the combination of IMT and IBT after the failure of previous treatments. The mean number of previous surgeries was 2.0 ± 0.2 in subgroup A and 3.3 ± 0.7 in subgroup B. Step 1 included Ilizarov frame placement and spacer introduction into the defect to generate the induced membrane which remained in the interfragmental gap after spacer removal. Step 2 was an osteotomy and bone transport of the fragment through the tunnel in the induced membrane, its compression and docking for consolidation without grafting. The outcomes were retrospectively studied after a mean follow-up of 20.8 ± 2.7 mo in subgroup A and

25.3 ± 2.3 mo in subgroup B.

RESULTS

The "true defect" after resection was 13.3 ± 1.7% in subgroup A and 31.0 ± 3.0% in subgroup B relative to the contralateral limb. Upon completion of treatment, defects were filled by 75.4 ± 10.6% and 34.6 ± 4.2%, respectively. Total duration of external fixation was 397 ± 9.2 and 270.1 ± 16.3 d, including spacer retention time of 42.4 ± 4.5 and 55.8 ± 6.6 d, in subgroups A and B, respectively. Bone infection was not observed. Postoperative complications were several cases of pin-tract infection and regenerate deformity in both subgroups. Ischemic regeneration was observed in two cases of subgroup B. Complications were corrected during the course of treatment. Bone union was achieved in all patients of subgroup A and in seven patients of subgroup B. One non-united CPT case was further treated with the Ilizarov compression method only and achieved union. After a follow-up period of two to three years, refractures occurred in four cases of united CPT.

CONCLUSION

The combination of IMT and IBT provides good outcomes in post-traumatic tibial defects after previous treatment failure but external fixation is longer due to spacer retention. Refractures may occur in severe CPT.

Key Words: Ilizarov bone transport; Induced membrane technique; Post-traumatic tibial defect; Congenital pseudarthrosis of the tibia; Distraction osteogenesis; Regeneration

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Core Tip: This study presents preliminary outcomes and the protocol of a developed technology that includes phase 1 of the Masquelet technique for induced membrane generation and Ilizarov bone transport. The technology did not comprise bone grafting or skin flaps. It was used in 16 patients with post-traumatic tibial defects and congenital pseudarthrosis of the tibia (CPT), after multiple failed treatments. The results were rated as good in patients with post-traumatic tibial defects. Congenital cases showed similar rates of pseudarthrosis union as other means currently used for CPT. Refractures may be expected in severe types of CPT after multiple previous treatments

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INTRODUCTION

The challenges of long-bone defect management have increased in contemporary orthopedic practice due to the severity of high-energy trauma and its complications[1]. These defects can lead to a multi-stage, long and costly treatment. The Ilizarov method of bone transport (IBT) and the Masquelet induced membrane technique (IMT) have been used in a great variety of challenging clinical situations including post-traumatic bone loss, infected nonunion, tumor resection, and congenital deficiency, such as congenital pseudarthrosis of the tibia (CPT)[2-4]. Both techniques have specific merits and shortcomings, but numerous studies have shown their efficacy in the management of extensive long-bone defects of various etiologies, including congenital defects[2-5].

The IBT has been praised for high union rates and its biological aspect of growing authentic bone tissue to close bone defects[5-7]. Its followers believe that it is an ideal type of non-free bone grafting by which a vascularized autologous osteotomized bone fragment is transported gradually in the interfragmental gap within the soft tissue envelope to grow the missing bone part of a required length and shape [2,6-8]. The Ilizarov system has been criticized due to complications such as pin-tract infection, pain, possible joint contractures, risk of ischemic regeneration in compromised soft-tissues around a large defect and impaired quality of life due to the long time needed to provide treatment tasks and new bone remodeling[9]. The IMT is also based on the biological tissues of the induced membrane (IM) and autologous bone grafting, and utilizes internal or external fixation[10,11]. It is not devoid of characteristic complications either, being a staged treatment that takes months to complete bone remodeling. However, it provides a better quality of life, especially if pathology is located in the upper limb and

femur[3,10].

Recent available studies have reported mostly good final outcomes of both procedures[6,7,10,11]. A study that compared the IBT (37 sources) and the IMT (41 sources) did not find statistical differences and reliable advantages between them in regard to consolidation, infection risks and failures that ended with amputation[12]. However, the study found that IBT patients had a higher rate of refractures. This may be associated with the fact that bone regeneration in large defects requires a longer time for remodeling and needs supportive internal fixation[8]. Nevertheless, several reviews and clinical studies doubt the superiority of IMT over IBT for long-bone defects in the lower extremity and point out that bone consolidation time may be unpredictable while non-weight bearing is prolonged in IMT[13,14]. High rates of infection and even amputation were reported for tibial defects after open fractures treated with IMT[14]. On the contrary, IBT allows weight-bearing from the first days. It is primarily used in patients with an infected tibia and rarely results in amputation[2,5]. In pediatrics, IMT has been frequently used for cancer surgery reconstructions[4]. Congenital anomalies, including CPT, may be treated with both options[4,15,16].

The importance of improving bone regeneration in the management of large bone defects and CPT is a very relevant issue due to treatment failures that diminish bone potential for regeneration. Management of CPT may take years in a growing child due to frequent recurrences and has a negative impact on the child's development. Therefore, a combination of the biological merits of IBT and IMT seemed to us a promising strategy in the management of cases with a history of failed attempts and impaired regeneration potential. Following use of the combined technique in an experimental canine model[17], we aimed to conduct clinical studies on the use of this new technological solution that integrates the IMT and IBT techniques for treating non-viable tibial defects of post-traumatic (PTD) etiology and CPT to improve bone regeneration at the docking site, bone consolidation and reduce the refracture rate.

MATERIALS AND METHODS

We retrospectively studied the treatment course and outcomes in a case series that included seven PTD patients (subgroup A) and nine CPT cases (subgroup B) managed using the combination of IMT and IBT. The patients were treated at the same specialized department in our orthopedic center by one team of surgeons in 2014–2019.

Tibial defects in subgroup A were caused by falls from a height, injuries at production sites and traffic accidents (Table 1). Time since injury was from one to 12 years (mean, 3.7 ± 0.9 years) and all subjects were adults (six males and one female with a mean age of 38.5 ± 4.1 years). Six cases had a history of infection and one had delayed wound healing. Patients' inclusion criteria in subgroup A were bone defects of post-traumatic origin after several failed previous treatments, with a disease history of one year or more, and non-viable types of nonunion (hypotrophic, torsion-wedge, defect-pseudarthrosis). Patients with active infection or hematogenous osteomyelitis were excluded. Subgroup B included nine children with a mean age of 6.1 ± 0.9 years and severe CPT types (Paley types 4 a-c)[15], mostly due to neurofibromatosis type I, who had had numerous failed interventions to unite pseudarthrosis and had no active infection (Table 2). Mean preoperative data of both subgroups are given in Table 3.

Surgical protocol

Step 1: Ilizarov frame mounting + spacer implantation. The Ilizarov frame was constructed of three ring supports with three wires in the proximal and distal rings and two wires in the middle ring at the level of the tibial diaphysis. Fibular osteotomy was performed in order to eliminate segment deformities. For pseudarthrosis resection, an anterior approach to the tibia was used. In subgroup A, the resection started from the level of the endplate and extended to the margin with the bleeding bone. The "blood dew" sign indicated an adequate level of resection. In subgroup B, the pseudarthrosis zone along with the surrounding pathologically altered periosteum was resected. After resection, the limb was fixed with the Ilizarov frame in a neutral position according to the tension of soft tissues with the correct anatomical axis of the segment. Next, the defect size was measured. A pre-shaped spacer was prepared from methyl methacrylate cement by molding in a syringe. Its diameter corresponded to the bone diameter of the specific patient, coinciding with the level of the cortical plates, or going beyond the cortices by 2-3 mm. The spacer was placed into the defect gap after being hardened and was fixed in the gap by applying compression with the Ilizarov frame. One dose of vancomycin was added to the spacer material for infection prevention in subgroup A. Wounds were closed in the regular manner. We used only the first phase of the IMT procedure.

Step 2: Osteotomy for bone fragment transport. The spacer was accessed through the previous incision. Careful handling was required to maximize preservation of the induced membrane. Upon removal of the spacer, the induced membrane that enveloped it remained in the interfragmental gap and the wound was sutured. In the frame being unchanged, a mainly proximal osteotomy for bone transport was performed. The distal fragment was osteotomized in PTD-case 5 (Table 1); osteotomy was

Table 1 Demographic, clinical and outcome data of subgroup A patients treated with a combined technology Masquelet induced membrane technique + Ilizarov bone transport

Patient	Age (yr), Gender	Mechanism of injury/Type the fracture	Disease duration (yr)	Type (number) of previous surgeries	Type of nonunion/Infection	Shortening/Bone defect (cm)	Joint Function before surgery	Regenerate/nonunion consolidation completeness	Nonunion consolidation (mo)	Postoperative complication (Paley classification)	Follow-up (mo)	Residual limb length discrepancy (cm)	Further surgery
PTD-1	51, F	MVA, OF	1	EF (1)	TW; Delayed wound healing	3/3	Knee and ankle stiffness	+/+	11	Pin-tract infection Regenerate deformity; Deep vein thrombosis	17	2	-
PTD-2	50, M	MVA, OF	4	Plate (1); EF (1)	HN; History of infection	3/5	Ankle ankyloses	+/+	10	Regenerate deformity	24	5	Rejected further surgery
PTD-3	48, M	IF, OF	3	Plate (1); EF (1)	HN; History of infection	0/3	Ankle stiffness	+/+	7	Pin-tract infection	12	-	-
PTD-4	18, M	IF, OF	3	Plate (2); EF (2)	HN; History of infection	6/3	Ankle ankyloses	+/+	11	Knee joint stiffness	36	6	3-cm lengthening
PTD-5	21, M	IF; OF	1	EF (2)	HN	0/4	Full function	+/+	5	Regenerate deformity	24	-	-
PTD-6	39, M	CT; CF	12	Plate (1); EF (1)	HN; History of infection	1/3	Ankle stiffness	+/+	7	Pin-tract infection	12	-	-
PTD-7	43, M	CT	2	Plate (1)	HN; History of infection	0/4	Ankle stiffness	+/+	8	-	n/a	-	N/A

PTD: Post-traumatic defect; F: Female; M: Male; MVA: Motor vehicle accident; IF: Isolated fracture; CT: Catatrauma; OF: Open fracture; CF: Closed fracture; EF: External fixation; TW: Torsion-wedge nonunion; HN: Hypotrophic nonunion; DP: Defect-pseudarthrosis; N/A: Not available.

performed at two levels in CPT-case 7 (Table 2). Distraction was initiated from day 5 to 7 at a rate of 1 mm/d produced with 4 increments. Condition of the regeneration was checked radiographically every ten days. In low optical density of the regenerate or its deformity, the rate of distraction was adjusted or reduced to 2 or 3 increments, a quarter of a mm each. The transported bone fragment ran in the membrane without technical problems. Distraction was carried out until close docking of the fragments. Upon docking, supportive compression of 1 mm was provided once every two weeks in the consolidation phase. Autologous grafting was not added.

Postoperative care and radiographic checks followed the standards of the Ilizarov method. Radiographic evidence of bony union, external fixation time, defect filling rate and complications were assessed. The primary outcome measure was radiographic bone union. Secondary outcomes were correction of limb length discrepancy and deformities.

Table 2 Demographic, clinical and outcome data of subgroup B patients treated with a combined technology Masquelet induced membrane technique + Ilizarov bone transport

Patient	Age (yr), Gender	Neurofibromatosis	Type (number) of previous surgeries	Paley CPT Type	Shortening/Bone defect (cm)	Joint Function	Regenerate/nonunion consolidation completeness	Consolidation time (mo)	Complications (Paley classification)	Follow-up (mo)	Residual limb length discrepancy (cm)	Recurrence/Further surgery
CPT-1	4, M	I type	-	4C	5/3	Full	+/+	7	Regenerate deformity	24	3	Refracture
CPT -2	3, M	-	EF (1); Nail (1)	4C	5/2	Ankle stiffness	+/+	9	Pin-tract infection	36	3	Refracture
CPT -3	15, F	I type	More than 10 including EF, Nail	4A	15/3	Ankle stiffness	+/+	10	Pin-tract infection	12	12	
CPT -4	5, M	I type	-	4B	3/1.5	Full	+/-	7.5	Pin-tract infection	24	3	Ilizarov monofocal compression
CPT -5	8, F	I type	Plate (1); Nail (2); EF (4)	4B	10/3	Ankle ankylosis	+/+	9	-	36	12	Twice Ilizarov lengthening by 6 cm
CPT -6	4, M	I type	EF (1); Autograft (1)	4C	5/1.5	Full	-/-	8	Ischemic regenerate	24	6	Bone defect, rejected further treatment
CPT -7	6, F	-	EF and allograft (2)	4A	5/5	Full	+/+	13.5	Ischemic regenerate	12	5	-
CPT -8	6, F	-	Plate (1); Nail (2); EF (4)	4B	4/3	Full	+/+	7	Pin-tract infection	24	2	Refracture
CPT -9	4, F	-	Plate (1); Nail (2); EF (4)	4A	2/2	Ankle stiffness	+/+	8	-	36	2	Refracture

CPT: Congenital pseudarthrosis of the tibia; F: Female; M: Male; EF: External fixation.

Thin fragments of the biomembrane formed around the cement spacer were harvested prior to bone transport for histological examination in all patients. The material was collected intraoperatively at step 2.

All adult patients and the children's parents gave informed consent for surgical treatment and inclusion in the study. The study was approved by the ethics board of our institution.

The subgroups had different etiologies of the defects and belonged to different age groups. Thus, we did not aim to compare them. The statistical method included calculation of mean values and their deviations using Microsoft Excel 2019. Moreover, the sample size of subgroups was small; therefore, only descriptive statistics were used.

Table 3 Main mean values of preoperative and postoperative data by combined use of Masquelet induced membrane technique + Ilizarov bone transport

Parameter	Subgroup A	Subgroup B
Number of previous surgeries per patient	2.0 ± 0.2	3.3 ± 0.7
LLD at admission (cm)	3.5 ± 0.5	6.0 ± 1.0
Defect size (cm)	3.6 ± 0.3	2.7 ± 0.3
True defect (LLD + bone gap) after debridement relative to the contralateral limb (%)	13.3 ± 1.7	31.0 ± 3.0
Time of spacer retention (d)	42.4 ± 4.5	55.8 ± 6.6
Duration of distraction (d)	43.0 ± 4.2	31.9 ± 4.2
Distraction regenerate size (cm)	3.1 ± 0.2	2.6 ± 0.2
Completeness of defect filling (%)	75.4 ± 10.6	34.6 ± 4.2
External fixation index per cm	143.5 ± 13.2	117.8 ± 8.5
Duration of total external fixation, including spacer retention time (d)	397.0 ± 15.3	270.1 ± 16.3
Mean follow-up time (mo)	20.8 ± 2.7	25.3 ± 2.3

LLD: Limb length discrepancy.

RESULTS

Table 1 and Table 2 present the main preoperative and treatment parameters along with outcomes of the combined technique of IMT + IBT in all patients. The mean values of the main measures are shown in Table 3. Bone union was achieved in all patients of subgroup A (Figure 1) and in seven patients of subgroup B (Figure 2). Total duration of external fixation was 397.0 ± 15.3 and 270.1 ± 16.3 d, including spacer retention time of 42.4 ± 4.5 and 55.8 ± 6.6 d, in subgroups A and B, respectively. One non-united CPT case was further treated with the Ilizarov compression method only and achieved union. Another failed CPT case was lost. After a follow-up period of one to three years, there were no refractures in subgroup A. Refractures occurred in four cases of CPT due to severe disease (mostly Paley CPT type 4 C) and multiple previous treatments. Cases CPT-8 and CPT-9 had seven previous surgeries each.

Bone transport in the membrane ran smoothly. Postoperative complications included several cases of pin-tract infection and regenerate deformity in both subgroups. Insufficient ischemic regeneration was observed in two cases of subgroup B. Bone regenerate deformity and pin-tract infection were resolved during the course of treatment. The regenerate zone was perforated with wires and supportive compression was performed with the same frame in ischemic hourglass-shaped regeneration for its stimulation. We prefer delayed lengthening to finally correct the length in non-viable nonunion, after bone consolidation has been secured. Thus, we subsequently performed this in two patients of subgroup A who applied for length compensation. Further treatment reduced limb length discrepancy from 12 to 6 cm in CPT-case 5 with two procedures.

Subgroup A patients could walk with crutches after frame removal gradually increasing weight-bearing. Subgroup B patients were recommended to use crutches for one month and then leg braces for one year.

DISCUSSION

Several surgeries are often required to manage extensive segmental bone loss after multiple failures or severe congenital deficiency. They may result in prolonged recovery times, poor outcomes, and even amputation as a complex of mechanical issues and biological factors should be utilized for reconstruction[1,2]. IBT has established itself as an efficient tool for long bone defect management, including patients with infections, especially in the tibia[5-9]. It is able to resolve the problematic triad of bone loss, soft-tissue compromise and bone infection. The IMT has recently been used for extensive defects in any long-bone segment[3,4,18]. According to several authors, the advantage of IMT over IBT lies in the fact that the consolidation time does not depend on the bone defect size as it is filled with autologous graft material[3,11]. Nevertheless, extensive defects need a lot of bone graft substance, especially in the lower extremities[18]. Alternately, the distraction procedure, being a part of IBT, is able to supply new regenerated bone substance[2].

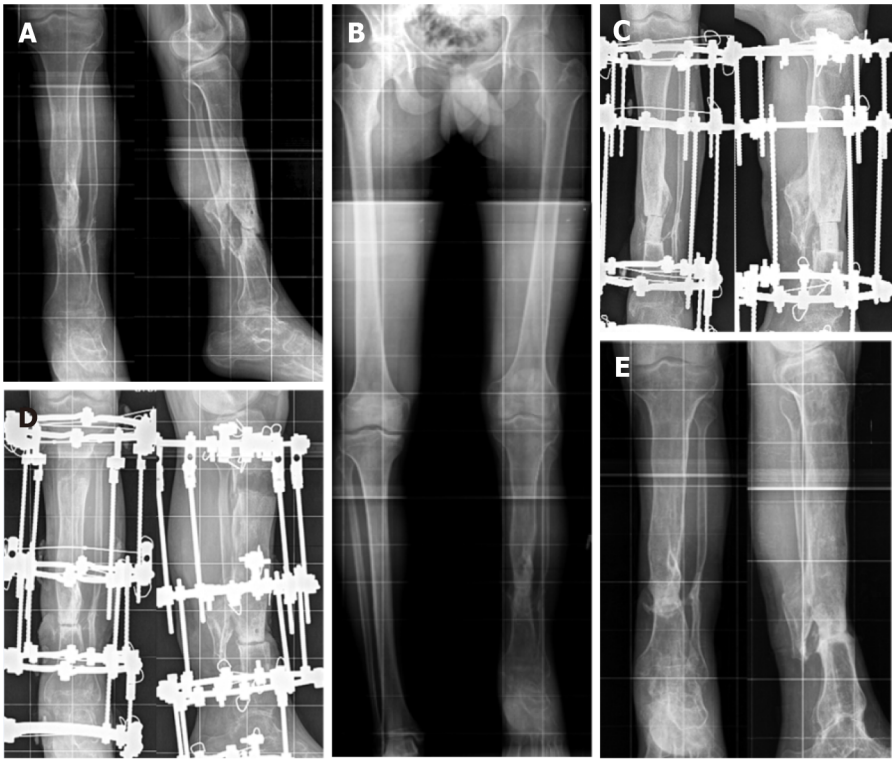

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Figure 1 Post-traumatic defect case 4 (Table 1). A: Preoperative radiographs of the right tibia capturing the adjacent joints showing a hypotrophic nonunion of the tibia; B: Preoperative telemetry compensated by a sole elevation 6-cm left leg discrepancy; C: Spacer fills the defect; D: Closed docking of the fragments and the regenerate of satisfactory optical density and zonal structure; E: Bone callus at the fragments docking and the regenerate with signs of its remodeling and cortical plates at 6-mo follow-up.

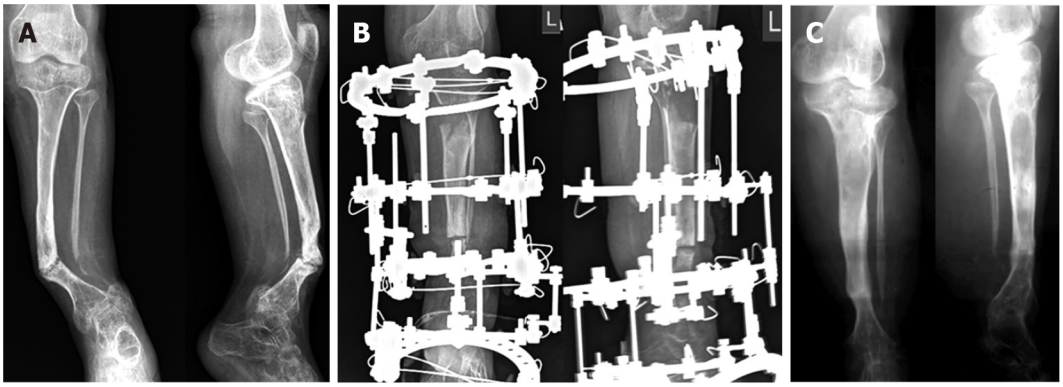

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Figure 2 Congenital pseudarthrosis of the tibia case 3 (Table 2). A: Preoperative radiographs of the left tibia capturing the adjacent joints showing valgus and antecurvatum at the pseudarthrosis level, extended sclerosis of fragments ends; B: Completion of distraction and defect filling at the time of docking between the ends without signs of ossification; C: Continuous distraction regenerate and consistent bone callus at the docking site at 1-year follow-up.

We assumed that defect filling would provide a particularly favorable environment for bone regeneration and the reparative process with the combined use of IMT and IBT. After extraction of a spacer there is a tunnel in the interfragmental gap the walls of which are formed by the induced membrane which was found to be a type of neoperiosteum[16,19]. Apart from a favorable mechanical effect, the combined conditions could provide a biological effect of the induced membrane on osteogenesis. It was shown that multiple microvessels of the biomembrane penetrate into the regenerate zone and promote the inflow of low differentiated pluripotent cells[16]. The cells of the membrane basal layer and perivascular osteopontin-positive cells that possess osteogenic differentiation ability contribute to the formation of a low mineralized bone matrix on the surface of the spacer. This could cause an osteoinductive effect on the pluripotent cells in the region of the compression regenerate formed at the docking site. According to the reported findings, the osteoinductive membrane is adequately vascularized and produces growth factors (vascular endothelial growth factor, transforming

growth factor-beta 1) and bone morphogenetic protein-2 that play a role in regeneration and may prevent lysis[19]. It is also assumed that the biomembrane features antimicrobial activity related to the synthesis of antioxidants which are secreted locally along with growth factors[20]. Another mechanism of the supposed bacteriostatic effect is the presence of local peptides in the membrane which are able to inhibit secretion of the bacterial biofilm[16]. There were no foci of infection in the biomembrane fragments harvested at step 2 of our procedure in all cases. In addition, none of the patients developed infection.

The results of the subgroups in our series could not be compared due to different etiologies and the pathogenesis of nonunion. For this reason, the outcomes were presented separately. Despite the absence of active infection, we chose the primary task to achieve radical debridement in order to prevent possible infection. In subgroup A, the spacer's role was also to sanitize the site of previous infection. The absence of infection recurrence is attributed equally to the impact of radical debridement and that of the vascularized membrane. The interval between the first operation and the osteotomy was a period of infection control that was based on the results of bacteriological tests for selection of antibiotic therapy. The spacer maintained the shape of the defect gap to exclude soft tissues invagination into the defect.

We also promoted osteogenesis at bone fragments docking. As the role of the periosteum in CPT pathogenesis has already been proven, we expected that the neoperiosteum-like nature of the induced membrane would have an effect on bone union and regeneration in the CPT subgroup. The induced membrane was supposed to supply blood to the area with a new vascular network, thereby excluding osteolysis. However, the results in subgroup B were similar to other current techniques used for this pathology[15].

The removal of the spacer presupposes repeated trauma to the skin and soft tissues in the pseudarthrosis zone. However, if we draw a parallel, classical bone transport involves an open co-aptation for fragments docking. According to the protocol for our combined technique, docking was performed in a closed way by compression at the junction of the fragments without grafting. The known approach to create the maximum "bone mass" in the area of pseudoarthrosis was implemented by the technique[15]. Therefore, to add autologous bone grafting or internal fixation to the described combination seemed to us extremely invasive. However, open docking and a graft were used in an earlier study of infected tibial defects treated with a similar technology[21]. Thus, there could be options to synergistically widen the integrated approach.

Consolidation of nonunion was achieved in all the defects of post-traumatic etiology but it should be noted that the IM effect was not strong enough for CPT consolidation and did not help to eliminate refractures in the long term. The refracture rate was comparable with the literature data on the use of other methods, including the Ilizarov method used separately[15].

The management of CPT has been much discussed recently and there is plenty of clinical research with variable results[15,22-30]. The superiority of one of the techniques for reconstruction in CPT has not yet been confirmed. The latest clinical studies predominantly describe patients where the Ilizarov method is the main component of CPT management in conjunction with intramedullary nailing and bone grafting[22-25]. The combined technique of the Ilizarov external fixation, stabilization with an intramedullary rod and corticocancellous bone autograft yields a statistically significant reduction in the number of refractures compared with standalone fixation methods. It was stated that the four methods of CPT treatment might achieve primary union of about 50% without refracture and this was attributed to the biological nature of CPT[15]. Improved union rates in IMT assisted by the Ilizarov external fixator and grafting for previously failed CPT treatment were reported[26].

However, regardless of the primary bone fusion rates, most of the authors state that the probability of long-term bone union retention remains unpredictable due to biological factors of the disease characterized by low osteogenic potential. Therefore, methods to enhance this potential have been identified such as wrapping, grafting, crossunion of the tibia and fibula, and application of several biological agents to promote osteogenesis[27-30]. Our technology might also be used.

The combination of technologies to treat orthopedic pathology is largely associated with the need to obtain a faster and a more efficient result in the most severe cases. Apart from our previous study[16], we found only three case reports that used the combined principles of IMT and IBT with satisfactory outcomes, although not quite the same as our technology[21,31,32]. The limitation of our series is the small sample of patients with two different etiologies of defects and various clinical situations, but all severe cases. Our preliminary results suggest that the etiological factor plays a significant role in the use of this combined technique. Both subgroups had impaired bone regeneration potential due to multiple previous failures and a worsened condition of the tibia, but undoubtedly this was greater in subgroup B.

We did not complete limb length compensation in our patients due to the severity of their tibial defects and pseudarthrosis. The primary goal was bone union. Of course, residual limb length discrepancy is the factor affecting the final result in post-traumatic cases. We recommend IBT for defects less than 12 cm, and free vascularized fibula or transverse Ilizarov transport of the fibular fragment for bigger defects[2]. Due to the fact that IBT is able to realize the potential of human bone regeneration for anatomical and functional restoration in large long-bone defects with minimal trauma, it is extensively used after the failure of other established methods of treatment or infection. The arguments against it as a primary treatment option are the complexity of the Ilizarov apparatus mounting and its size, the

number of adjustments, pin-tract infection, multi-stage and long treatment course that needs a lot of compliance both from the patient and the surgeon. Although IMT seems simple, it is not so easy to complete successfully in severe cases[33]. Finally, it is worth noting the significant disadvantage of the combined approach which is an increase in the duration of total external fixation[21]. Due to these facts, the integration is a more complex procedure. Its effects, modification or failures should be studied further.

CONCLUSION

The combination of IMT and IBT may provide good outcomes in post-traumatic tibial defects after previous treatment failures, although the external fixation is longer due to spacer retention time. This combination might also be used for severe types of CPT despite possible refractures.

ARTICLE HIGHLIGHTS

Research background

The challenges of long-bone defect management have increased in contemporary orthopedic practice due to the severity of high-energy trauma and its complications. They lead to a multi-stage, long and costly treatment. The Ilizarov method of bone transport (IBT) and the Masquelet induced membrane technique (IMT) have been used in a great variety of challenging clinical situations including post-traumatic bone loss, infected nonunion, tumor resection, and congenital pseudarthrosis of the tibia (CPT).

Research motivation

The importance of improving bone regeneration in the management of large bone defects and CPT is a very relevant issue due to treatment failures that diminish bone potential for regeneration. Therefore, a combination of the biological merits of IBT and IMT seemed a promising strategy for the management of cases with a history of failed attempts and impaired regeneration potential.

Research objectives

We aimed to conduct clinical studies on the use of a new technological solution that integrates the IMT and IBT techniques for treating non-viable tibial defects of post-traumatic (PTD) etiology and CPT to improve bone regeneration at the docking site, bone consolidation and reduce refracture rate.

Research methods

We retrospectively studied the treatment course and outcomes in a case series that included seven PTD patients (subgroup A) and nine CPT cases (subgroup B) managed by the combined technology of IMT and IBT. Adult patients in subgroup A had bone defects of post-traumatic origin after several previous treatments failed and non-viable types of nonunion (hypotrophic, torsion-wedge, defect-pseudarthrosis). Subgroup B included nine children with a mean age of 6.1 ± 0.9 years with severe CPT types who had numerous failed interventions to unite pseudarthrosis. Step 1 included Ilizarov frame placement and spacer introduction into the resected defect to generate the induced membrane which remained in the interfragmental gap after spacer removal. Step 2 was an osteotomy and bone transport of the fragment through the tunnel in the induced membrane, its compression and closed docking for consolidation without grafting. Upon docking, supportive compression of 1 mm was provided once every two weeks in the consolidation phase. Postoperative care and radiographic checks followed the standards of the Ilizarov method. Radiographic evidence of bony union, external fixation time, defect filling rate and complications were assessed. The primary outcome measure was radiographic bone union. Secondary outcomes were correction of limb length discrepancy and deformities. The outcomes were retrospectively studied after a mean follow-up period of 20.8 ± 2.7 mo in subgroup A and 25.3 ± 2.3 mo in subgroup B.

Research results

Upon completion of treatment, defects were filled by 75.4 ± 10.6% and 34.6 ± 4.2%, in subgroups A and B, respectively. Total duration of external fixation was 397 ± 9.2 and 270.1 ± 16.3 d, including spacer retention time of 42.4 ± 4.5 and 55.8 ± 6.6 d, respectively. Bone infection was not observed. Postoperative complications included several cases of pin-tract infection and regenerate deformity in both subgroups. Ischemic regeneration was observed in two cases of subgroup B. Complications were corrected during the course of treatment. Bone union was achieved in all patients of subgroup A and in seven patients of subgroup B. One non-united CPT case was further treated with the Ilizarov compression method only and achieved union. After a follow-up period of two to three years, refractures occurred in four cases of

united CPT.

Research conclusions

The combination of IMT and IBT may provide good outcomes in post-traumatic tibial defects after previous treatment failures, although the external fixation is longer due to spacer retention time. This combination might also be used for severe types of CPT, despite the fact that refractures may occur.

Research perspectives

There are ways to further investigate the adjuncts to our protocol such as grafting at the docking site and intramedullary nailing, especially in severe CPT.

FOOTNOTES

Author contributions: All authors contributed to the conception and design, drafting of the manuscript, analysis and interpretation of data, and critical revision of the manuscript; Malkova TA and Kolchin SN contributed to the acquisition of literature data; Kolchin SN performed statistical analysis. Borzunov DY, Kolchin SN, Mokhovikov DS performed the interventions in the cases included into this study.

Institutional review board statement: The study was approved by the ethical committee at the Ilizarov Center.

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

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ORIGINAL ARTICLE

Retrospective Study

Diagnostic role of Xpert-MTB RIF assay in osteoarticular tuberculosis: A retrospective study

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Abstract

BACKGROUND

Osteoarticular tuberculosis (OATB) is a severe form of extrapulmonary tuberculosis (TB), which causes notable morbidity and warrants a high index of suspicion for prompt management. The diagnosis of OATB poses a challenge, because of the difficulty of collecting the samples and, secondarily, the paucibacillary nature of lesion, which gives poor sensitivity and reproducibility, with long turnaround time of routine/conventional laboratory tests and the requirement for invasive procedures and expertise. The Xpert MTB/RIF assay has been approved by the World Health Organization as a rapid diagnostic tool for diagnosing pulmonary and extrapulmonary TB.

AIM

To emphasize the diagnostic efficiency of gene Xpert for OATB in suspected patients in a tertiary care hospital of Eastern India.

METHODS

This retrospective study was conducted in the Department of Microbiology and Orthopaedics by analyzing the data of the gene Xpert assay over a 3-year duration from January 2018 to February 2021. Demographic and clinical data were recorded. The diagnostic efficiency of gene Xpert was evaluated against the composite reference standard (CRS).

RESULTS

A total of 37 cases fell into positive, probable, and possible categories of osteoarticular TB out of 112 patients included in the study by CRS; gene Xpert result was positive in 35 out of the 37 different CRS categorized cases. Of the 112 cases, culture was put in 40 cases, and, of these cultures, 5 cases showed the growth of MTB. Of these, 4 cases were included in the 35 cases diagnosed by gene Xpert.

Smear microscopy was positive in 6 out of 37 CRS categorized cases. When compared with CRS, the sensitivity of gene Xpert assay, culture, and smear was found to be 94.6%, 13.5%, and 16.2%, respectively, while specificity in all the three types of tests was 100%. When kappa statistics were applied, the percentage of agreement gene Xpert, culture, and microscopy with CRS was found to be 95%, 20%, and 22.6%, respectively. Follow-up of the gene Xpert positive patients after getting anti-tubercular treatment revealed improved conditions.

CONCLUSION

Gene Xpert could detect 31 extra cases with a low and very low mycobacterial load that were missed by the routine culture methods. Hence, more samples should be processed for molecular diagnostic methods like gene Xpert along with other conventional methods for the validation of the molecular test prospectively for the timely diagnosis of osteoarticular TB.

Key Words: Tuberculosis; Extrapulmonary; Osteoarticular; Gene Xpert assay; Composite reference standard

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Core Tip: Osteoarticular tuberculosis (OATB) is a severe form of extrapulmonary tuberculosis (TB) that needs prompt management. However, there is difficulty in collecting samples and, secondarily, the paucibacillary nature of the lesion gives poor sensitivity and reproducibility, often with long turnaround time of the routine conventional laboratory tests. Xpert MTB RIF assay has been approved by the World Health Organization for rapid diagnosis of pulmonary/extrapulmonary TB. This study aims to find the diagnostic efficiency of gene Xpert for OATB in suspected patients. We found sensitivity of gene Xpert assay, culture, and smear when compared with CRS to be 94.6%, 13.5%, and 16.2%, respectively, while specificity in all the three types of tests was 100%. The kappa percentage of agreement for gene Xpert, culture, and microscopy were found to be 95%, 20%, and 22.6%, respectively. Follow-up of the gene Xpert positive patients after getting anti-tubercular treatment revealed improvement of their conditions. We conclude that gene Xpert has higher sensitivity than other conventional tests for the timely diagnosis of OATB.

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INTRODUCTION

Tuberculosis (TB) is among the top ten causes of mortality worldwide. In 2019, an estimated 10.0 million (range, 8.9–11.0 million) were affected with TB globally, of which 1.2 million died, including 208000 human immunodeficiency viruses (HIV)-positive patients[1]. Most people who developed TB in 2019 belonged to the World Health Organization (WHO) regions of South-East Asia (44%). India topped the list of eight high burden TB countries contributing to almost 26% of the global TB cases[1].

Primarily, it is a disease of the lower respiratory tract, but it can involve other organs with multitudinous presentations. It can be classified as pulmonary TB and extrapulmonary TB (EPTB), with the latter contributing to approximately 14% of all the reported TB cases[2]. Osteoarticular TB (OATB) is a form of EPTB that comprises 1%-4.3% of total tuberculosis cases and 10%-15% of all EPTB cases[3,4]. Osteoarticular involvement usually results from paucibacillary hematological dissemination and fixation of a colony of mycobacteria inside the active bone marrow. OATB can cause notable morbidity, and a high index of suspicion is required for prompt diagnosis to avoid unwanted sequelae[5,6]. OATB remains a significant problem worldwide, leading to severe deformities and functional disability due to difficulty in diagnosis and delay in the initiation of specific treatment. Moreover, India is an endemic focus of TB, where most orthopedic surgeons continue to practice diagnosing OATB solely on clinical and radiological findings and initiating empirical anti-TB treatment (ATT)[5-7]. This is partly attributed to the challenges faced in collecting the samples from the appropriate site (which at times are difficult anatomically) and the paucibacillary nature of lesion, causing poor sensitivity reproducibility and long turnaround time of the routine conventional laboratory tests and the requirement for invasive procedures and expertise[8]. Hence, there is a need for a molecular diagnostic test with a short turnaround time to diagnose OATB rapidly.

In 2010, the WHO recommended using Xpert MTB/RIF assay (Xpert) in pulmonary TB cases for concurrent diagnosis and rifampicin resistance of TB bacilli. WHO also contemplated the same for EPTB in the year 2013[9,10]. The automated Xpert MTB/RIF (Cepheid, Sunnyvale, CA, United States) assay is based on hemi-nested real-time polymerase chain reaction principle for the concurrent detection of MTB complex and RIF resistance[11]. The present study aims to estimate the efficacy of the gene Xpert assay for the precise diagnosis of OATB.

MATERIALS AND METHODS

This is a retrospective study conducted jointly by the Department of Microbiology and Orthopaedics at a tertiary center in eastern India. The study was conducted by analyzing the data of the gene Xpert assay and follow-up data of patients spread over a 3-year duration from January 2018 to February 2021. Clinical specimens of 112 OATB TB cases were received for diagnosis of TB by the Gene-Xpert-MTB-Rif assay. A part of the sample was processed according to the standard protocol of gene Xpert and subjected to the assay[11]. Tissue samples were cut into small pieces followed by crushing, mixing with buffer, and then vortexing for homogenization. Samples were then incubated for 15 min or more till the tissue was dissolved and centrifuged at 3000 rpm; the supernatant was used for the assay. Synovial fluid and pus samples were also processed according to standard protocol. Cartridges were put inside the device for extraction of DNA and simultaneous amplification of *rpoB* gene (192bp) and generation results[11]; the remaining part of the samples was subjected for smear microscopy by Ziehl–Neelsen stain. Forty samples were subjected to culture. The demographic details and part of involvement were retrieved from files in the medical records. A follow-up telephonic survey of the health status survey, including compliance to ATT, using short form survey-12 free online calculator was performed by one of the researchers (Jain M)[12].

Composite reference standard (CRS) was taken into account to evaluate the diagnostic efficacy of the different test methods used in the study. According to CRS, patients were categorized into four groups: (1) confirmed OATB cases (culture-positive); (2) probable OATB cases (culture-negative but gene Xpert positive, and the patient responded well to anti-TB therapy); (3) possible OATB cases (condition improved after getting anti-TB therapy and had radiographic findings consistent with OATB but lack of bacteriological evidence); and (4) non-TB (culture and all other tests for TB were negative, and the patient improved without getting any anti-TB treatment)[13-15].

The data were entered into a Microsoft Office Excel sheet. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated to evaluate the diagnostic performance of gene Xpert assay and microscopy against the culture method. Kappa statistics was applied to derive the percentage of agreement between gene Xpert and culture.

RESULTS

Synovial fluid was the most common sample (86/112) received in the laboratory. The other samples included tissues of the intervertebral disc and bone fragments (n = 11/112) and aspirated pus (n = 25/112). All 112 samples were subjected to smear microscopy and CBNAAT by gene Xpert MTB-Rif assay, and 40 samples were put on culture. According to CRS, 5 cases were confirmed to have OATB; of the 35 gene Xpert positive cases, 31 belonged to the probable OATB category, and 1 showed improvement after getting ATT despite being culture. Gene Xpert negative belonged to possible OATB category. Of the 112 samples, 35 samples were positive for MTB complex by gene Xpert. Smear microscopy was positive in 6 cases; all of these were detected by gene Xpert and culture was positive in 5 cases; of these, 4 were also positive by gene Xpert (Table 1).

The study population aged between 10-60 years. However, most of the cases (27.0%) confirmed OATB belonged to age group 21-30 years (Table 2). The positivity rate was equal for gender (male: female = 51.4%: 48.6% (Table 2). The spine was the most common confirmed site involved, followed by the knee, as shown in Table 3. The duration of the illness in the confirmed cases varied from 1-12 mo. All the cases were human immunodeficiency virus-negative.

Of the 35 gene Xpert confirmed cases, smear microscopy was positive only in 6 cases where MTB was detected in the range of low; in the remaining 29 cases, the detection of MTB was very low. None of the cases were resistant to rifampicin. Of the 35 cases, 18 cases could be followed up with clinical outcome and treated with ATT, and these 18 cases responded to standard combination ATT (Table 1).

Sensitivity of Xpert assay, culture, and smear, when compared with CRS, was found to be 94.6%, 13.5%, and 16.2%, respectively; specificity in all three types of the test was found to be 100%. When kappa statistics were applied, the percentage of agreement among Gene Xpert, culture, and microscopy with that of CRS was found to be 95.0%, 20.0%, and 22.5%, respectively (Table 3).

Table 1 Categorization of cases according to composite reference standard

Cases	Smear microscopy	Culture	Gene Xpert	ATT course (in mo)	Outcome (SF-12)		CRS category
					PCS-12	MCS-12	
Case No. 1	Negative	No growth	Positive	12	48.76	55.50	Probable OATB case
Case No. 2	Negative	Positive	Positive	Lost to follow-up			Confirmed OATB case
Case No. 3	Negative	No growth	Positive	15	46.03	56.9	Probable OATB case
Case No. 4	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 5	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 6	Positive	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 7	Negative	No growth	Positive	24	56.57	60.75	Probable OATB case
Case No. 8	Negative	No growth	Positive	24	46.03	56.9	Probable OATB case
Case No. 9	Negative	No growth	Positive	6	48.60	33.57	Probable OATB case
Case No. 10	Positive	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 11	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 12	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 13	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 14	Positive	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 15	Positive	Contamination	Positive	Lost to follow-up			Probable OATB case
Case No. 16	Negative	Contamination	Positive	Lost to follow-up			Probable OATB case
Case No. 17	Negative	No growth	Positive	6	56.57	60.75	Probable OATB case
Case No. 18	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 19	Negative	No growth	Positive	6	52.23	56.51	Probable OATB case
Case No. 20	Negative	No growth	Positive	21	52.23	56.51	Probable OATB case
Case No. 21	Negative	No growth	Positive	15	52.23	53.63	Probable OATB case
Case No. 22	Positive	Contamination	Positive	12	56.57	60.75	Probable OATB case
Case No. 23	Negative	No growth	Positive	15	48.60	33.57	Probable OATB case
Case No. 24	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 25	Positive	Positive	Positive	Lost to follow-up			Confirmed OATB case
Case No. 26	Negative	No growth	Positive	12	51.81	48.67	Probable OATB case
Case No. 27	Negative	Positive	Positive	12	48.76	55.50	Confirmed OATB case
Case No. 28	Negative	No growth	Positive	6	56.57	60.75	Probable OATB case
Case No. 29	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 30	Negative	No growth	Positive	12	51.81	48.67	Probable OATB case
Case No. 31	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 32	Negative	No growth	Positive	12	40.76	40.94	Probable OATB case
Case No. 33	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 34	Negative	Positive	Positive	2	28.93	40.32	Confirmed OATB case
Case No. 35	Negative	No growth	Positive	1.5	28.93	40.32	Probable OATB case
Case No. 36	Negative	Positive	Negative	12	48.76	55.50	Confirmed OATB case
Case No. 37	Negative	No growth	Negative	1.5	28.93	40.32	Possible OATB case

CRS: Composite reference standard; ATT: Anti-tuberculosis treatment; OATB: Osteoarticular tuberculosis; SF-12: Short form survey-12; PCS-12: Physical composite scale-12; MCS-12: Mental health composite scale-12.

Table 2 Demographic and clinical distribution of composite reference standard positive, probable and possible osteoarticular tuberculosis cases, *n* (%)

Characteristics		Cases (*n* = 37)
Age group (yr)	0 - 10	1 (2.7)
	11 - 20	5 (13.6)
	21 – 30	10 (27.0)
	31 - 40	6 (16.2)
	41- 50	6 (16.2)
	51 - 60	6 (16.2)
	> 60	3 (8.1)
Sex	Male	19 (51.4)
	Female	18 (48.6)
Site if OATB	Knee	8 (21.6)
	Spine	20 (54.1)
	Elbow	1 (2.7)
	Wrist	1 (2.7)
	Psoas abscess	7 (18.9)

OATB: Osteoarticular tuberculosis.

Table 3 Performance assay and statistical analysis of gene Xpert, culture and, smear microscopy against composite reference standard (*n* = 40)

Methods	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa statistics (% agreement)
Gene Xpert	94.6	100.0	94.6	100.0	95.0
Culture	13.5	100.0	13.5	100.0	20.0
Smear microscopy	16.2	100.0	16.2	100.0	22.5

PPV: Positive predictive value; NPV: Negative predictive value.

DISCUSSION

OATB remains a nuisance as the provenance of functional disability, which could lead to severe deformities and cause lifetime stigma. Therefore, making an early diagnosis and treatment is imperative to avoid unacceptable consequences. India is one of the high burden TB countries where many orthopedic surgeons diagnose OATB by relying on clinical and radiological findings and start ATT empirically[5].

The incidence of OATB ranges from 1.0%-4.3% of all TB cases and comprises 5-15% of all EPTB[5,14-16]. In a study by Gogia *et al*[5], 16 cases out of 120 were diagnosed with OATB over 3 years. However, Muangchan *et al*[7] reported 99 cases of OATB during a 2 year period, which seems to be quite a high number. In the present study, 37 cases were proven of the 112 cases (33.03%) to have OATB after a retrospective analysis of 3 years of data, similar to the study by Yoon *et al*[16].

Enache *et al*[8], in their study on EPTB, found that two-third of patients were older than 40 years. In some other studies, the median age was reported in the higher range of 50-60 years[9,13]. However, in our study, maximum cases belonged to the younger age group; the highest was in the 21-30 age group (27.0%). Female predominance was observed in some studies[7,16], and in others, the maximum cases were males[5,8]. In our study, it was almost equally distributed. Clinically, pain is the most common

symptom[7], which was the finding in our study also.

The spinal area was the most common (54.1%) site affected in our study, followed by knee joint and psoas abscess (21.6% and 18.9%, respectively), which is in concordance with several other studies with a preponderance of spinal involvement[3,17].

Yoon *et al*[16], in their study, observed that there are limited diagnostic options for EPTB, which led them to analyze retrospectively the different spectrums of EPTB regarding clinical patterns, underlying diseases, and diagnostic methods. Synovial fluid or any drained purulent fluid from the suspected lesion site can be examined for acid-fast bacteria (AFB) in cases of OATB. A direct smear of the sample can show positivity for AFB in as low as 27% of cases[17]. Six out of 35 gene Xpert confirmed cases in our study were AFB positive. Low positivity in OATB may be due to the paucibacillary nature of the lesion[18]. Culture on various specimens like a biopsy, cold abscess, or synovial fluid is considered the standard gold method for diagnosis[17]. A lower range of culture positivity has been observed in different studies, such as 11.2% and 19.2 % by Yoong *et al*[16] and Muangchan *et al*[7]. However, a higher positivity (63%) was seen in the review article by Haider *et al*[17].

In our study, we also found a lower culture positivity rate (13.7%) in samples subjected for culture, which could be due to a less amount of such samples, as the maximum amount was subjected for gene Xpert. The long turnaround time and the possibilities of contamination were the major disadvantages of the conventional culture technique. Similarly, the microscopy method also has the drawback of lack of reproducibility and low reliability, particularly in EPTB cases with a low bacterial load[18-20]. Molecular tests like gene Xpert, on the other hand, have the advantage of short turnaround time, which can help the physician determine the correct management of cases[21]. In the present study, the sensitivity, specificity, and percentage of agreement compared with CRS of gene Xpert were similar (94.6%, 100%, and 95%, respectively)[22]. These results may be because fewer samples were put in culture, and the statistical analysis was made using those small proportions of samples; in addition, the sample size was also less. Despite the statistical values, it cannot be ignored that the gene Xpert could detect 31 extra cases with low and very low bacterial load, which were missed by the culture methods. All the cases detected by gene Xpert were sensitive to rifampicin, and the clinical outcome was favorable.

Since this is a retrospective study and not all samples were processed for culture, accurate analysis of all the samples could not be done, which is the limitation of our study. Moreover, clinical data were retrieved from the database, and some patients were lost to follow-up; if the follow-up data of all the patients had been included in the present study, then the utility of the molecular methods could have been more established.

CONCLUSION

Hence, to conclude, conventional diagnostic methods such as smear are done everywhere for mycobacterium TB diagnosis, but this test is negative in most orthopedic cases. Therefore, more samples should be processed using molecular diagnostic methods like gene Xpert along with other conventional methods in order to validate the molecular test prospectively for the timely diagnosis of OATB. When more cases can be diagnosed early and treatment initiated at the right time, the likelihood of cure is greater and the severe consequences of the disease can be prevented.

ARTICLE HIGHLIGHTS

Research background

Tuberculosis (TB) is among the top ten causes of mortality worldwide. In 2019, an estimated 10.0 million were affected with TB globally, of which 1.2 million died. India topped the list of eight high burden TB countries, which contribute to almost 26% of the global TB cases. Osteoarticular tuberculosis (OATB) is a form of extrapulmonary TB that comprises 1.0%-4.3% of total tuberculosis cases and 10%-15% of all extrapulmonary TB cases. OATB remains a significant problem worldwide, leading to severe deformities and functional disability due to difficulty in diagnosis and delay in the initiation of specific treatment. Moreover, India is an endemic focus of TB, where most orthopedic surgeons continue to practice diagnosing OATB solely on clinical and radiological findings and initiating empirical anti-TB treatment.

Research motivation

There is a need for a molecular diagnostic test with a short turnaround time to diagnose OATB rapidly. In 2010, the World Health Organization recommended using Xpert MTB/RIF assay in pulmonary TB cases for concurrent diagnosis and rifampicin resistance of TB bacilli.

Research objectives
The objective is to estimate the efficacy of gene Xpert assay for the precise diagnosis of OATB.

Research methods
This retrospective study was conducted by analyzing the data of the gene Xpert assay over a 3-year period. The diagnostic efficiency of gene Xpert was evaluated against the composite reference standard.

Research results
A total of 37 cases fell into positive, probable, and possible categories of OATB out of 112 patients included in the study by composite reference standard; gene Xpert result was positive in 35 out of the 37 different composite reference standard categorized cases. Follow-up of the gene Xpert positive patients after getting anti-tubercular treatment revealed improved conditions.

Research conclusions
Conventional diagnostic methods such as smear are done everywhere for mycobacterium TB diagnosis, which is negative in most orthopedic cases.

Research perspectives
More samples should be processed for molecular diagnostic methods like gene Xpert along with other conventional methods for the validation of the molecular test prospectively for the timely diagnosis of osteoarticular TB.

FOOTNOTES

Author contributions: Mohanty M and Mishra B conceived the idea; Jain M created the proposal and Mishra B received the clearance; Mohanty M and Puthiyapura LK collected the data; Jain M and Mohanty M wrote the paper; Mishra B and Puthiyapura LK revised the manuscript for important intellectual content; All authors have read and agreed to the content of the manuscript.

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ORIGINAL ARTICLE

Prospective Study

Plate *vs* reverse shoulder arthroplasty for proximal humeral fractures: The psychological health influence the choice of device?

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Abstract

BACKGROUND

Proximal humeral fractures represent the third most common observed osteoporotic fracture; the treatment in three and four-part proximal humeral fractures in patients over 65 years is still controversial. Among the treatments described in literature, open reduction and internal fixation (O.R.I.F) and reverse shoulder arthroplasty (RSA) are gaining an increasing popularity.

AIM

To investigate the correct treatment for three and four-part proximal humeral fractures according to psychological aspects.

METHODS

It was conducted a prospective study with a series of 63 patients treated with O.R.I.F. (group A) and with RSA (group B) for three and four-part proximal humeral fractures according to Neer classification system. A conservative treatment group, as control, was finally introduced. One independent observer performed clinical and a psychological evaluation at one (T0), six (T1) and twelve months (T2) postoperatively. The Constant's score and The Disabilities of the

Arm, Shoulder and Hand (DASH score) were used for clinical evaluation, while General Anxiety Disorder-7 (GAD-7) and Caregiver Strain Scale (CSS) were used for psychological evaluation.

RESULTS

At one month follow up in group A the mean values were DASH score 50.8, Constant score 36.1, GAD-7 score 5.4, CSS 5.0. For the group B, the average values at T0 were: DASH score 54.6, Constant score 32.0; GAD-7 score 6.4, CSS 6.2. At six months in group A the average values were DASH score 42.1, Constant score 47.3, GAD-7 score 4.3, CSS 3.9. For the group B, the average values at T1 were: DASH score 39.1, Constant score 43.2, GAD-7 score 5.7, CSS 5.5. At twelve months in the group A, the mean values were DASH score 32.8, Constant score 60.0, GAD-7 score 3.2, CSS 3.1. For the group B shown these mean values: DASH score 33.6, Constant score 52.9, GAD-7 score 4.3, CSS 4.5. We demonstrated a better clinical and psychological outcome at T2 in the group treated with osteosynthesis compared to the group treated with arthroplasty (Constant $P = 0.049$, GAD-7 $P = 0.012$ and CSS $P = 0.005$). A better clinical and psychological outcome emerged in control group at T2 comparing with surgical group (DASH score $P = 0.014$, Constant score $P < 0.001$, GAD-7 $P = 0.002$ and CSS $P = 0.001$).

CONCLUSION

Both open osteosynthesis and reverse shoulder arthroplasty are valid treatments for proximal humeral fractures. According to the best osteosynthesis results the authors suggested to perform a psychological analysis for each patient in order to choose the appropriate treatment.

Key Words: Proximal humerus fractures; Open reduction and fixation; Reverse shoulder arthroplasty; Psychological health; General Anxiety Disorder-7 scale; Caregiver Strain scale

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Core Tip: This was a prospective study with 63 patients seeking to evaluate how psychological factors can influence the choice of device for proximal humeral fractures.

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INTRODUCTION

Proximal humeral fractures account for 6%-8% of all fractures and around 85% occurs in patients over 50 years old[1]. Most patients sustaining these fractures are women above the age of 60. These fractures represent the third most common observed osteoporotic fracture in elderly patients, after wrist and hip fractures[2-4], with an incidence of 82 per 100000 person-years. It has been suggested that the overall fracture rate is increasing along with the increase in the elderly population[5,6]. Furthermore, a Finnish study estimated the incidence of fall-related proximal humerus fractures has tripled since 1970[7]. The Neer classification, based on the number of bone fragments, is used for the therapeutic decision[8]. This remains the most commonly used classification, but additional systems have been described more recently, giving other useful indications to surgeon for type of surgery to adopt. About 80% of the proximal humeral fractures is nondisplaced or minimally displaced, therefore in these cases the treatment is conservative. In the remaining 20% of cases, the surgical strategy probably is the first option, although conservative treatment is chosen by some surgeons[9]. In relation to different factors, such as age, daily activity, and fracture pattern, operative treatment options include: synthesis and joint replacement[10-13]. Many studies compared the clinical and radiological outcomes of three and four-part proximal humeral fractures in patients over 65 years old treated with open reduction and internal fixation (O.R.I.F.) and joint replacement. Giardella *et al*[14], in their retrospective study enrolling patients over 65 years old, reported better clinical and functional results in patients treated with reverse shoulder arthroplasty (R.S.A.) respect to O.R.I.F, confirming that R.S.A. is the best treatment in proximal humeral fractures in elderly patients, especially in case of a rotator cuff tear or degeneration.

The aim of our study was to compare O.R.I.F. with R.S.A. in terms of clinical and psychological outcomes of three- and four-part proximal humeral fractures in patients older than 65 years evaluating

whether post-operative psychological symptoms may influence the clinical results after surgery.

MATERIALS AND METHODS

The Authors conducted a prospective observational study with a sequential recruitment of subjects affected by proximal humeral fractures, which was approved by the local Ethics Committee (No. 6809). The study was also registered on ClinicalTrials.gov, Protocol Registration and Result System (NCT04821180).

At the University Hospital of Bari, 63 patients who had undergone shoulder surgery between January 2016 and January 2019 were enrolled.

The inclusion criterion for enrollment was: (1) three and four-part proximal humeral fractures according to Neer classification system; (2) patients seventy years or older; and (3) shoulder surgery within one week after trauma.

The exclusion criteria were: (1) exposed fractures; (2) pathological fractures; (3) proximal humerus fractures with metaphyseal or diaphyseal extension; (4) contraindications to surgery associated with organ dysfunctions or with coagulopathy, allergy or hypersensitivity to the orthopedic implants; (5) patients who were unable to attend the different follow-ups; and (6) patients with psychiatric disorders.

We assumed that all enrolled patients suffered cuff tear arthropathy based on biological and anagraphic age.

All patients were properly informed of the nature of the study and they signed an informed consent document according to the Declaration of Helsinki.

The study group was stratified according to age class (class 1: 70-74 years; class 2: 75-79 years; class 3: 80-85 years) and gender differences (Table 1).

All patients were then divided into two groups according to the choice of surgery treatment: Group A: O.R.I.F. by angle-stable plate PHILOS (PHLPSYNTHES®, Oberdorf, Switzerland) (Figure 1A); and Group B: reverse total shoulder arthroplasty by Modular Shoulder Replacement SMR (LIMA® Corporate, San Benedetto del Friuli, Italy) (Figure 1B).

All patients were treated by the same surgical team with more than five years of experience in upper limb surgery.

The type of treatment was due to rotator cuff status, and shoulder clinical history.

We introduced a control group (Group C), made up of patients with the same characteristics of the study groups, but treated conservatively.

One independent observer performed clinical [Constant score and Disabilities of the Arm, Shoulder and Hand (DASH) score[15,16]] evaluation at one-month (T0), six months (T1) and at one year (T2) post operatively for each groups.

Furthermore the Clinical Psychology Service of our University Hospital performed a psychological evaluation (General Anxiety Disorder-7 scale and Caregiver Strain scale[17,18]) at the same follow-ups for each groups.

The Constant score determines the shoulder functionality and a higher score is indicative of high functional outcomes. The DASH score analyzes individual ability to perform certain activities and a higher score is indicative of worse functional outcomes.

The General Anxiety disorder 7 scale and the Caregiver Strain scale are two screening psychological tools used to define the level of stress. A higher score is indicative of poor outcomes.

In each case we evaluated the antero-posterior, lateral and transthoracic humerus X-rays at the T0, T1 and T2.

Statistical analysis

All data were collected electronically and were analyzed using R version 3.5.2 (released on 2018-12-20). In order to account for non-normality (Shapiro-Wilk test), continuous variables were reported as median and interquartile range (IQR) and compared (univariable analysis) through Wilcoxon rank sum test. Categorical variables were reported as absolute and relative frequencies. A multivariable linear regression model was then fitted for each score and time in order to evaluate the effect of PI intervention compared to O.R.I.F. intervention ("beta" coefficients) adjusted for age and sex. Linearity of dependent variable and normality and homoscedasticity of residuals were checked for each model through a test of significance. Statistical significance "alpha" was fixed to 0.05. The primary endpoint examined was psychological outcomes of proximal humeral fractures using General Anxiety disorder 7 scale. The secondary endpoint was clinical and shoulder functionality using Constant score. In addition, the Caregiver Strain scale and DASH score were used to complete psychological and clinical outcomes.

RESULTS

The study group was made up of sixty-three patients, 5 males (7.9%) and 58 females (92.1%). The

Table 1 The range value of variables analyzed for the study group

Age (yr)	Female	Men
CLASS 1 (70-74)	30	1
CLASS 2 (75-80)	15	3
CLASS 3 (80-85)	13	1
Total	58	5

CLASS: Age class.

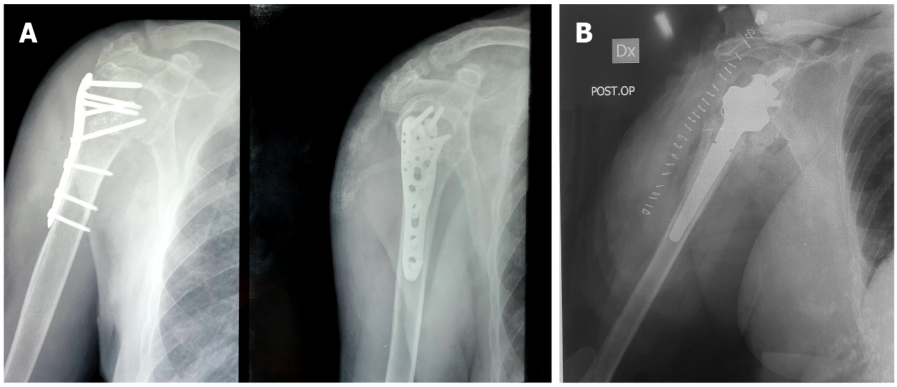

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Figure 1 X-rays images of a patient. A: Post-operative X-rays of a patient treated with open reduction and internal fixation for three-parts proximal humeral fractures; B: Post-operative X-rays of a patient treated with reverse shoulder arthroplasty for three-parts proximal humeral fractures.

average age was 76.0 (4.0) years, range 70-82. Median (IQR) age was 76.0 (4.0) years.

In 70% of cases the right limb was involved and in 65.1% of cases (41 of 63 cases) were three-part proximal humeral fractures (Table 2).

The analysis showed a prevalence of the four-part proximal humeral fracture in the class 3 age group whilst the three-part proximal humeral fracture in the class 2 (Table 3).

Domestic accident was responsible for 70% of cases whilst road traffic accident was the commonest mechanism in 30% of cases.

The 48.2% (31) of patients were treated by angle stable plate PHILOS (PHLP-SYNTHES®, Oberdorf, Switzerland) with O.R.I.F. (group A) while the 50.8% (32) of patients were treated by reverse total shoulder arthroplasty SMR (LIMA®Corporate, San Benedetto del Friuli, Italy) (group B). The Control group, 32 patients, was treated conservatively.

For the group A, the average values at T0 were: DASH score 50.8 (range 44-62), Constant score 36.1 (range 22-49) (Table 4); as regards the psychological test, the average values at T0 were: General Anxiety Disorder-7 scale 5.4 (range 2-9), Caregiver Strain Scale 5.0 (range 2-9) (Table 4).

For the group B, the average values at T0 were: DASH score 54.6 (range 28-65), Constant score 32.0 (range 23-53) (Table 4); as regards the psychological test, the average values at T0 were: General Anxiety Disorder-7 scale 6.4 (range 3-9), Caregiver Strain Scale 6.2 (range 2-9) (Table 4).

For the group A, the average values at T1 were: DASH score 42.1 (range 32-58), Constant score 47.3 (range 25-63) (Table 5); as regards the psychological test, the average values at T1 were: General Anxiety Disorder-7 scale 4.3 (range 1-8), Caregiver Strain Scale 3.9 (range 1-8) (Table 5).

For the group B, the average values at T1 were: DASH score 39.1 (range 21-60), Constant score 43.2 (range 28-65) (Table 5); as regards the psychological test, the average values at T1 were: General Anxiety Disorder-7 scale 5.7 (range 3-9), Caregiver Strain Scale 5.5 (range 2-9) (Table 5).

At T2 in the group A, the mean values were: DASH score 32.8 (range 16-60), Constant score 60.0 (range 30-80) (Table 6); as regards the psychological test, the average values at T2 were: General Anxiety Disorder-7 scale 3.2 (range 1-7), Caregiver Strain Scale 3.1 (range 1-7) (Table 6).

At T2 the group B shown these mean values: DASH score 33.6 (range 17-55), Constant score 52.9 (range 35-79) (Table 6); as regards the psychological test, the average values at T2 were General Anxiety Disorder-7 scale 4.3 (range 1-7), Caregiver Strain Scale 4.5 (range 1-8) (Table 6).

At T0 median (IQR) DASH score was 53.0 (11.0), Constant score was 34.0 (10.5), General Anxiety Disorder-7 scale was 6.0 (2.0) and Caregiver Strain Scale was 6.0 (3.0).

Table 2 Analysis of the fracture pattern

	Total	Three-part fractures	Four-part fractures
Number	63	41	22

Table 3 Analysis of distribution considering age class and fracture personality

	Age class (yr)		
Neer classification	70-75	75-80	80-90
Three-part fractures	10	27	4
Four-part fractures	5	7	10

Table 4 Postoperative clinical and psychological mean values at T0 follow-up

	Group A	Group B
DASH	50.8	54.6
CONSTANT	36.1	32.0
GAD-7	5.4	6.4
CSS	5.0	6.2

DASH: The Disabilities of the Arm, Shoulder and Hand score; CONSTANT: The Constant score; GAD-7: General Anxiety Disorder-7; CSS: Caregiver Strain Scale.

Table 5 Description of clinical and psychological scores at T1 follow-up

	Group A	Group B
DASH	42.1	39.1
CONSTANT	47.3	43.2
GAD-7	4.3	5.7
CSS	3.9	5.5

DASH: The Disabilities of the Arm, Shoulder and Hand score; CONSTANT: The Constant score; GAD-7: General Anxiety Disorder-7; CSS: Caregiver Strain Scale.

Table 6 Analysis of clinical and psychological scores at T2 follow-up

	Group A	Group B
DASH	32.8	33.6
CONSTANT	60.0	52.9
GAD-7	3.2	4.3
CSS	3.1	4.5

DASH: The Disabilities of the Arm, Shoulder and Hand score; CONSTANT: The Constant score; GAD-7: General Anxiety Disorder-7; CSS: Caregiver Strain Scale.

At T1 median (IQR) DASH score was 38.0 (12.0), Constant score was 44.0 (11.5), General Anxiety Disorder-7 scale was 5.0 (2.5) and Caregiver Strain Scale was 5.0 (3.0).

At T2 median (IQR) DASH score was 32.0 (13.5), Constant score was 55.0 (20.0), General Anxiety Disorder-7 scale was 4.0 (2.5) and Caregiver Strain Scale was 4.0 (3.0).

For the group C, the mean values are reported separately (Table 7).

The univariable analysis (Table 8) showed a significant difference between the two treatment groups for Dash score at T0 (O.R.I.F. *vs* PI, median 50.0 *vs* 57.5, $P = 0.002$), Constant at T0 (O.R.I.F. *vs* PI, median 38.0 *vs* 31.5, $P = 0.008$), GAD-7 at T0 (O.R.I.F. *vs* PI, median 5.0 *vs* 6.0, $P = 0.015$), CSS at T0 (O.R.I.F. *vs* PI, median 5.0 *vs* 6.5, $P = 0.008$), GAD-7 at T1 (O.R.I.F. *vs* PI, median 4.0 *vs* 6.0, $P = 0.002$), CSS at T1 (O.R.I.F. *vs* PI, median 4.0 *vs* 6.0, $P = 0.001$), Constant at T2 (O.R.I.F. *vs* PI, median 60.0 *vs* 51.0, $P = 0.049$), GAD-7 at T2 (O.R.I.F. *vs* PI, median 3.0 *vs* 4.0, $P = 0.012$) and CSS at T2 (O.R.I.F. *vs* PI, median 3.0 *vs* 4.0, $P = 0.005$).

A second univariable analysis (Table 9) between conservative and surgical treatment (using values of the two treatments) was made to enhance the relevance of the study. We reported no statistical difference at T0 regarding clinical and psychological outcomes. On the contrary, conservative treatment has shown to have better clinical and psychological outcomes, although not statistically significant at T1 and statistically significant at T2.

We did not observe complications in the study and control group.

DISCUSSION

Three- and four-part fractures account for 21% to 23% of proximal humerus fractures[19,20], are usually treated surgically by O.R.I.F. in younger patients and by arthroplasty in the elderly[21,22].

Many risk factors patient-related such as osteoporosis, degenerative joint disease of the shoulder, rotator cuff dysfunctions, comorbidities and non-modified risk factors such as gender and age class may influence the choice of treatment[23,24].

In accordance with the literature, we reported a gender differences and age class stratification in favor of female and first class which was most represented (Table 1, Table 3)[25,26].

Due to the poor outcomes associated with conventional anatomic replacement of the humeral head, an extended use of the reverse shoulder arthroplasty has emerged in the literature, linked to good results as both a primary procedure and as a secondary procedure for failed open reductions[27-29].

Until now all the studies described in the literature comparing open reduction and osteosynthesis with reverse shoulder arthroplasty as surgical options of treatment for three and four-part proximal humeral fractures in patients over 65 years old, used clinical and radiological methods of evaluation[30-33].

Our study is the first in literature that compares the psychological and functional results in order to underline the importance of each one or both for the pre-operative planning.

In our study, the Authors reported a tendency to the improvement of functional outcomes for the two groups. As regards the DASH and the Constant score, the Authors reported good results in both groups from T0 to T2 by analyzing the average value of Table 4, Table 5, and Table 6.

The univariable analysis (Table 8) showed a significant difference between the two treatment groups in favor of Group A as regards DASH score at T0 (O.R.I.F. *vs* PI, median 50.0 *vs* 57.5, $P = 0.002$) and Constant at T0 (O.R.I.F. *vs* PI, median 38.0 *vs* 31.5, $P = 0.008$).

The Authors linked these results to reach more confidence with the plate respect to the prosthesis. Furthermore, we did not report any statistically significance difference between the two groups at T1 ($P = 0.256$; $P = 0.110$).

The univariable analysis (Table 8) did not show a statistically significant difference between the two treatment groups for DASH score at T2 (O.R.I.F. *vs* PI, median 30.0 *vs* 32.0, $P = 0.587$); as regard the Constant score at T2 (O.R.I.F. *vs* PI, median 60.0 *vs* 51.0, $P = 0.049$), there emerged a statistically significant difference in favor of group A who obtained better results but these were very near to the significance limit.

According to the literature, the functional results of the two surgical options (O.R.I.F. *vs* reverse prosthesis) overlapped at 1 year post operatively[34].

As regards the psychological evaluation, the Authors observed a tendency to the improvement for both groups from T0 to T2 according to Table 4, Table 5, and Table 6.

By better analysis, the Authors highlighted an improvement of psychological evaluation for the group A at T0.

Analyzing GAD-7 at T0 (O.R.I.F. *vs* PI, median 5.0 *vs* 6.0, $P = 0.015$) and CSS at T0 (O.R.I.F. *vs* PI, median 5.0 *vs* 6.5, $P = 0.008$), the Authors reported the superiority in terms of results for the group A respect to the group B according to Table 8.

The statistical evaluation was significant for both tests in the group A and also at T1 and at T2 as reported in the Table 8 analyzing GAD-7 at T1 (O.R.I.F. *vs* PI, median 4.0 *vs* 6.0, $P = 0.002$), CSS at T1 (O.R.I.F. *vs* PI, median 4.0 *vs* 6.0, $P = 0.001$), GAD-7 at T2 (O.R.I.F. *vs* PI, median 3.0 *vs* 4.0, $P = 0.012$) and CSS at T2 (O.R.I.F. *vs* PI, median 3.0 *vs* 4.0, $P = 0.005$).

Patients underwent primary reverse shoulder arthroplasty (group B) showed in each postoperative follow-ups a generalized anxiety disorder and a greater irritability then patients underwent osteosynthesis (group A).

Table 7 Group C clinical and psychological mean values at three different follow-ups

	DASH	CONSTANT	GAD-7	CSS
T0	51.1	33.2	5.9	5.7
T1	38.8	46.9	4.9	4.5
T2	29.9	65.5	3.1	3.0

DASH: The Disabilities of the Arm, Shoulder and Hand score; CONSTANT: The Constant score, GAD-7: General Anxiety Disorder-7; CSS: Caregiver Strain Scale.

Table 8 Score distribution between treatment open reduction and internal fixation and PI

	TO			T1			T2		
	O.R.I.F. (*n* = 31)	RSA (*n* = 32)	*P* value	O.R.I.F. (*n* = 31)	RSA (*n* = 32)	*P* value	O.R.I.F. (*n* = 31)	RSA (*n* = 32)	*P* value
DASH	50.0 (7.5)	57.5 (7.0)	**0.002**	45.0 (12.5)	36.5 (12.3)	0.256	30.0 (24.0)	32.0 (5.5)	0.587
CONSTANT	38.0 (7.5)	31.5 (6.0)	**0.008**	48.0 (19.0)	42.0 (7.3)	0.110	60.0 (31.0)	51.0 (5.8)	**0.049**
GAD-7	5.0 (2.5)	6.0 (2.3)	**0.015**	4.0 (2.5)	6.0 (2.0)	**0.002**	3.0 (3.0)	4.0 (1.3)	**0.012**
CSS	5.0 (2.0)	6.5 (2.3)	**0.008**	4.0 (2.5)	6.0 (1.3)	**0.001**	3.0 (2.5)	4.0 (2.3)	**0.005**

Data are median (Interquartile range). *P* values are from Wilcoxon rank sum test. O.R.I.F: Open reduction and internal fixation; RSA: Reverse shoulder arthroplasty; DASH: The Disabilities of the Arm, Shoulder and Hand score; CONSTANT: The Constant score, GAD-7: General Anxiety Disorder-7; CSS: Caregiver Strain Scale.

Table 9 Comparison between surgical and conservative treatment

n = 32	T0	*P* value	T1	*P* value	T2	*P* value
DASH	53 (44.5)	0.344	39 (35)	0.421	30 (26)	0.014
CONSTANT	32 (30)	0.223	48.5 (42)	0.063	65.5 (60)	< 0.001
GAD-7	6 (5)	0.827	5 (3.3)	0.548	3 (2)	0.002
CSS	6 (5)	0.481	5 (3)	0.090	3 (2)	0.001

Data are median (Interquartile range) of conservative group. *P* values are from Wilcoxon rank sum test. DASH: The Disabilities of the Arm, Shoulder and Hand score; CONSTANT: The Constant score, GAD-7: General Anxiety Disorder-7; CSS: Caregiver Strain Scale.

We revealed a residual fear during shoulder movement in patients underwent primary reverse shoulder arthroplasty, unlike the group of patients which have done osteosynthesis, who seemed more confident and secure in shoulder movements.

The authors linked these results for group B to the anxiety about loosening of humeral head. In fact, the patients underwent osteosynthesis, showed better results in terms of anxiety due to the idea to preserve their humeral head. The perception of own humeral head could play a role in the genesis of anxiety.

Moreover, the comparison between the surgical (group A and B) and the conservative group (group C) revealed better clinical and functional results at 12 mo for the group C. In fact, with mean values of 3.1 and 3.0 for the GAD-7 and CSS scales respectively, the group C showed less anxiety and fear at T2 notwithstanding at 12 mo no statistically differences were found. These results are consistent with a previous study that underlined the importance of conservative treatment which remains a valid option mainly in the three-part proximal humeral fractures in selected cases with good functional results and low complications[9].

This study has some limitations: the number of participants is limited to 63; the maximum follow-up achieved was 12 mo; the device for open reduction and internal fixation used was a single type of angle stable plate with specific surgical technique.

CONCLUSION

The aim of our study was to compare open osteosynthesis and reverse shoulder arthroplasty in the three and four-part proximal humeral fractures, in terms of functional and psychological scores at one, six months and at one year follow-ups in order to underline the importance of each one or both of them for the pre-operative planning.

Based on the results obtained, we highlighted the best results for group A in terms of psychological results respect to group B.

For this reason, we suggest to evaluate before surgical choice not only anatomical parameters but also patient psychological profile, always evaluating the possibility of a hypothetical conservative treatment.

The strong point of our study is the type of the study in fact it is a prospective observational comparative study.

Instead, the weak point is the lack of psychological evaluation for each patient enrolled before the surgery.

Due to the pain after the trauma, the Authors did not administer the psychological evaluation because it may be influenced negatively.

According to recent data of bibliography, we confirm the efficacy at 1 year of the osteosynthesis and shoulder arthroplasty in terms of functional evaluation.

As pointed out by the Authors, it is very important to perform a psychological analysis of each patient, in order to identify correctly the patient and to reserve the shoulder arthroplasty for a very limit case in which the bone stock is very poor.

ARTICLE HIGHLIGHTS

Research background

Patient affected by fractures is evaluated only from a surgical point of view. Psychological aspect is very often underestimated.

Research motivation

More studies are needed in literature, to evaluate before surgical choice not only anatomical parameters but also patient psychological profile.

Research objectives

The aim of our study was to compare open reduction and internal fixation with joint replacement in terms of clinical and psychological outcomes of three- and four- part proximal humeral fractures in patients older than 65 years evaluating whether post-operative psychological symptoms may influence the clinical results after surgery.

Research methods

An observational prospective single-center study with 12 mo follow-up was performed with a sequential recruitment of subjects affected by proximal humeral fractures treated with open reduction and internal fixation and joint replacement. A conservative treatment group, as control, was introduced.

Research results

Patients underwent primary reverse shoulder arthroplasty showed in each postoperative follow-ups a generalized anxiety disorder and a greater irritability then patients underwent osteosynthesis.

Research conclusions

Patient psychological profile should be evaluated by the surgeon before surgery for the choice of surgical devices.

Research perspectives

Future investigations are needed to confirm the role of the psychological profile in the field of orthopedic surgical treatment. In addition, long- term analysis needs to clarify if differences in outcomes are really related to the patient's mental state.

FOOTNOTES

Author contributions: Maccagnano G drafted the manuscript, and assisted with data analysis; Solarino G participated in design and oversight of the study; Pesce V drafted the manuscript, and assisted with data analysis; Vicenti G participated in study design and performed statistical analysis; Nappi VS participated in design of the study, and

was involved with data collection; Coviello M was involved with data collection, and assisted with data analysis; Giannico OV participated in study design and performed statistical analysis; Notarnicola A participated in design of the study; Moretti B participated in design and oversight of the study.

Institutional review board statement: The authors conducted a prospective observational study with a sequential recruitment of subjects affected by proximal humeral fractures, which was approved by the local Ethics Committee (No. 6809).

Clinical trial registration statement: The study was also registered on ClinicalTrials.gov, Protocol Registration and Result System (PRS) (NCT04821180).

Informed consent statement: All patients were properly informed of the nature of the study and they signed an informed consent document according to the Declaration of Helsinki.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest regarding the publication of this paper.

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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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SYSTEMATIC REVIEWS

Impact of enhanced recovery pathways on safety and efficacy of hip and knee arthroplasty: A systematic review and meta-analysis

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Abstract

BACKGROUND

Over the past decades, clinical pathways (CPs) for hip and knee arthroplasty have been strongly and continuously evolved based on scientific evidence and innovation.

AIM

The present systematic review, including meta-analysis, aimed to compare the safety and efficacy of enhanced recovery pathways (ERP) with regular pathways for patients with hip and/or knee arthroplasty.

METHODS

A literature search in healthcare databases (Embase, PubMed, Cochrane Library, CINAHL, and Web of Science) was conducted from inception up to June 2018. Relevant randomized controlled trials as well as observational studies comparing ERP, based on novel evidence, with regular or standard pathways, prescribing care as usual for hip and/or knee arthroplasty, were included. The effect of both CPs was assessed for (serious) adverse events [(S)AEs], readmission rate, length of hospital stay (LoS), clinician-derived clinical outcomes, patient reported outcome

measures (PROMs), and financial benefits. If possible, a meta-analysis was performed. In case of considerable heterogeneity among studies, a qualitative analysis was performed.

RESULTS

Forty studies were eligible for data extraction, 34 in meta-analysis and 40 in qualitative analysis. The total sample size consisted of more than 2 million patients undergoing hip or knee arthroplasty, with a mean age of 66 years and with 60% of females. The methodological quality of the included studies ranged from average to good. The ERP had lower (S)AEs [relative risk (RR): 0.9, 95% confidence interval (CI): 0.8-1] and readmission rates (RR: 0.8, 95%CI: 0.7-1), and reduced LoS [median days 6.5 (0.3-9.5)], and showed similar or improved outcomes for functional recovery and PROMs compared to regular pathways. The analyses for readmission presented a statistically significant difference in the enhanced recovery pathway in favor of knee arthroplasties (P = 0.01). ERP were reported to be cost effective, and the cost reduction varied largely between studies (€109 and $20573). The overall outcomes of all studies reported using Grading of Recommendation, Assessment, Development and Evaluation, presented moderate or high quality of evidence.

CONCLUSION

This study showed that implementation of ERP resulted in improved clinical and patient related outcomes compared to regular pathways in hip and knee arthroplasty, with a potential reduction of costs.

Key Words: Hip arthroplasty; Knee arthroplasty; Joint arthroplasty; Clinical pathway; Enhanced recovery pathway; Systematic review; Meta-analysis

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Core Tip: Enhanced recovery pathways for hip and knee arthroplasty help the patient and the multidisciplinary team to achieve the best possible results. Based on the results presented, it may help health care providers to make informed decisions regarding the optimization of currently used regular pathways. We strongly recommend orthopedic surgeons worldwide to keep up-to-date with the latest literature and to optimize their regular pathway with the latest evidence. This study involves an extensive literature search for care pathways for hip and knee arthroplasty, and the effects on multiple outcomes have been analyzed in terms of (serious) adverse events, readmissions, length of hospital stay, functional recovery, patient reported outcome measures, and costs.

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INTRODUCTION

The numbers of hip and knee arthroplasties performed worldwide are growing as a result of the increased incidence of osteoarthritis[1-5]. With the increasing life expectancy, hip and knee osteoarthritis will become a significant health issue in the upcoming years[6] and thereby arthroplasty surgeries will increasingly be performed. Clinical pathways (CPs) have been introduced to improve the quality of hip and knee arthroplasty, by optimizing recovery, minimizing variation in care, and reducing costs[7,8]. Due to scientific advancement, innovation, and novel technologies, CPs for hip and knee arthroplasty are continuously being changed. The enhanced recovery pathways (ERP) are based on novel evidence, while regular pathways are not necessarily based on the latest evidence. Because the optimizations in CPs are accomplished with an increase in costs, time, and resources[9], but might also be able to reduce costs in the long term[10], it is essential to gain knowledge on the actual benefits of the ERP. Therefore, we included all ERP studies for hip and knee arthroplasty and investigated the impact of the optimization process. This study, as far as we know, is the most extensive systematic review (SR) and meta-analysis on CPs for hip and knee arthroplasty.

The purpose of this SR and meta-analysis was to investigate the effect of *enhanced recovery pathways* compared to *regular pathways* for total hip arthroplasty (THA), total knee arthroplasty (TKA), and/or unicompartmental knee arthroplasty (UKA) on (serious) adverse events [(S)AEs], readmission rate,

length of hospital stay (LoS), clinician-derived clinical outcomes (*e.g.*, Knee- and Hip Society Scores), patient reported outcome measures (PROMs), and costs. This present SR and meta-analysis is complementary to previous reviews[1,11-18].

MATERIALS AND METHODS

A review protocol was developed according to the Preferred Items for Reporting Systematic Reviews and Meta-Analysis (PRISMA-P) statement[19] and registered in PROSPERO, the International Prospective Register of Systematic Reviews, in September 2016 (CRD42016040210).

Literature search

A systematic literature search in five key healthcare databases was conducted (MH). Embase.com, PubMed, Wiley/Cochrane Library, Clarivate Analytics/Web of Science, and Ebsco/CINAHL were searched from inception until June 10, 2018. Three trial registers were searched to identify ongoing unpublished trials, including the World Health Organization portal, ClinicalTrials.gov, and PROSPERO. The first terms used, including all synonyms, were 'knee arthroplasty' or 'hip arthroplasty' combined with 'clinical pathways' or 'enhanced recovery' or 'ambulatory care' or 'outpatients'. There was no restriction on language or publication type or date.

Eligibility criteria

Randomized controlled trials (RCTs) and observational studies written in English, comparing within the studies ERP with the foregoing regular pathway, including patients 18 years or older undergoing THA, TKA, and/or UKA, were included. At least one of the following outcomes needed to be evaluated for inclusion for one of the arthroplasties: (S)AEs, readmission rate, LoS, functional recovery, PROMs, and costs. Descriptive articles (*e.g.*, historical articles) and studies investigating patients who underwent revision, fracture, or bilateral arthroplasty were excluded.

Study selection

The results of the literature search were collated and de-duplicated in RefWorks[20]. All articles were screened on title and abstract independently by two reviewers (MH and MS). After retrieving and examining the full text of all potentially relevant articles, both reviewers indicated independently if the study should be included. Disagreements regarding study inclusion were resolved by consensus between the two reviewers.

One reviewer (MH) extracted and added data into Review Manager (RevMan)[21] and the other (MS) verified the accuracy of the data; disagreements were resolved by discussion and if no agreement was reached, by the involvement of a third reviewer (BS).

Clinical pathways

We divided the CPs into ERP and regular pathways. It is challenging to get consensus on a definition for ERP[32], because of the different concepts of care under different health care systems. CPs with rapid or enhanced recovery, fast-track, day care, or outpatient surgery, including novel experimental evidence, are an updated version of the regular pathway and were defined as ERP. These pathways are continually evolving, aiming to improve the standard of care. Several factors may streamline these ERP, during the pre-, peri-, and/or post-operative stage. We used the definitions as stated by Galbraith *et al* [11] for the specific elements of ERP. The regular pathways, maintaining the standard or non-optimized program and containing the previous evidence, prescribe care as usual. The regular pathways were considered to be the initial procedures. A pragmatic approach was chosen to distinguish between regular and enhanced. Results between ERP and regular pathways were compared for (S)AEs, LoS, functional recovery, PROMs, and costs.

Outcomes

The following data were extracted systematically from the included papers by both reviewers (MH and MS): Author, publication year, study design, procedure, clinical pathways, number of participants, patients' characteristics, country, and outcomes. We determined AEs as patient events and wound disorders, surgical and/or prosthesis related[3]. SAEs were reported as undesired medical events, not necessarily associated with the treatment[22]. Classification as AE or SAE was analyzed together as one outcome measure in (S)AE. Readmission rate was registered as the number of readmissions related to the hip or knee surgery. LoS was evaluated as time in days between hospital admission and discharge. Clinical outcomes were assessed in terms of functional recovery and with the use of PROMs. Costs included only intramural hospital costs and were reported in the monetary unit of the study.

Risk of bias

For all included studies, a risk-of-bias (RoB) table was used to identify potential sources of bias with the

use of the Cochrane Collaboration tool[23] or the ROBINS-I tool[24] for RCTs and non-randomized studies, respectively. Two authors (MH and MS) independently assessed the RoB. The outcomes of all studies were reported using Grading of Recommendation, Assessment, Development and Evaluation (GRADE)[25].

Statistical analysis

Outcomes were summarized using RevMan 5.3[21]. We extracted all data used from the original studies. To quantify the statistical heterogeneity in the studies, the I^2 value was used. Only if studies were sufficiently clinically, methodologically, and statistically homogenous, the data were pooled in a meta-analysis. In case of considerable heterogeneity (> 75%), a qualitative analysis was performed[23] and outcomes between included studies were described. In the situation where one of the sensitivity analyses showed no considerable heterogeneity (< 75%), a meta-analysis was performed on this outcome. For the meta-analysis, we used a random effects model and report relative risk (RR) with 95% confidence interval (CI). We present the results within forest plots, subdivided for type of arthroplasty (THA, TKA, and/or UKA). If no distinction between the different arthroplasties was possible, analysis for the combined group were included as a subgroup (THA and/or TKA and/or UKA). In a sensitivity analysis, we also combined (S)AE with a follow-up time of 30 d or more and readmission rate as one combined outcome, as they are interrelated in clinical practice. Studies for (S)AE with a follow-up time of 30 d or more were analyzed because of their clinical relevance. P value ≤ 0.05 was considered statistically significant.

RESULTS

The full search strategies can be found in the Supplementary material (Databases and search strings). This systematic search identified 7901 references. The literature search and selection process are shown in Figure 1. After removal of duplicates, 4502 references remained for screening on title and abstract. Of these, 106 full-text articles were assessed for eligibility. No additional records were identified by checking reference lists. Eventually, 40 studies were included[3,7,26-63]. A summary of the characteristics of these studies is given in Table 1.

We included five RCTs[7,28,30,35,38], six prospective cohort studies[31,33,37,41,50,52], thirteen retrospective cohort studies[36,42-44,46,51,53,54,57-59,62,63], five observational cohort studies[27,34,45,47,60], four case control studies[3,48,49,56], four comparative studies with prospective[32,61] and retrospective designs for the standard CPs[39,55], and one each prospective pilot study[26], prospective follow-up study[29], and propensity score matched study[40]. Nine articles studied THA[26,29,38,41,50,52,54,60,63], nineteen studied TKA[3,7,30-33,36,37,39,42,44,48,49,51,55,58,59,61,62], six studied UKA[3,43,45,48,55,56], and eleven studied both hip and knee arthroplasty[27,28,34,35,40,43,46,47,53,56,57]. Of the included studies, which were published between 1999 and 2018, eighteen were conducted in the United States[26,30,31,36,38,40,42-46,51,53-55,59,60,63], five in the Netherlands[3,27,48,50,56], three each in the United Kingdom[34,37,41], Germany[7,32,33], and Canada[35,49,61], two in Spain[29,57], and one each in Australia[28], Malaysia[39], Italy[58], New Zealand[47], Denmark[52], and Finland[62]. The setting varied from a hospital[3,26,27,34,41,47,48,50,56,57,60-62] to a medical[36,40,42,43-46,53,54,59] or orthopedic center[7,35,37,38,51,52,55,58,63], a tertiary[28,30,49] or a university hospital[29,32,33,39], or a single institution[31].

The total sample size consisted of 2223534 patients undergoing hip or knee arthroplasty; 997765 patients were treated according to ERP compared with 1225769 patients with regular pathways (Table 1). Overall, more female patients were included (60.1%). Of 5095 (0.2%) patients, sex was not reported. The mean age was 65.1 years for patients with ERP and 66.5 years for those with regular pathways. The mean body mass index was similar for both CPs (30 kg/m^2). In ERP, 25 studies applied enhanced elements during the pre-operative phases, mostly for education[27,32-36,41,47,50,52,57,61,62], 19 applied during the peri-operative phase, *e.g.*, for pre-medication or neuraxial-regional anesthesia[3,26,34-37,41,47,50,57,58,60], and 35 during the postoperative phase, mostly for the rehabilitation program or early discharge home[3,7,26,27,29,31,32,35,36,38,40,42-49,51,54,55,57,59-61]. An overview of the pre-, peri-, and postoperative management during ERP is listed in Table 2.

Risk of bias

The methodological quality is presented in a RoB summary (Figures 2 and 4) and as percentages (Figures 3 and 5) for the RCTs and non-randomized studies, respectively. Blinding of participants and personnel was not possible because of the content of the CPs. Selection bias was unclear in three RCTs (60%) and blinding of outcome in two RCTs (40%). Five non-randomized studies were of high quality with a low RoB, whereas three were of low-quality with a serious RoB. All low-quality studies had bias due to confounding. A serious or critical bias in the selection of the reported results was found in the majority of studies (71%). In 31% of the studies, the outcome could have been influenced by knowledge of the applied CPs. Five studies reported missing data (14%), and four had bias due to selection of participants (11%). Overall, the methodological quality of the included studies ranged from average to

Table 1 Characteristics of the included studies, patient demographics, ERP versus regular pathways, and outcome

Author/year	Procedure	Study design	Country/setting	ERP/regular pathway	Number participants ERP/regular pathway	Participants characteristics ERP/regular pathway	Outcome
Arshi *et al*[42]; 2017	TKA	Retrospective cohort	United States; Humana subset of the pearl-diver patient record database	Outpatient/inpatient	*n* = 133.342; 4.391/128.951	Age: (70-74), modus 65-69; Men-women: (1.560-2.831)/(46.805-82.146)	LoS, (S)AE
Auyong *et al* [36]; 2015	TKA	Retrospective cohort	United States; Medical center	Updated ERAS/ERAS	*n* = 252; 126/126	Age: 66.02 (10.02)/68.44 (9.98); Men-women: (44-82)/(41-85); BMI: 31.88 (7.629)/31.3 (6.562)	LoS, (S)AE, functional recovery, PROMs, readmission
Basques *et al* [43]; 2017	THA; TKA	Retrospective matched cohort	United States; NSQIP database	Same day/inpatient	*n* = 177.818, 1.236/176.582; THA: *n* = 63.360, 368/368; TKA: *n* = 110.410, 608/608; UKA: *n* = 4.048, 260/260	Age: Most between 65-74; Men-women: (46.6%-53.4%)/(39.8%-60.2%); BMI: Most between 25-29.9	LoS, (S)AE, readmission
Bertin *et al*[26]; 2005	THA	Pilot study, retrospectively chosen control group	United States; Hospital	Outpatient/existing protocol	*n* = 20; 10/10	Age: 62/63; Men-women: (6-4)/(5-5); BMI: 30.024/29.64	LoS, (S)AE, costs
Bovonratwet *et al*[44]; 2017	TKA	Retrospective cohort	United States; NSQIP database	Outpatient/inpatient	*n* = 112.922; 642/112.280	Age: 64/67; Men-women: (265-377)/(41.821-70.459); BMI: 32/33	LoS, (S)AE, readmission
Bovonratwet *et al*[45]; 2017	UKA	Cohort	United States; NSQIP database	Outpatient/inpatient	*n* = 5880; 568/5312	Age: 62.9/63.7; Men-women: (284-284)/(2501-2811); BMI: 31.5/31.6	LoS, (S)AE, readmission
Brunenberg *et al* [27]; 2005	THA; TKA	Before-after trial	Netherlands; University hospital	Joint recovery programme/usual care	*n* = 160; THA: *n* = 98, 48/50; TKA: *n* = 62, 30/32	Age: 64.4 (28-87); THA: Age 63.38 (11.48)/ 65.4 (13.04), Men-women% (35.4-64.6)/(24-76); TKA: Age 64.9(9.43)/63.94 (12.6), Men-women % (33.3-66.7)/(31.3-68.7)	LoS, functional recovery; PROMs; costs
Castorina *et al* [58]; 2017	TKA	Retrospective observational cohort study	Italy; Orthopedics traumatology and rehabilitation unit	Fast track/traditional group	*n* = 132; 95/37	Age: 71.1 (7.77)/74.62 (± 6.42)	Functional recovery; (S)AE
Courtney *et al* [46]; 2017	THA; TKA	Retrospective cohort	United States; NSQIP database	Outpatient/inpatient	*n* = 169.406; 1220/168.186	Age: 63.1/65.9; Men-women: (539-681)/(67.687-100.499); BMI: 32.1/31.7	LoS, (S)AE, readmission
Courtney *et al* [59]; 2018	TKA	Retrospective cohort	United States; NSQIP database	Outpatient/short stay/LOS ≥ 2 d	*n* = 49.136; 365/3033/45.738		LoS, (S)AE, readmission
den Hertog *et al* [7]; 2012	TKA	Randomized prospective study	Germany; Hospital	Fast-track group/standard care re-habilitation	*n* = 147 (ITT), 74/73; *n* = 140 (PP), 71/69	Age: 66.58 (8.21)/68.25 (7.91); Men-women: (23-51)/(20-53); BMI: 31.17 (5.82)/30.38 (6.05)	LoS, (S)AE, functional recovery, PROMs
Dowsey *et al* [28]; 1999	THA; TKA	Prospective randomized controlled study	Australia; Tertiary hospital	Clinical pathway/control	*n* = 163; 92/71	Age: 64.2/68.2; Men-women: 56/107	LoS, (S)AE, functional recovery, readmission
Featherall *et al* [60]; 2018	THA	Cohort	United States; Clinic	Full protocol/transition cohort/Pre-protocol	*n* = 6090; 2081/2009/2000	Age: 63.77 (11.72)/64.09 (12.04)/64.03 (12.09); Men-women: (1033-1048)/(983-1026)/(960-1040); BMI: 30.13 (6.17)/ 29.93 (6.19)/ 30.09 (6.38)	LoS, (S)AE, cost

Gauthier-Kwan *et al*[61]; 2018	TKA	Prospective comparative cohort	Canada; Hospital	Outpatient/inpatient	*n* = 86; 43/43	Age: 62.5 (50.4-75), 62.5 (51.2-74); Men-women: (29-14)/(22-21); BMI: 28.6 (23.7-35.8)/30.4 (23.5-41.6)	LoS, (S)AE, readmission, functional outcome, PROMs
Gooch *et al*[35]; 2012	THA; TKA	RCT	Canada; Bone and Joint Health Institute	New clinical pathway/standard care	*n* = 1570, 1066 (THA: 615; TKA: 451)/504 (THA: 278; TKA: 226)	Age: 69 (11.1)/69 (10.4); Men-women%: (39.6-60.4)/(40.1-59.9); BMI: 29.5 (5.6)/29.4 (5.4)	(S)AE, functional recovery, PROMs
Goyal *et al*[38]; 2017	THA	Prospective randomized study	United States; Two reconstruction centres	Outpatient/inpatient	*n* = 220; 112/108	Age: 59.8 (8.5) (59.3) (27-74)/60.2 (8.9) (61) (34-74); Men-women: (59-53)/(58-50); BMI: 27.6 (4.1) (27.1) (18-38.4)/ 28.3 (4.7) (27.7) (18.4-39.9)	LoS, (S)AE, readmission, functional recovery, PROMs
Gwynne-Jones *et al*[47]; 2017	THA; TKA	Matched cohort study	New Zealand; Hospital	Post ERAS/pre ERAS	*n* = 1035, 528/507; THA: 318/314; TKA: 210/193	THA: Age 68.3 (11.8)/66.8 (11.8), Men-women (146-172)/(146-168); TKA: Age 70.4 (8.9)/69.8 (9.0), Men-women: 107-103/83-110	LoS, (S)AE, readmission, PROMs
Ho *et al*[30]; 2007	TKA	Randomized controlled trial; retrospective cost analysis	United States; Tertiary teaching hospital	Critical pathway/no uniform CP	*n* = 90; 3 cohorts: 30/30/30	Age: 66/67/68; Men-women: (14-16)/(14-16)/(14-16); Weight: 89/91/88	LoS, (S)AE, costs
Hoorntje *et al*[48]; 2017	UKA	Case control study	Netherlands; Hospital	Outpatient/fast-track	*n* = 40; 20/20	Age: 62.2 (5.5)/63.8 (7.5); Men-women: (10-10)/(7-13); BMI: 27.8 (3.7)/30.5 (7.0)	LoS, PROMs
Huang *et al*[49]; 2017	TKA	Prospective case control study	Canada; Tertiary academic medical centre	Same day discharge/inpatient	*n* = 40; 20/20	Age: 58.5 (5.6)/61.5 (5.9); Men-women: (14-6)/(14-6); BMI: 29.0 (3.7)/30.6 (5.3)	LoS, (S)AE, readmission, cost
Ismail A *et al*[39]; 2016	TKA	Non-randomized control trial	Malaysia; University hospital	CP/control	*n* = 152; 73/79	Age: 66.1/64.7	LoS, (S)AE, readmission
Jimenez Muñoz *et al*[29]; 2006	THA	Prospective follow-up study	Spain; University general hospital	After CP/prior CP	*n* = 487; 384/98; 309/75	Not present	LoS, (S)AE
Klapwijk *et al*[50]; 2017	THA	Prospective cohort	Netherlands; Hospital	Outpatient/inpatient	*n* = 94; 42/52	Age: 61 (41-78)/68 (48-82); Men-women: (17-25)/(21-31); BMI: 29 (20-35) /26 (18-39)	LoS, (S)AE, functional recovery, PROMs
Klingenstein *et al*[51]; 2017	TKA	Retrospective cohort	United States; Joint replacement centre	Short stay/traditional stay	*n* = 2287; 1502/785	Age: 71.7 (5.4)/73.3 (6.1); Men-women%: (39-61)/(25-75); BMI ≥ 30 (%): 50/57	LoS, (S)AE, readmission
Kolisek *et al*[31]; 2009	TKA	Prospective matched cohort	United States; Hospital	Outpatient/conventional inpatient stay	*n* = 128; 64/64	Age: 55 (42-64)/55 (42-63); Men-women: (40-24)/(40-24); BMI: 30.8 (24.3-38)/30.8(24.2-37.8)	LoS, (S)AE, functional recovery, PROMs, readmission
Kort *et al*[3]; 2017	UKA	Case control study	Netherlands; Hospital	Outpatient/rapid recovery	*n* = 40; 20/20	Age: 60.5 (5.65)/61.2 (5.15); Men-women: (13-7)/(11-9); BMI: 29.1 (3.85)/27.7 (3.27)	LoS, (S)AE, readmission, PROMs
Larsen *et al*[52]; 2017	THA	Observational cohort	Denmark; Orthopedic clinic	Day case (< 12 h)/standard 2-d	*n* = 56; 20/36	Age: 64.6; Men-women: 15-5; BMI: 28.8 (23.8-33.7)	LoS, (S)AE, readmission, PROMs
Lovecchio *et al*[40]; 2016	THA; TKA	Propensity score matched study	United States; NSQIP database	Outpatient/fast-track inpatients	*n* = 1968, 492/1476; THA/TKA: (183-585)/(309-891)	Age: Most between 60 to 69; Men-women: (217-275)/(664-812); BMI between 25-30	LoS, (S)AE, readmission
Maempel *et al*	THA	Prospective cohort	United Kingdom; Hospital	ERP/traditional rehabilitation	*n* = 1161; 550/611	Age: 64 (18-94)/66 (23-90); Men-women: (212-	LoS, (S)AE,

[41]; 2016						338)/(242-369); BMI: 30 (7)/29 (7)	functional recovery, PROMs
Maempel *et al* [37]; 2015	TKA	Non-randomized prospective cohort	United Kingdom; Arthroplasty clinic	ERP/traditional rehabilitation	*n* = 165; 84/81	Age: 69.8 (8.9)/70.1 (10.5); Men-women: (42-42)/(37-44); BMI: 32.4 (22.6-46.6)/31.8 (20.5-41.9)	LoS, (S)AE, functional recovery
Malviya *et al* [34]; 2011	THA; TKA	Observational study	United Kingdom; Hospital	ERP/traditional pathway	*n* = 4500; 1500 (THA: 630; TKA: 870)/3000 (THA: 1368; TKA: 1632)	Age: 68/69; Men-women: (711-789)/(1482-1518)	LoS, (S)AE, readmission
Nelson *et al*[54]; 2017	THA	Retrospective cohort, data prospectively collected	United States; NSQIP database	Outpatient/inpatient	*n* = 63.844; 420/63.424	Age: 62/65; Men-women: (222-198)/(28.587-34.833); BMI most between 25-30	LoS, (S)AE, readmission
Pamilo *et al*[62]; 2018	TKA	Retrospective cohort	Finland; Finnish Hospital Discharge Register	Fast-track CP/non-fast-track	*n* = 4256, 2310/1946; Hospital A: 624/437	Age and sex: No statistically significant difference between CP's	LoS, (S)AE, readmission
Renkawitz *et al* [32]; 2010	TKA	Prospective parallel group design	Germany; Orthopaedic university medical centre	Optimized accelerated CP/standard CP	*n* = 143; 67/76	Age: 67 (9)/68.1 (11.1); Men-women: (14-53)/(23-53); BMI: 31.4 (5.1)/30.7 (5.6)	LoS, (S)AE, readmission, functional recovery
Richter *et al*[55]; 2017	UKA	Retrospective chart review	United States; Surgical outpatient center	Outpatient/inpatient	*n* = 22; 12/10	Age: 67.2 (9.2)/64.5 (9.8); Men-women: (7-5)/(8-2); BMI: 28.7 (5.1)/25.8 (8.1)	LoS, (S)AE, readmission, cost
Schotanus *et al* [69]; 2017	TKA; UKA	Case control study	Netherlands; Hospital	Outpatient/ERP	*n* = 361; 94/267	Age: 63.4 (8.0)/68.4 (9.0); Men-women: (49-45)/(94-173); BMI: 28.25 (3.68)/29.49 (5.05)	LoS, PROMs
Toy *et al*[63]; 2018	THA	Retrospective cohort	United States; Ambulatory surgery centers	Later outpatient pathway/initial outpatient pathway	*n* = 145; 72/73	Age: 55 (27-70); Men-women: 76-49; BMI: 29.7 (19.6-43)	LoS, (S)AE, readmission
Wilche *et al*[57]; 2017	THA; TKA	Retrospective review	Spain; Hospital	Fast-track recovery/conventional recovery	*n* = 200; THA: 50/50; TKA: 50/50	Age: 69.24 (9.64)/73.07 (8.33); Men-women: (40-60)/(40-60)	LoS, (S)AE, readmission, cost

Age in years, mean ± SD (median) (range); Weight in kg. BMI: Body mass index; NSQIP: National Surgical Quality Improvement Program; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; CP: Clinical pathway; UKA: Unicompartmental knee arthroplasty; Los: Length of hospital stay; (S)AE: (Serious) adverse events; PROMS: Patient reported outcome measures; ERP: Enhanced recovery pathways; ERAS: Enhanced Recovery After Orthopedic Surgery; RCT: Randomized controlled trial.

good.

Heterogeneity

The studies varied clinically (*e.g.*, patient characteristics and CPs) and methodologically. Different measurement tools were used, and outcome measures were reported in different ways across studies. Therefore, a meta-analysis was only feasible with studies that used the same measurement tools. For this study, data for the sensitivity analyses were pooled for (S)AEs and readmission rate. A qualitative analysis was performed for the results of LoS, functional recovery, PROMs, and costs.

(S)AEs and readmission rate

Thirty-five studies examined AEs, SAEs, or both[3,7,26,28-32,34-47,49-52,54,55,57-63] and twenty four examined readmission rate[3,28,31,32,34,36,38,39,40,43-47,49,51-52,54,55,57,59,61-63]. The follow-up time

Table 2 Pre-, peri-, and post-operative management during enhanced recovery pathways

Author	Year	ERP			Preoperative					Peri-operative							Post-operative				
		Pre-operative	Peri-operative	Post-operative	Education	Outpatient consultation	Discharge planning	Physiotherapy	Pre-assessment outpatient clinic	Day of surgery admission	Premedication	Optimal hydration	Neuraxial-regional anaesthesia	Multimodal blood loss reduction	+/- peri articular injection	Avoid surgical drains	Multimodal analgesia regimen	Day of surgery mobilisation	Venous thromboembolic prophylaxis	Rehabilitation programme	Early discharge home
Arshi *et al*[42]	2017			X																	X
Auyong *et al*[36]	2015	X	X	X	X						X		X				X	X			X
Basques *et al*[43]	2017			X																	X
Bertin *et al*[26]	2005	X	X	X				X			X		X							X	X
Bovonra-twet *et al*[44]	2017			X																	X
Bovonra-twet *et al*[45]	2017			X																	X
Brunenberg *et al*[27]	2005	X		X	X				X											X	
Castorina *et al*[58]	2017	X	X	X									X				X				
Courtney *et al*[46]	2017			X																	X
Courtney *et al*[59]	2018			X																	X
den Hertog *et al*[7]	2012	X		X														X		X	X
Dowsey *et al*[28]	1999		X	X																	

Feathe-rall *et al*[60]	2018	**X**	**X**	**X**					X						X		X			X	
Gau-thier-Kwan *et al*[61]	2018	**X**	**X**	**X**	X						X		X				X			X	X
Gooch *et al*[35]	2012	**X**	**X**	**X**	X	X	X	X			X		X					X		X	
Goyal *et al*[38]	2017			**X**													X				X
Gwynne-Jones *et al*[47]	2017	**X**	**X**	**X**	X					X	X		X	X				X		X	
Ho *et al* [30]	2007	**X**	**X**																		
Hoorn-tje *et al*[48]	2017	**X**	**X**	**X**								X								X	X
Huang *et al*[49]	2017	**X**	**X**	**X**		X				X					X					X	
Ismail A *et al*[39]	2016																				
Jimenez Muñoz *et al*[29]	2006			**X**																X	X
Klapwi-jk *et al*[50]	2017	**X**	**X**	**X**	X						X		X			X		X			
Klingen-stein *et al*[51]	2017			**X**																	X
Kolisek *et al*[31]	2009	**X**		**X**														X		X	X
Kort *et al*[3]	2017	**X**	**X**	**X**			X	X		X	X									X	X
Krumm-enauer *et al*[33]	2011	**X**		**X**	X	X														X	
Larsen *et al*[52]	2017	**X**		**X**	X													X			

Lovecchio *et al*[40]	2016			**X**																		X
Maempel *et al*[41]	2016	**X**	**X**	**X**	X	X	X	X						X				X				
Maempel *et al*[37]	2015	**X**	**X**	**X**		X					X			X				X				
Malviya *et al*[34]	2011	**X**	**X**	**X**	X				X			X		X				X				
Molloy *et al*[53]	2017																					
Nelson *et al*[54]	2017			**X**																		X
Pamilo *et al*[62]	2018	**X**			X	X																
Renkawitz *et al*[32]	2010	**X**	**X**	**X**	X	X			X									X		X		
Richter *et al*[55]	2017			**X**																		X
Schotanus *et al*[69]	2017	**X**	**X**	**X**			X				X							X				
Toy *et al* [63]	2018	**X**				X																
Wilches *et al*[57]	2017	**X**	**X**	**X**	X				X			X	X	X	X			X		X		

ERP: Enhanced recovery pathways.

varied from 8 d up to 24 mo postoperatively.

In the ERP, there were less (S)AEs (RR: 0.9; 95%CI: 0.8-1) and a lower readmission rate (RR: 0.8; 95%CI: 0.7-1) when compared to the regular pathways. The analyses for overall (S)AEs resulted in considerable heterogeneity (I^2 = 83%, P = 0.2). Studies of (S)AEs with a follow-up time of 30 d or more yielded a RR of 0.9 (95%CI: 0.8-1), with substantial heterogeneity (I^2 = 74%, P = 0.3) (Figures 6 and 7). Only the THA subgroup showed heterogeneity (I^2 = 89%, P = 0.7) while the TKA (I^2 = 21%, P = 0.2) and the combined groups (THA and TKA; I^2 = 47%, P = 0.1) were homogeneous.

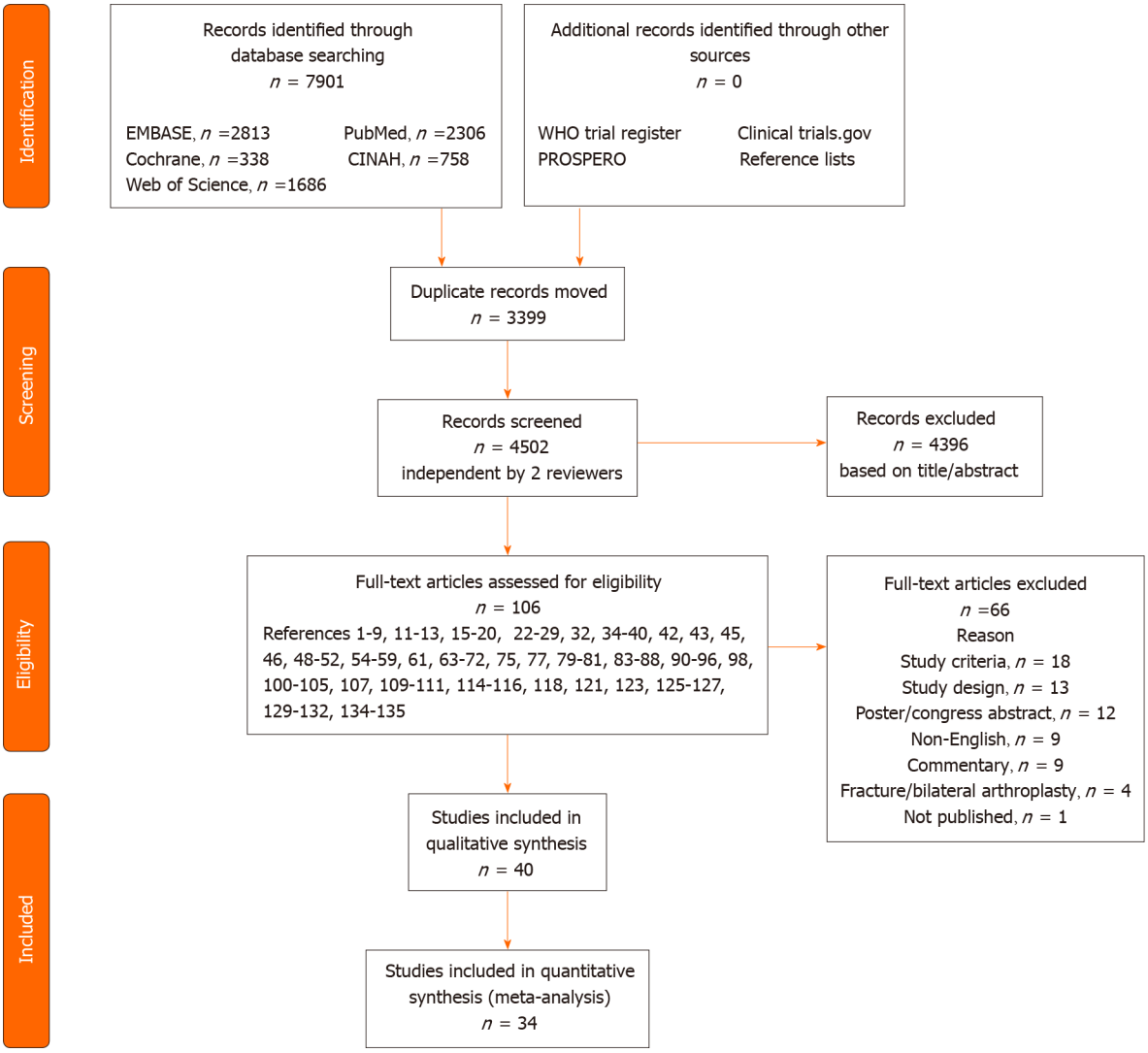

Figure 1 Flow diagram of the literature search and selection procedure. WHO: World Health Organization.

The analyses for readmission rate were homogenous (I^2 = 48%, P = 0.2). The readmission rate in ERP was statistically significant different in favor of the knee arthroplasties without heterogeneity (TKA: I^2 = 15%, P = 0.01; UKA: I^2 = 0%, P = 0.01). The plots for readmission rate for THA, TKA, UKA, and the combined subgroups (THA and TKA) are shown in Figures 8 and 9.

Sensitivity analyses of (S)AEs together with readmission rate resulted in a RR of 0.9 (95%CI: 0.7-1) with substantial heterogeneity (I^2 = 84%, P = 0.1). According to GRADE, there was moderate quality of evidence for (S)AE and readmission rate (Table 3).

Length of hospital stay

Thirty-eight studies described LoS[3,7,26-34,36-57,59-63]. A reduced LoS was found in all ERPs, of which 20 studies reported a statistically significant reduction ranging between 0.5-10.1, 3.2-10.0, 2.8-7.1, and 2.6 d for the THA[29,41,50,52,60,63], TKA[7,30,32,36,37,39,62], the combined outcome of THA and TKA[27,28,34,47,53,57], and UKA[3], respectively. The overall median LoS reduced up to 6.5 d. For regular pathways, the median values were between 0.5 and 16 d and the mean values were between 1.5 to 19.5 d. All the analyzed arthroplasties showed high heterogeneity for LoS (> I^2 = 98%). The GRADE table shows high evidence for LoS (Table 3).

Clinician-derived outcome and PROMs

Functional recovery was assessed in 13 studies for THA[38,41,50], TKA[7,31,32,36,37,58,61], and the combined subgroup THA and TKA[27,28,35], respectively. The Harris Hip Score, Range of Motion, and scores from the American Knee Society were mostly reported. Four articles studied THA[38,41,50,52], six studied TKA[7,31,33,36,56,61], and three each studied UKA[3,48,56] and both THA and TKA[27,35,47] regarding the PROMs, using similar measurement types. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, EuroQual, Oxford Knee Score, and pain scales were mostly used as PROMs.

Table 3 Grading of Recommendation, Assessment, Development and Evaluation evidence profile: Enhanced recovery pathways compared to regular pathways for hip and knee arthroplasty

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(S)AE	Control	Relative (95%CI)	Absolute		
Functional recovery (follow-up 24 mo)												
12	Randomised trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	0/2289 (0%)	0/1802 (0%) 0%	Not pooled	Not pooled Not pooled	Moderate	Important
PROMs (follow-up 24 mo; Better indicated by lower values)												
15	Randomised trials	No serious risk of bias	Serious[2]	No serious indirectness	No serious imprecision	None	2966	2388	-	Not pooled	Moderate	Important
LoS (follow-up 24 mo; Better indicated by lower values)												
38	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	997447	1573895	-	MD 2.45 lower (3.42 to 1.48 lower)	High	Important
(S)AEs												
34	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[3]	No serious imprecision	None	2103/18344 (11.5%)	83989/540864 (15.5%) 11.7%	RR 0.91 (0.78 to 1.06)	14 fewer per 1000 (from 34 fewer to 9 more) 11 fewer per 1000 (from 26 fewer to 7 more)	Moderate	Important
Readmission (follow-up 24 mo)												
23	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	273/9846 (2.8%)	8360/406167 (2.1%) 2.7%	RR 0.83 (0.65 to 1.07)	3 fewer per 1000 (from 7 fewer to 1 more) 5 fewer per 1000 (from 9 fewer to 2 more)	Moderate	Important

[1]Different outcomes for functional recovery: HHS [with/without range of motion (ROM), pain], American Knee Society Score, ROM.
[2]Different patient reported outcome measures: SF-36, WOMAC, KATZ.
[3]No clear distinction between adverse event (AE) and serious AE.
[4]Wide confidence interval.
(S)AE: (Serious) adverse event; CI: Confidence interval; PROMS: Patient reported outcome measures; LoS: Length of hospital stay; RR: Relative risk.

The follow-up time differed from the first postoperative day up to 24 mo postoperatively. In view of the clinician-derived outcomes and PROMs, the results in the ERP were similar or improved for THA [41,50,52], TKA[31-33,58,61], UKA[48], and the combined group THA and TKA[27], or were statistically significant better than those in the regular pathways for TKA[7,36,56], UKA[3], and the combined group THA and TKA[35,47]. Moderate quality for functional recovery and PROMs is presented in GRADE (Table 3).

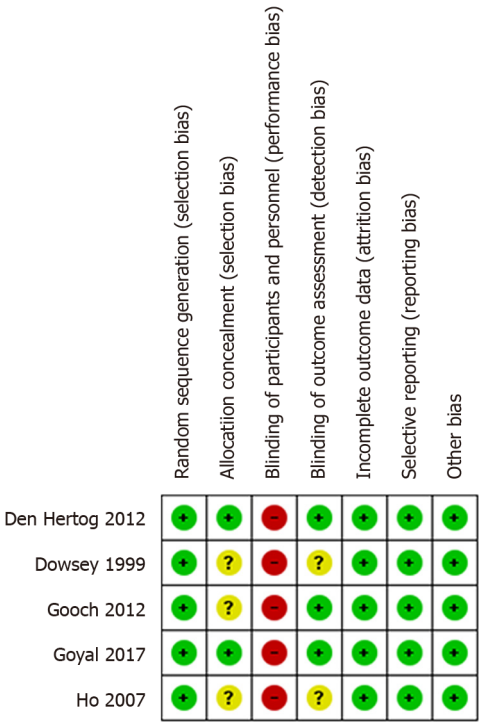

Figure 2 Cochrane risk of bias summary of the randomized controlled trials. Review authors' judgements about each risk of bias item. Low RoB (green + symbol), high RoB (red - symbol), or unclear RoB (yellow - symbol) is shown.

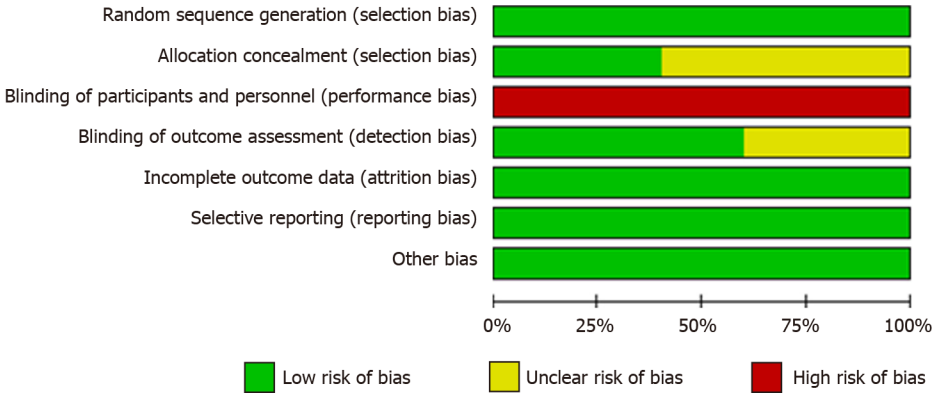

Figure 3 Cochrane RoB graph: Review authors' judgements about each risk of bias item presented as percentages across all included randomized studies.

Costs

Nine observational studies analyzed costs[26,27,30,33,49,53,55,57,60]. The reduction in LoS resulted in statistically significant cost savings for THA in an ERP compared to the regular pathways[26]. Preadmission, physical therapy, and home care charges resulted in a saving for the combined group (THA and TKA) per patient[27] and reduced hospital costs after TKA[30]. Hospital costs were reduced significantly in patients operated for knee arthroplasty in an ERP because of the reduction in room costs, fewer laboratory tests, used medications, physical therapy, and meal costs[30,49,55]. The cost reduction per patient for knee arthroplasty was in favor of the ERP[27,30,33,49,55,57], with a range between €109 and $20573. The cost savings per patient for hip arthroplasty was also higher for the ERP[26,27,57,60] with a range between €581 and $2500. The ERP resulted in a statistically significant economic saving for both knee and hip arthroplasty[49,55,57,60] without affecting complication rate[34], functional improvement, and satisfaction of the patient operated after THA or UKA[26,55]. The individual cost/benefit relation was inferior only in one TKA study[33].

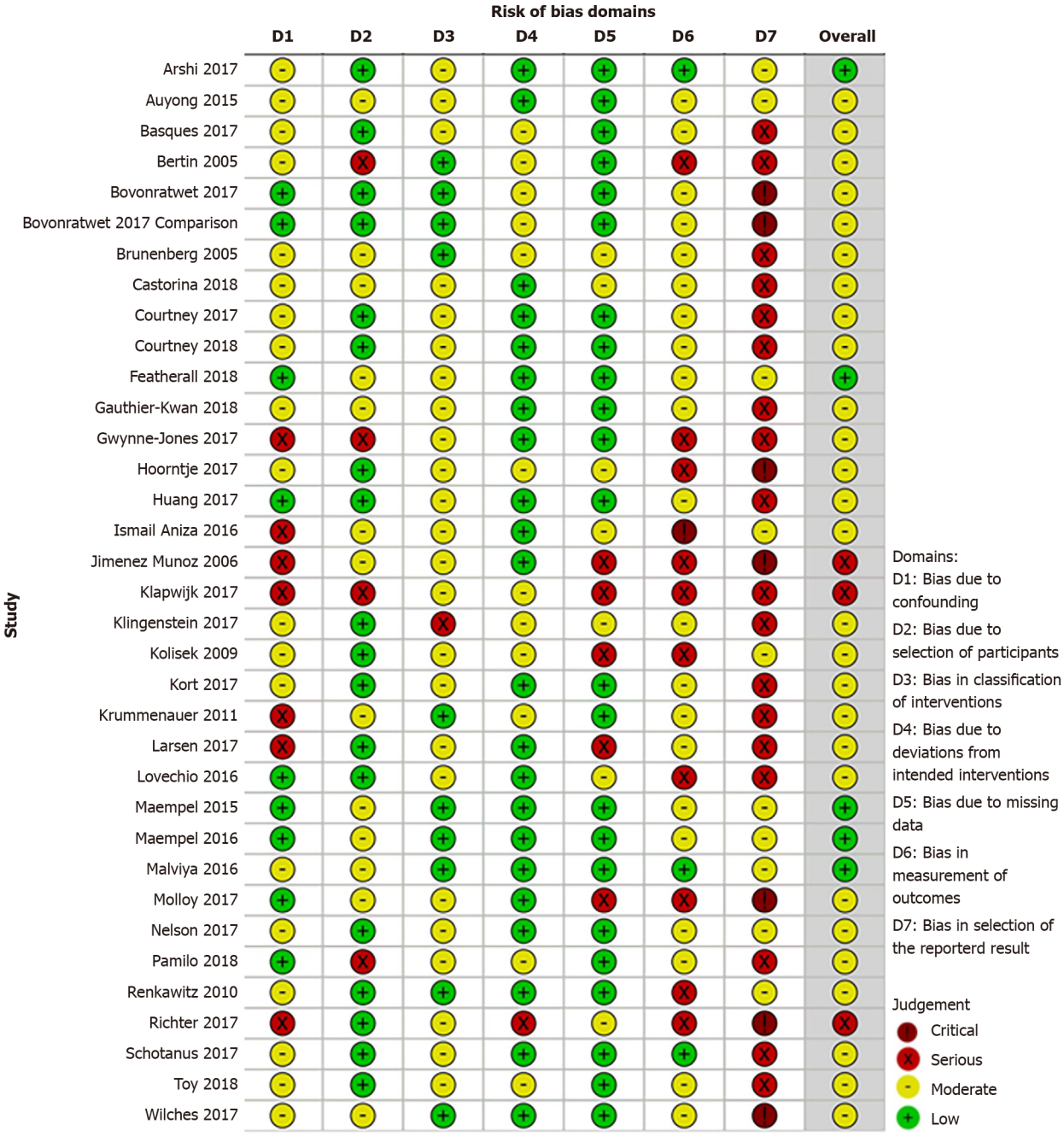

Figure 4 ROBINS-I bias assessment of the non-randomized studies. Review authors' judgements about each risk of bias domain.

DISCUSSION

The most important findings of the present SR and meta-analysis were that the use of ERP yielded similar or improved outcomes for patients with hip and/or knee arthroplasty. In the ERP, there were less (S)AEs and a lower readmission rate when compared to the regular pathways. The readmission rate in the ERP was statistically significant different in favor of the knee arthroplasties without heterogeneity. There were improved results for clinician-derived outcomes and PROMs, reduced LoS, and saved costs compared to regular pathways.

Multiple enhancements can be taken during the pre-, peri-, or post-operative program, to upgrade a regular pathway to enhanced, with respect to local situations. Continuously looking for improvements is important for successful hip and/or knee CPs.

Explanation of findings

The overall methodological quality varied due to the inclusion of five RCTs and 35 observational studies. The studies were heterogeneous regarding patient populations, hospital resources and procedures, multi-disciplinary teams, surgical and anesthetic techniques, practice variation, and follow-up times. Most of the heterogeneity was probably due to methodological differences between the

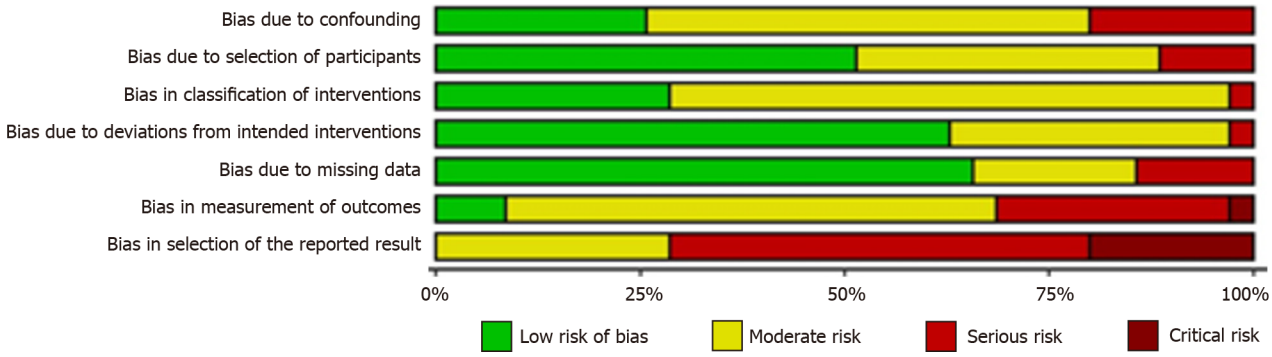

Figure 5 ROBINS-I weighted summary plot.

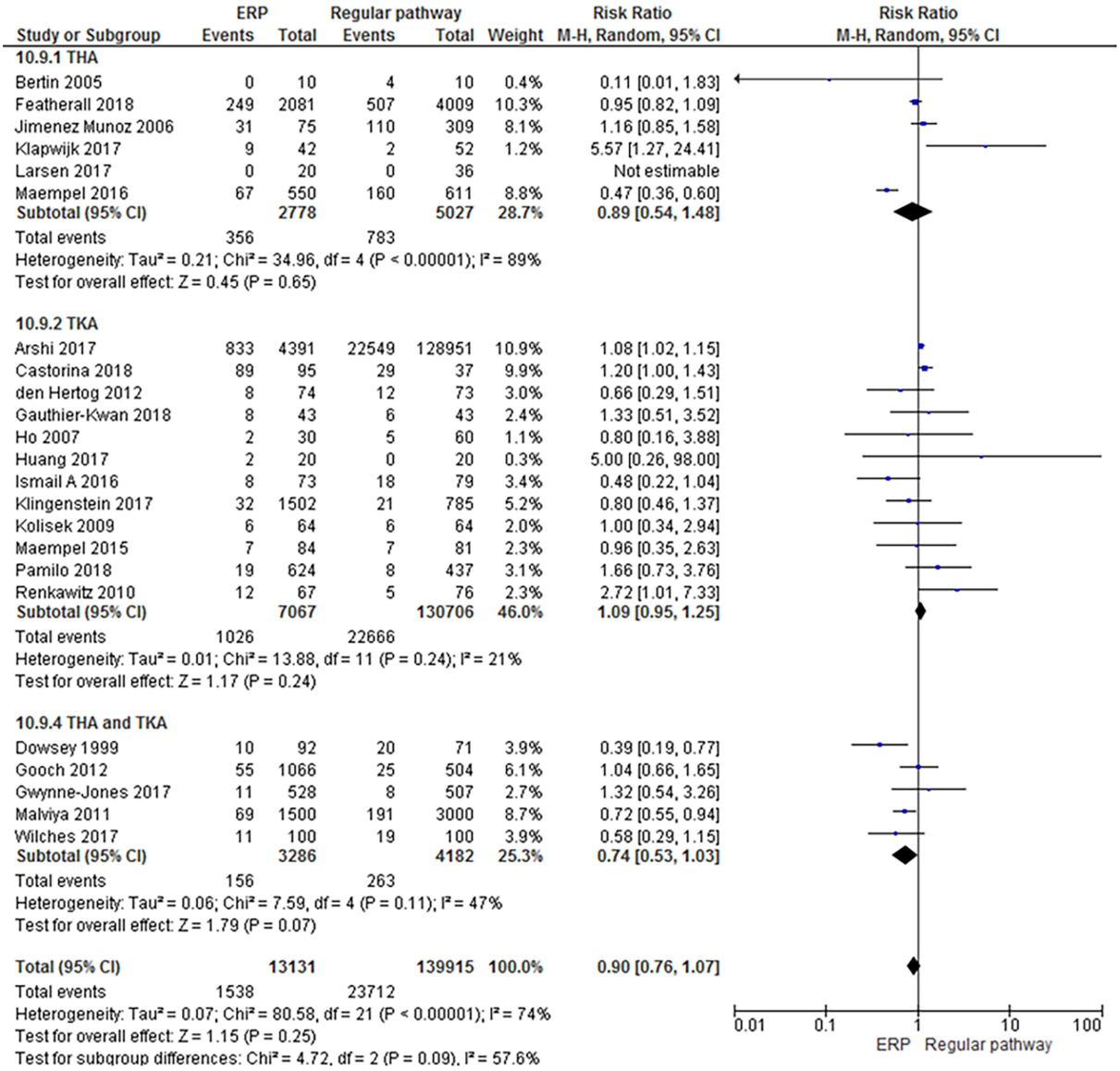

Figure 6 Forest plot with relative risk for each study and pooled relative risk with 95% confidence interval for (serious) adverse events with a follow-up time of 30 d or more for enhanced recovery pathways *vs* regular pathways for hip and knee arthroplasty. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; CI: Confidence interval; ERP: Enhanced recovery pathways.

included studies. The included studies were published throughout the past 20 years, the view of hospital stays after an operation and discharge criteria have been changed over time. And, the obtained data came from different healthcare systems from different countries, from retrospective studies or from national registries. Nevertheless, even within all this practical and methodological variation, the

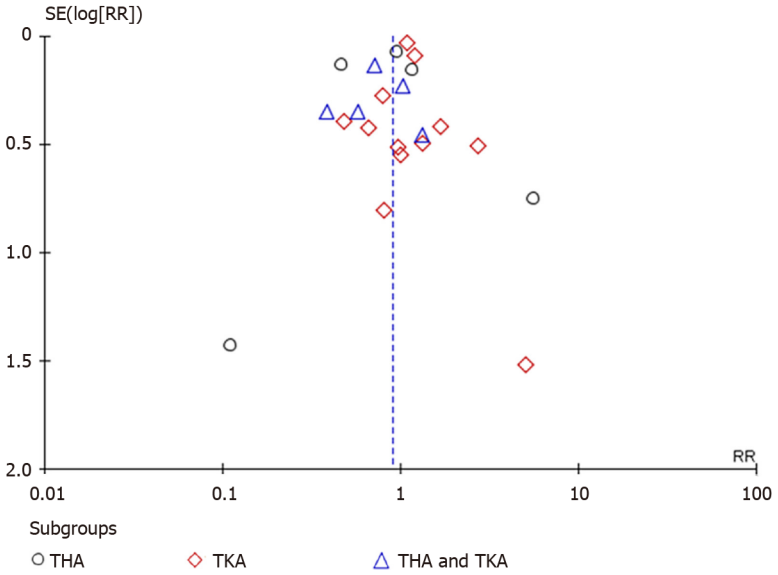

Figure 7 Funnel plot for the studies with described (serious) adverse events with a follow-up time of 30 d or more. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; RR: Risk ratio.

outcomes indicated a positive effect in favor of ERP.

The results of the meta-analysis demonstrated less (S)AEs in patients following the ERP, with fewer readmissions compared to the regular pathways (P = 0.25). Substantial heterogeneity was present when AE and SAE were analyzed together and separately for the different arthroplasties (THA, TKA, and both combined). This heterogeneity was probably due to the lack of definition in primary studies. Also, not all studies made a distinction between AE and SAE. For further investigation, consensus on terminology is recommended. Compared to our findings, another study found statistically significant fewer complications for the ERP compared to the regular pathway[18]. Because of the relative high risk of postoperative complications, careful patient selection for outpatient joint arthroplasty is crucial to obtain successful outcomes[42,44-46,54,63].

All studies showed a reduction in LoS after implementing ERP. In half of these studies, this reduction was statistically significant, which is in line with previous SRs[13,17,18]. LoS can be influenced by preoperative patient education and patient expectations[11,27,28,31,36,37,41,48,57,62,64,65], training in home-based rehabilitation settings[3], and a positive influence from relatives[28,52,53]. The discharge also influenced LoS from the hospital to a rehabilitation center or a center with care facilities instead of discharge to the home environment[28,32,33,47,50]. The reduction of LoS allowed more joint replacements without additional bed capacity and could therefore have a potential positive economic effect[34].

Implementation of CPs for hip and knee arthroplasty were associated with similar or improved outcome for clinician-derived outcome and PROMs. These outcomes represent the best subjective measurement of clinical outcome[66]. However, there is no single best outcome measurement tool after arthroplasty. Besides the positive results of PROMs, various scores are not capturing changes due to a lack of power as averse to a lack of change, *e.g.*, floor and ceiling effects[67]. It could therefore be that further improvement in one of the CPs was not detected. In order to characterize the objective changes in physical activity after arthroplasty in detail, activity monitoring can be used to capture changes over time and to detect potential objective differences[68,69].

This study indicated that patients in the ERP had a substantial reduction in hospital costs, mainly explained by the shorter stay. With a hip arthroplasty incidence of 468000, national cost savings of CP implementation would amount to greater than $1.2 billion annually in costs from a payer perspective in the United States[60]. For joint arthroplasty, the mean hospital cost from 2002-2013 increased about 50%, as a result of rising total joint arthroplasties and prices of implants[53]. Long waiting lists and the contribution to health expenditure growth since joint replacement are expensive interventions, and the increasing economic burden on public healthcare providers should also be taken into account[1,70]. Besides, the improvement of CPs is accomplished with investment in training, knowledge, and adjustments to daily practice for the surgeon, nurse, and physiotherapist[3,58,71]. Establishing the real cost and saving obtained by a CP can be complicated. Savings also depend on charge systems and reimbursement[55,57].

Strengths and limitations

Some limitations should be noted. Due to methodological as well as statistical heterogeneity, a meta-analysis could not be performed for most outcomes. In most of these studies, a high RoB was present,

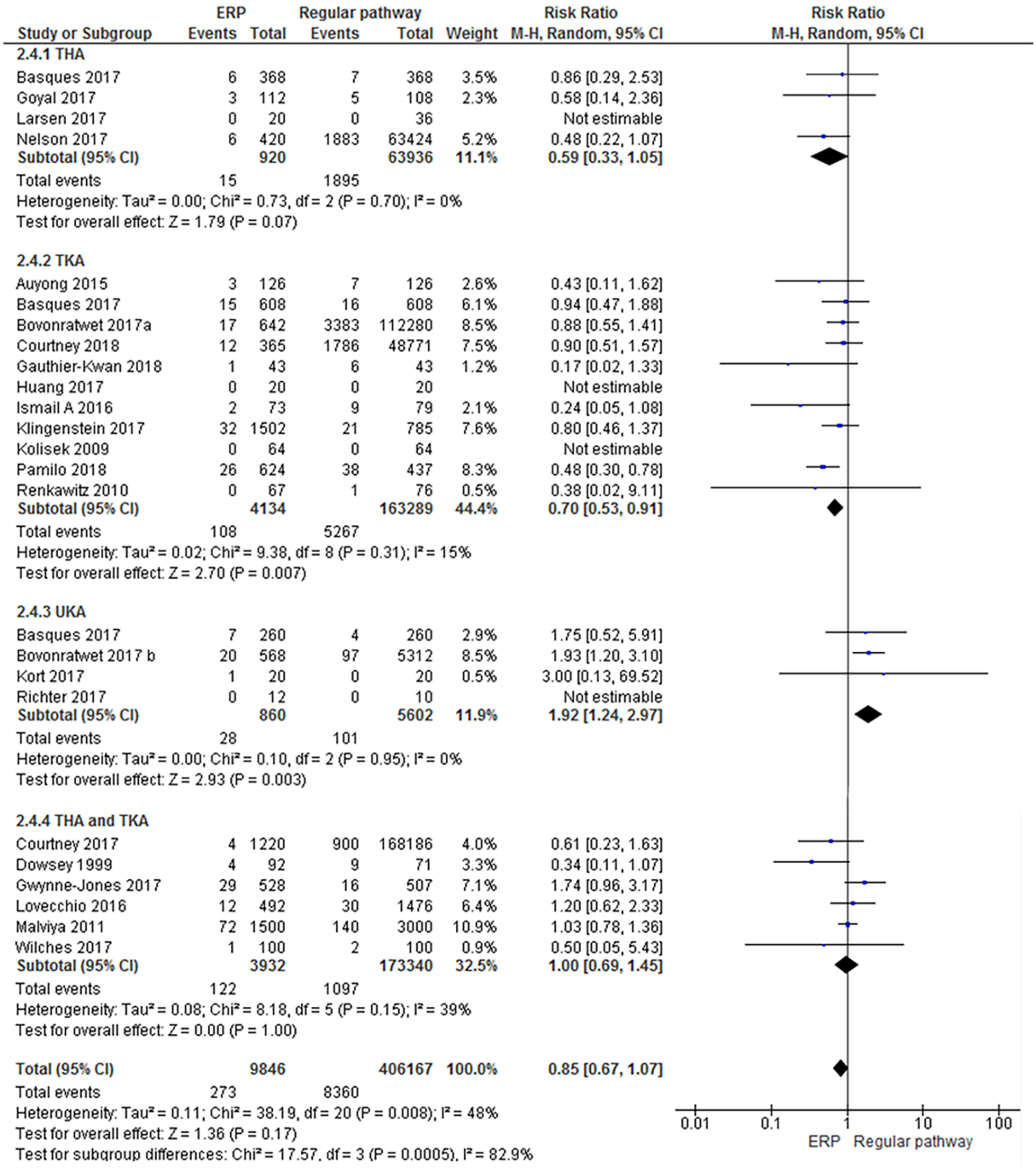

Figure 8 Forest plot with relative risk for each study and pooled relative risk with 95% confidence interval for readmission for enhanced recovery pathways *vs* regular pathways. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; CI: Confidence interval; ERP: Enhanced recovery pathways.

which could have overestimated our results. Selection bias occurred due to the lack of randomization. Performance bias was present because the staff and patients were not blinded to the CP strategy. Clinical bias during data collection was possible because data from large databases were used. Reporting bias is a problem in primary studies because of the selective reporting of outcomes.

Due to the high heterogeneity, it was only possible to perform a meta-analysis for (S)AEs and readmission rate for the different arthroplasties. Although a cut-off I^2 value of 75% has been chosen beforehand, we also present results that exceed this limit, to indicate the trend, *e.g.*, (S)AEs with a follow-up of 30 d or more in the THA (I^2 = 89%, P = 0.7).

The lack of a clear definition for regular pathways and ERP makes it difficult to pool results and compare between large groups of studies. By pointing out the enhanced aspects, we tried to solve this limitation as much as possible.

The strengths of this review include an extensive literature strategy. All included studies compared outcomes from an enhanced recovery pathway with a regular pathway. Data from a large population of

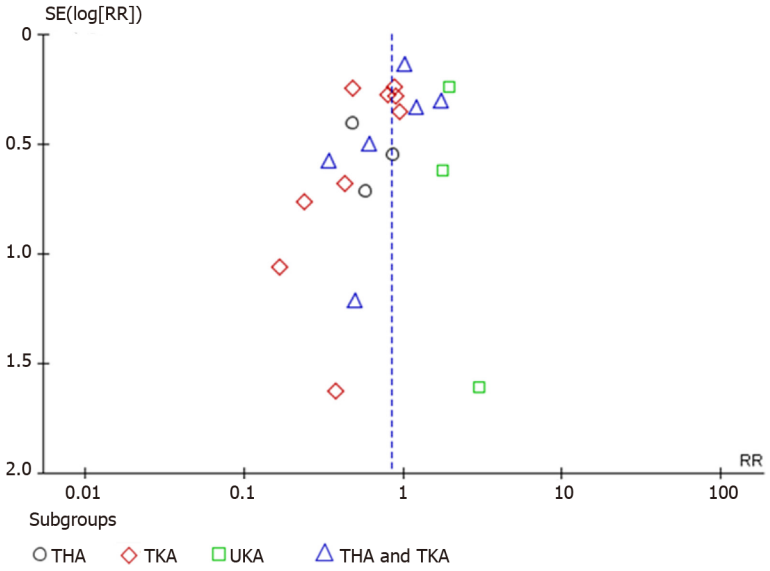

Figure 9 Funnel plot for the studies with described readmission. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; UKA: Unicompartmental knee arthroplasty; RR: Risk ratio.

over 2 million patients were analyzed, including both hip and/or knee arthroplasty, with different follow-up times and outcome measures. Even, an update with the recent literature will provide comparable insights to continuously updating CPs to achieve the most optimal results for patients, professionals, and organizations.

CONCLUSION

Based on the present SR and meta-analysis, it can be concluded that ERPs for hip and/or knee arthroplasty can result in less SAEs with reduced readmission rate and length of stay, and similar or improved clinical outcomes and PROMs with financial benefits, when compared to regular pathways.

ARTICLE HIGHLIGHTS

Research background

Over the past 20 years, clinical pathways (CPs) for total knee and hip arthroplasty have been evolved and optimized. Based on novel evidence and new standards, at this moment we can safely discharge patients on the day of surgery. Whereas in the past, 2-wk bed rest was the standard.

Research motivation

A clinical pathway is a stochastic process that needs to be updated with the latest evidence so the hospital, orthopedic surgeon, and other staff involved in this multidisciplinary approach will be satisfied, with financial benefits for the hospital and improved outcome for the patients. Although, these days in modern medicine, orthopedic surgeons, nurses and hospital staff still needs to be convinced by these optimized CPs. For this reason, we did this systematic review and meta-analysis.

Research objectives

The aim of the present review was to compare the effect of enhanced recovery pathways with regular pathways for adult patients with elective hip and/or knee arthroplasty for (serious) adverse events [(S)AEs], readmission rate, length of hospital stay (LoS), clinician-derived clinical outcomes, patient reported outcome measures (PROMs), and costs.

Research methods

A systematic literature search was conducted in EMBASE, PubMed, Cochrane Library, Web of Science, and CINAHL. All relevant studies were considered for analysis based on the defined eligibility criteria. For the included studies, the risk of bias was assessed. Data for sensitivity analysis were pooled for (S)AE and readmission. A qualitative analysis was performed for the results of LoS, clinician-derived outcome, PROMs, and costs.

Research results

A total of 40 studies were included, 34 in meta-analysis and 40 in qualitative analysis, with data of more than 2 million patients. The meta-analysis presented less (S)AEs in patients following the enhanced recovery pathways (ERP), with fewer readmissions when compared to the regular pathways. The readmission rate was statistically different in favor for the knee arthroplasties without heterogeneity. A reduced LoS was found in all ERP, and in half of these studies, this reduction was statistically significant. The implementation of CPs for hip and knee arthroplasty was associated with similar or improved outcome for clinician-derived outcome and PROMs. ERP were reported to be cost effective. The overall outcomes of all studies reported using Grading of Recommendation, Assessment, Development and Evaluation, presented moderate or high quality of evidence.

Research conclusions

The implementation of ERP for hip and/or knee arthroplasty results in improved clinical and patient related outcomes with financial benefits, compared to regular pathways.

Research perspectives

Based on the results presented, we recommend orthopedic surgeons worldwide, to keep optimizing their standard pathway with the latest evidence. This paper highlights the importance that regular pathways for hip and knee arthroplasty continuously need to be updated according to the latest scientific evidence, which can result in improved clinical outcomes with satisfied patients and financial benefits for patients, healthcare organizations, and hospital management. In this context, high-quality care for hip and/or knee arthroplasty can be achieved.

FOOTNOTES

Author contributions: Heymans MJ designed the study, gathered and analyzed the data, wrote the initial draft of the manuscript, and managed the study; Kort NP is initiator of pathway optimization; Snoeker BA ensured the accuracy of the data; Schotanus MG conceived the study, analyzed the data, and wrote the manuscript; Kort NP, Snoeker BA, and Schotanus MG revised the manuscript; and all authors read and approved the final manuscript.

Conflict-of-interest statement: One author (Kort NP) is a paid consultant for Stryker and Zimmer-Biomet. The other authors declare that they have no conflicts of interest to disclose.

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SYSTEMATIC REVIEWS

Surgical treatment of femoral deformities in polyostotic fibrous dysplasia and McCune-Albright syndrome: A literature review

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Abstract

BACKGROUND

Surgical correction of femoral deformities in polyostotic fibrous dysplasia (PFD) or McCune-Albright syndrome (MAS), such as coxa vara or shepherd's crook deformity, is a challenge.

AIM

To evaluate the treatment of patients with femoral deformities caused by PDF or MAS treated by osteotomies and stabilized with different methods, by analyzing the most relevant studies on the topic.

METHODS

A literature search was performed in Medline database (PubMed). Articles were screened for patients affected by PFD or MAS surgically managed by osteotomies and stabilized with different methods.

RESULTS

The initial search produced 184 studies, with 15 fulfilling the eligibility criteria of our study. Selected articles (1987-2019) included 111 patients overall (136 femurs).

CONCLUSION

Based on our results, the preferred method to stabilize corrective osteotomies is intramedullary nailing with neck cross pinning. When the deformity is limited to the proximal part of the femur, a screw or blade plate may be used, although there is a high risk of fracture below the plate. When the femur is entirely involved, a two-stage procedure may be considered.

Key Words: Polyostotic fibrous dysplasia; McCune-Albright syndrome; Coxa vara; Shepherd's crook deformity; Femoral osteotomy; Intramedullary nailing

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Core Tip: Polyostotic fibrous dysplasia and McCune-Albright syndrome commonly affect the femur, causing deformities and fractures. The proximal third of the femur represents the site where the most difficult to treat deformities are located, such as coxa vara and shepherd's crook deformity. Surgical correction is difficult, since the fibrodysplastic bone is much weaker and more vascularized compared to normal bone and, in the most severe forms, the medullary canal is absent. The best device to stabilize corrective osteotomies seems to be the cervico-diaphyseal intramedullary nail, but the surgical technique may be difficult, because of the absence of the medullary canal and the high risk of bleeding.

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INTRODUCTION

Fibrous dysplasia of bone is an uncommon hereditary genetic skeletal disorder, characterized by the replacement of the bone marrow organ with a tissue formed by pre-osteogenic fibroblast-like cells and trabeculae of immature bone. The disease is due to a sporadic, congenital mutation that causes an increased synthesis of the G protein, a factor stimulating the mitosis of pre-osteoblastic cells, with the consequence that only some pre-osteoblastic cells reach a more mature stage. These immature pre-osteoblastic cells form thin bone trabeculae with structural anomalies and poor mineralization, causing bone fragility with possible deformities and fractures[1-3]. The disease was first defined as polyostotic fibrous dysplasia (PFD) by Lichtenstein in 1938, and subsequently Lichtenstein and Jaffe in 1942 described the clinical, radiographic, and histological aspects of the disease[3]. There are monostotic and polyostotic forms (PFD) that may be associated with cafè-au-lait skin spots and hyperfunctioning endocrine disorders in the McCune-Albright syndrome (MAS) or with intramuscular myxomas in the Mazabraud's syndrome. In MAS, the most frequent endocrinopathies including precocious puberty, hyperthyroidism, growth hormone excess, rickets, and osteomalacia amongst others[4]. PFD and MAS commonly affect the femur and tibia, causing deformities and fractures; however, other bones including the spine and the craniofacial bones may also be affected[4-6]. The proximal third of the femur represents the site where the most difficult deformities that require surgical correction are located, such as coxa vara and shepherd's crook deformity, sometimes associated with deformities of the diaphysis or of the distal part of the femur. A classification of femoral deformities has recently been proposed[7]. Surgical correction of femoral deformities in patients with PFD or MAS is a challenge, since the fibrodysplastic bone is much weaker and more vascularized than the normal bone and, in the most severe form, the medullary canal is completely absent. To stabilize corrective osteotomies performed in PFD, a cervico-diaphyseal interlocking intramedullary nail may be preferred, because failures are very likely to occur with either screw or blade plates. However, in some deformities, such as isolated coxa vara, screw or blade plate remain the most appropriate devices for stabilizing corrective valgus osteotomy[8-10]. Curettage and bone grafting, both with allograft and autograft, have been commonly used in PFD. However, this treatment usually fails, since no retention of any graft material has been observed over time, as reported in long-term follow-up studies[11,12].

The aim of our study was to analyze a series of papers published from 1987 to 2019, to identify the correct indications for surgical treatment of femoral deformities in patients with PDF, the effectiveness over time of the different corrective osteotomies performed, and finally the best devices to better stabilize the fibrodysplastic bone.

MATERIALS AND METHODS

Inclusion and exclusion criteria were formulated according to the population, intervention, comparator, outcome (PICO) method and are summarized in Table 1[13].

Search strategy and sources of information: authors of this review (GG, AC, LN, FDM, PF) performed a literature search about the topic by querying Medline database, Scopus and Web of Science (WOS). Studies were located by searching the database *via* Pubmed, Scopus and WOS. The search strategy covers PICO and was performed independently by each author on March 2021. Keywords and Medical Subject Headings (MeSH) terms were identified by a preliminary search and selected by discussion. The

Table 1 Inclusion and exclusion criteria (population, intervention, comparator, outcome)

	Inclusion criteria	Exclusion criteria
Population	(1) Patients affected by polyostotic fibrous dysplasia or MAS; and (2) Patients affected by femoral deformities	(1) Patients affected by monostotic fibrous dysplasia; (2) Patients affected by PFD or MAS originally treated for fractures or impending fractures; (3) Patients affected by other kind of dysplastic pathologies as fibrocartilaginous dysplasia; and (4) Patients treated for deformities caused by PFD but not affecting femur
Intervention	(1) Osteotomies; and (2) Internal fixation by intramedullary nailing	(1) External fixation only; (2) Bone grafting or transplantations techniques only; and (3) Other surgical techniques
Comparison group	Internal fixation by peripheral plate	Not applicable
Outcome	Studies reporting clinical, radiographic evaluation	Not applicable
Time	Studies published from any date to 2021	Not applicable
Study type	(1) Cohort studies; (2) Case-control studies; and (3) Randomized control trials	(1) Letters; and (2) Case reports
Language	English	Other languages

MAS: McCune-Albright syndrome; PFD: Polyostotic fibrous dysplasia.

search was conducted using the following keywords and their synonyms, assembled in various combination to obtain most pertinent articles: PFD, fibrous dysplasia, MAS, femoral deformities, intramedullary nailing, surgical treatment, surgical procedure. The following is the list of all of the terms used and the Boolean operators used to combine them: (("Fibrous Dysplasia of Bone" [Mesh] OR "Fibrous Dysplasia, Polyostotic" [Mesh] OR "Fibrous Dysplasia, Monostotic" [Mesh] OR "Mc CUNE-ALBRIGHT SYNDROME" [Title/Abstract]) AND (("Surgical Procedures, Operative" [Mesh] OR "surgical" [Title/Abstract]) OR (((("fracture fixation, intramedullary" [MeSH Terms] OR ("fracture" [All Fields] AND "fixation" [All Fields] AND "intramedullary" [All Fields]) OR "intramedullary fracture fixation" [All Fields] OR ("intramedullary" [All Fields] AND "nailing" [All Fields]) OR "intramedullary nailing" [All Fields])))) OR "intramedullary" [All Fields] OR "nailing" [All Fields])) AND ("femur" [Title/Abstract] OR "femoral" [Title/Abstract] OR "Femur" [Mesh])) OR ((("surgical procedures, operative" [MeSH Terms] OR ("surgical" [All Fields] AND "procedures" [All Fields] AND "operative" [All Fields]) OR "operative surgical procedures" [All Fields] OR ("surgical" [All Fields] AND "treatment" [All Fields]) OR "surgical treatment" [All Fields]) OR ((((("fracture fixation, intramedullary" [MeSH Terms] OR ("fracture" [All Fields] AND "fixation" [All Fields] AND "intramedullary" [All Fields]) OR "intramedullary fracture fixation" [All Fields] OR ("intramedullary" [All Fields] AND "nailing" [All Fields]) OR "intramedullary nailing" [All Fields])))) OR "intramedullary" [All Fields] OR "nailing" [All Fields])) AND ("femur" [All Fields] OR "femoral" [All Fields] OR "femur" [MeSH Terms] OR "femur" [All Fields] OR "femoral" [All Fields]) AND ("abnormalities" [MeSH Subheading] OR "abnormalities" [All Fields] OR "deformities" [All Fields] OR "congenital abnormalities" [MeSH Terms] OR ("congenital" [All Fields] AND "abnormalities" [All Fields]) OR "congenital abnormalities" [All Fields] OR "deformity" [All Fields] OR "deform" [All Fields] OR "deformabilities" [All Fields] OR "deformability" [All Fields] OR "deformable" [All Fields] OR "deformably" [All Fields] OR "deformation"[All Fields] OR "deformational" [All Fields] OR "deformations" [All Fields] OR "deformative" [All Fields] OR "deformed" [All Fields] OR "deforming" [All Fields] OR "deforms" [All Fields]) AND ("fibrous dysplasia, polyostotic" [MeSH Terms] OR ("fibrous" [All Fields] AND "dysplasia" [All Fields] AND "polyostotic" [All Fields]) OR "polyostotic fibrous dysplasia"[All Fields] OR ("polyostotic"[All Fields] AND "fibrous" [All Fields] AND "dysplasia" [All Fields]))) OR ((("surgical procedures, operative" [MeSH Terms] OR ("surgical" [All Fields] AND "procedures" [All Fields] AND "operative" [All Fields]) OR "operative surgical procedures" [All Fields] OR ("surgical" [All Fields] AND "treatment" [All Fields]) OR "surgical treatment" [All Fields])) OR ((((("fracture fixation, intramedullary" [MeSH Terms] OR ("fracture" [All Fields] AND "fixation" [All Fields] AND "intramedullary" [All Fields]) OR "intramedullary fracture fixation" [All Fields] OR ("intramedullary" [All Fields] AND "nailing" [All Fields]) OR "intramedullary nailing" [All Fields])))) OR "intramedullary" [All Fields] OR "nailing" [All Fields]) AND ("femur" [All Fields] OR "femoral" [All Fields] OR "femur" [MeSH Terms] OR "femur" [All Fields] OR "femoral" [All Fields]) AND ("fibrous dysplasia, polyostotic" [MeSH Terms] OR ("fibrous"[All Fields] AND "dysplasia" [All Fields] AND "polyostotic" [All Fields]) OR "polyostotic fibrous dysplasia" [All Fields] OR ("polyostotic" [All Fields] AND "fibrous" [All Fields] AND "dysplasia" [All Fields]))).

No publication date filter was applied to select articles and review articles. Language restriction was applied to identify only English articles. In addition, a manual search was performed of the references cited in the studies included.

The reviewers (GG, AC, LN, FDM, PF) retrieved the data and independently analyzed each selected study; instances of disagreement were resolved by the senior investigator (PF).

The articles were screened for the presence of the following inclusion criteria: patients affected by PFD or MAS; patients affected by femoral deformities (coxa vara, shepherd's crook deformity, *etc.*); patients surgically treated by corrective osteotomies and internal fixation; studies providing an adequate level of evidence, including retrospective studies; availability of full text. The studies were excluded if they provided information regarding: patients affected by monostotic fibrous dysplasia or affected by different dysplastic pathologies as fibrocartilaginous dysplasia; patients affected by PFD but originally treated for fractures; patients treated for deformities caused by fibrous dysplasia that did not affect the femur; and patients treated exclusively with external fixation or bone grafting or transplantation techniques.

Figure 1 shows the flowchart for study selection.

RESULTS

The initial search produced 146 studies from the Medline database, 28 studies from Scopus and 10 from WOS, for a total of 184 papers. After a first screening, we eliminated 21 duplicates. Of the remaining 163 studies, after a detailed evaluation based on inclusion and exclusion criteria, articles were screened and only 14 studies fulfilled the eligibility criteria of our study. The other studies were excluded for the following reasons: 4 included monostotic forms, 5 included fractures or impending fractures, 27 included different type of dysplasia or other pathologies, 6 included deformities not affecting femur, one included patients treated by external fixation, 7 included patients treated by curettage and bone grafting, 14 included patients non surgically treated, 20 included patients treated with other surgical techniques, 26 studies were case reports, and 39 articles were published in a different language other than in English. After screening the references by reading the full-text studies included, we added one more article. In conclusion, a total of 15 articles were enrolled in the present review (Table 2).

All of the selected articles were published from 1987 to 2019 and included 111 patients overall (136 femurs). Table 2 presents a list of the studies, summarizing the number of patients and femurs, type of deformity, age at surgery, surgical technique performed, length of follow-up, results and conclusions.

DISCUSSION

The femur is the most common skeletal segment affected in PFD with a high incidence of severe deformities, especially of the proximal part of the bone, which may cause a progressive and disabling condition[2]. The most frequent deformities are represented by coxa vara and shepherd's crook deformity that, in severe cases, may be associated[3]. Treatment of these deformities is challenging; surgery based on curettage and bone grafting are usually inadequate in symptomatic lesions of the femur, especially in polyostotic form and skeletally immature patients. This treatment generally fails with a high percentage of relapses of the deformity and requires internal fixation in order to achieve satisfactory result[12].

Freeman *et al*[14] first reported the results obtained in a series of four patients affected by PFD (six femurs) treated by multiple osteotomies and fixation using a Zickel intramedullary nail. The authors concluded that in complex deformities of the femur, Zickel nail applied after multiple corrective osteotomies, provides a good control of the deformity, and allows the patients to return to normal activities. In fact, this cervico-diaphyseal device gives a good stabilization of the entire skeletal segment including the femoral neck through the screw inserted into the femoral head. The same authors stated that internal fixation with peripheral plate avoids prolonged immobilization, but a progression of the deformity often occurs, with a high risk of fracture below the plate. Ten years later, some authors[15] reported a long term-follow-up study on eight patients (7 PFD and 1 MAS) with an average age at diagnosis of 8.4 years and an average follow-up of 19.5 years. Of these patients, only two were operated on at 7 years and 5 years of age respectively, by valgus osteotomy for coxa vara, twice in one case. However, in both children the deformity continued to progress until puberty. Over 80% of patients younger than 18 years, treated by curettage and bone grafting, have an unsatisfactory result[12]. In the subsequent decade, other authors[16-19] reported the results of treatment of four series of patients affected by femoral deformities caused by PFD or MAS, with 24 patients overall (9 PFD and 15 MAS) with 37 femurs involved. The authors performed one or multiple femoral osteotomies stabilized with an intramedullary rigid nail. In some cases, curettage and bone grafting and cryosurgery or medical treatment with bisphosphonates was used in concomitance. Most of the patients were surgically treated in adolescence and followed up at least 2 years after surgery. Better results were obtained using a cervico-diaphyseal nail that Freeman *et al*[14] had proposed many years earlier, which allows a good stabilization of the femoral neck that in PFD represents an anatomical site where the bone is particularly weak. In fact, some of these authors[18], using an elongating intramedullary rod, without stabilization of the femoral neck in a younger series of patients, observed at follow-up, a progressive coxa vara in

Table 2 Summary of literature data on surgical treatment of femoral deformities in polyostotic fibrous dysplasia and McCune-Albright syndrome

Ref.	Patients (femurs)	Type of deformities	Mean age at surgery	Surgical treatment	Length of follow-up	Results	Complications	Conclusions
Freeman *et al*[14], 1987	4 (6)	Complex	14.5 yr	Multiple osteotomies and fixation with Zickel nail	2.8 yr	Patients return to normal activities	Intraoperative fracture (1), Respiratory distress syndrome (1), Delayed union (1)	Definitive control of deformities and recurrent fracture
Ozaki *et al* [15], 1996	8 (11)	Coxa vara, Shepherd's crook deformity	6 yr	Valgus osteotomy in 2 cases + curettage and bone grafting	19.5 yr	Deformities continue to progress until puberty	None	The lesions stop progressing after puberty, with the change in activity of pathologic tissue from childhood to adult life
Keijser *et al* [16], 2001	7 (10)	Complex	14.5 yr	Several corrective osteotomies + curettage, cryosurgery and grafting with definitive I.M. fixation	6 yr	Progression of the deformities in patients with MAS	None	Functional outcomes of extended lesions are satisfactory although some lesions need multiple procedures
Ippolito *et al*[17], 2002	7 (10)	Complex	17 yr	Single or multiple osteotomies and fixation with UFN nail with spiral blade	2 yr	All patients were painless and able to walk, one with brace and another with crutches	Delayed union (1)	Provide mechanical support to the weak and fragile dysplastic bone through intramedullary nailing
O'Sullivan *et al*[18], 2002	5 (10)	Complex	8.6 yr	Elongating intramedullary rods + biphosphonates	> 2 yr	Improvement of quality of life, decreasing pain and fracture rate and improving walking ability	None	Elongating rod without stabilization of the femoral neck is effective but doesn't prevent coxa vara
Jung *et al* [19], 2006	5 (7)	Shepherd's crook deformity	24 yr	Multiple osteotomies and I.M. nailing with neck cross pinning	2.5 yr	All patients were able to return to normal activities of daily living	Loosening of the distal locking screw (1)	Good correction of progressing shepherd's crook deformity and prevention of recurrences and fractures
Yang *et al* [20], 2010	7 (8)	Coxa vara, Shepherd's crook deformity	22.7 yr	Valgus osteotomy, curettage, massive allograft and I.M. nailing with neck cross pinning	6.2 yr	Correction of coxa vara from 75° to 120°. No progression of deformity	None	The device represents the first choice of internal fixation, improving limb function and preventing fractures. Good incorporation of allografts
Li *et al* [21], 2013	12 (12)	Coxa vara, Shepherd's crook deformity	14.3 yr	Valgus osteotomy stabilized by DHS plate	1.5 to 10.6 yr	Correction of coxa vara from 89° to 129°	Fracture below the plate (1)	Restore the neck-shaft angle and the mechanical alignment of the femur and improve function
Kushare *et al*[22], 2014	5 (5)	Coxa vara, Shepherd's crook deformity	21.6 yr	Valgus osteotomy stabilized with different devices (plate, I.M. nail, E.F.)	2.2 yr	Satisfactory in 3 patients and unsatisfactory in 2 for persistent pain	Loosening of External Fixator (1)	I.M. implants with neck cross pinning are the preferable method of stabilizing osteotomies in shepherd's crook deformities
Ippolito *et al*[23], 2015	11 (12)	Complex	14 yr	Two stages: (1) Valgus osteotomy for correction of coxa vara and hip plate; and (2) Definitive fixation by I.M. nail with spiral blade	4.5 yr	Neck-shaft angle and shepherd's crook deformities were fully corrected	Cut out of the spiral blade (2), Plate's screw loosening (1), Fracture below the plate (1)	Restore femoral alignment, pain relief and gait improvement, avoiding complications related to peripheral plates
Benedetti *et al*	5 (8)	Complex	6 yr	Valgus osteotomy	3 yr	Correction of	Nail breaking	Proximal humeral nail

[24], 2015				stabilized by I.M. nail with spiral blade		deformities in all cases. Loss of coxa vara correction in 2 cases. Nail breakage in one case	below the spiral blade (1)	connected to a spiral blade may represent a useful device to fix deformities in PFD in young children
Hefti *et al* [25], 2017	13 (15)	Shepherd's crook deformity	14.5 yr	Corrective osteotomy stabilized by a custom made retrograde intramedullary nail	4.5 yr	Most patients were pain free. All patients but one were able to walk, 3 of them with crutches	Nail breaking (1), Screw penetration into the acetabulum (1), Proximal screw migration (1)	This new operative method corrects and stabilizes severe difficult deformities. The operation is technical demanding requiring a careful ability to manage significant blood loss
Majoor *et al*[27], 2018	6 (6)	Shepherd's crook deformity	15.7 yr	Corrective osteotomy stabilized by angle blade plate or I.M. nail (1 case), plus grafting in 3 cases	11.2 yr	No significant change of the femoral neck shaft angle	Fractures of the distal part of the plate (2)	PDF deformities can be adequately and safety treated with angled blade plates. Based on literature review, they propose an individu-alized patient-tailored approach
Fang *et al* [26], 2018	6 (6)	Shepherd's crook or complex deformity	25.8 yr	Corrective osteotomy stabilized with I.M. nail (PFNA) plus curettage and grafting	3 yr	All patients except one had satisfactory functional and radiologic results	Cut out of the spiral blade (1)	Internal fixation with I.M. nail plus curettage and bone grafting is recommended for treating large lesions with deformity
Wan *et al* [28], 2019	10 (10)	Shepherd's crook deformity	31.2 yr	Corrective osteotomy stabilized by DHS plate or I.M. nail (3 cases) plus PMMA augmentation in 5 cases	2.8 yr	Correction of coxa vara from 88.1° to 128.5°. Longer operating times and greater blood loss in I.M. nailing	Wound superficial infection (1)	3D printing osteotomy templates facilitate the correction of shepherd's crook deformity. DHS plus PMMA yields excellent results

DHS: Dynamic hip screw; I.M.: Intramedullary; MAS: McCune-Albright syndrome; PFD: Polyostotic fibrous dysplasia; PMMA: Polymethyl methacrylate.

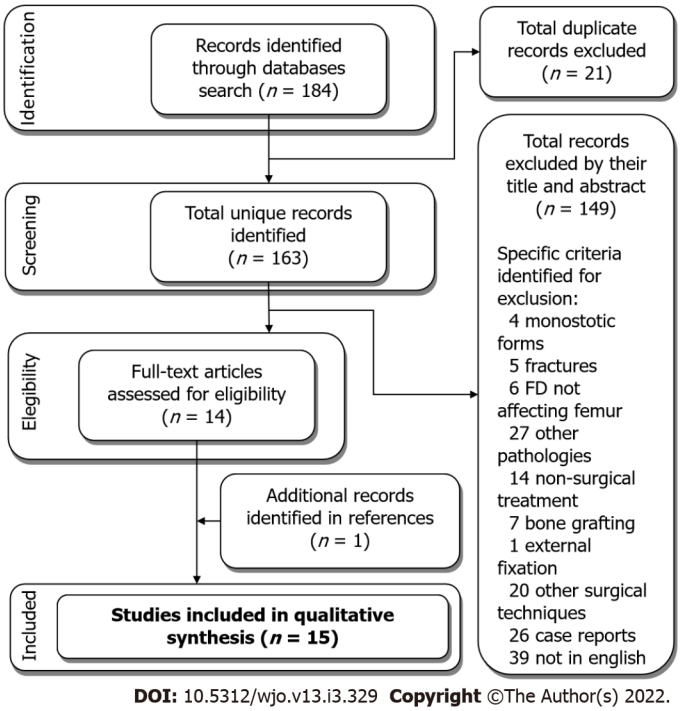

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Figure 1 Flow diagram of the search process.

half of their patients. The main intraoperative technical problems reported in these studies were the difficulty to ream a new medullary canal through the fibrodysplastic bone and the considerable amount of blood loss. Some authors[16] were forced to stop surgery for the massive bleeding observed during exposure of the proximal femur. From 2010 to 2015, we selected five studies on the surgical treatment of PFD or MAS femoral deformities in five corresponding series of patients with coxa vara and shepherd's crook deformity[20-24]. Some authors[20] suggested correcting the deformity by valgus osteotomy or medial displacement valgus osteotomy and stabilizing it by an intramedullary nail with neck cross pinning associated to curettage and massive impaction allograft. They reported a series of 7 patients with PFD (8 femurs) in adolescent or adult age, followed up 6.2 years after surgery, obtaining a mean correction of the coxa vara from 75° to 120°. By contrast, other authors[21] suggested to stabilize the corrective valgus osteotomy by a dynamic hip screw-plate without grafting. They reported a series of 12 patients with PFD (12 femurs), of average age similar to the previous study, and a length of follow-up from 1.5 years to 10.6 years, with an improvement of the neck-shaft angle from 89° to 129°. One of these patients had a fracture below the plate and he was reoperated, stabilizing the femur by an intramedullary nail with a neck cross screw. To avoid this complication, the remaining authors[22-24] preferred to stabilize the corrective osteotomy by a cervico-diaphyseal intramedullary nail. Other possible devices are not recommended, such as the external fixator used by Kushare *et al*[22] that reported a failure of treatment for an early loosening of the hardware which had to be removed. The same authors reported that the additional procedures as curettage and bone grafting using autograft, allograft or calcium sulfate are questionable, because none of their patients had complete radiographic resolution of the fibrodysplastic lesion[22]. Ippolito *et al*[23] first proposed to treat these complex femoral lesions by a two-stage surgical treatment: The first stage was performed by correction of the coxa vara and fixation with a hip plate, while the second stage, by correction of a shepherd's crook deformity and a definitive fixation with a cervicodiaphyseal nail connected to a spiral blade. The second stage procedure was performed as soon as the valgus osteotomy had healed. The authors reported a series of 11 patients (12 femurs) with a mean age of 14 years, followed up after an average of 4.5 years after the second stage procedure. They concluded that the proposed treatment restored a satisfactory femoral alignment with pain relief and gait improvement, avoiding all the complications related to the peripheral plate. The same authors in another study[24] which involved 5 children (8 femora), aged from 4 years to 7 years, proposed to use intramedullary nailing also in young patients, using a custom-modified adult humeral nail 7-mm thick with a spiral blade. They concluded that this device may represent a useful method of treatment in fixing femoral deformities in young children with PFD.

Regarding the most recent literature, two studies[25,26] recommended stabilizing the corrective osteotomy of the classic shepherd's crook deformity using an intramedullary nail, while two other studies[27,28], suggested an angle blade plate or a dynamic hip screw plate, adding bone graft or polymethyl methacrylate. Of the first two papers (overall 19 patients, 21 femurs), Hefti *et al*[25], introduced a new type of custom made retrograde intramedullary nail, reporting 15 operated femurs followed up 4.5 years after surgery, with satisfactory results, although the surgical technique is demanding with significant blood loss. By contrast, the other two studies reported a total of 16 patients (16 femurs), in which the deformities were stabilized with plates; 10 patients were followed up after more than 10 years. They concluded that all the corrections obtained were stable over time, although in two cases, a fracture of the distal part of the plate occurred. Wan *et al*[28], underlined that using the plate instead of the intramedullary nail reduced operation time and blood loss.

According to our review, we believe that isolated coxa vara should be corrected by an osteotomy and stabilized with a peripheral plate, while isolated shepherd's crook deformity should be treated by multiple osteotomies and stabilized by a cervicodiaphyseal intramedullary nail. Complex deformities in which coxa vara is associated to shepherd's crook deformity should be treated by two staged procedures.

The main strength of this review is the topic, as PFD and MAS are uncommon disease that, especially when they are presented in severe form, are difficult to manage. The main limitation lies in the papers included in the review, as they are all retrospective studies without a control group. Further studies are needed to address points that remain controversial in the treatment this disease.

CONCLUSION

In conclusion, we believe, in accordance with the majority of the authors, that correction of coxa vara and shepherd's crook deformity as well as the other deformities of the femur when it is entirely involved, remains a demanding procedure and, especially in severe cases, more than one operation is necessary. Intramedullary nailing is often preferred to stabilize osteotomies performed in fibrodysplastic bone, while peripheral plating remains the device of choice to stabilize osteotomies performed for coxa vara. The use of cancellous or cortical bone graft in addition to corrective osteotomy is still controversial. Significant blood loss represents a surgical problem, which must be kept in mind during the operation by the surgeon and the anesthesiologist, especially in patients affected by MAS with complex deformities. High X-ray exposure for both the patient and surgeon must also be considered.

ARTICLE HIGHLIGHTS

Research background

Surgical correction of femoral deformities in polyostotic fibrous dysplasia (PFD) or McCune-Albright syndrome (MAS), such as coxa vara or shepherd's crook deformity, is a challenge. Different surgical fixation devices have been described in the past.

Research motivation

No common consensus on the optimal surgical treatment for this pathology among orthopedic surgeons is present.

Research objectives

The aim of our study was to identify the correct indications for surgical treatment of femoral deformities in patients with PDF and MAS, the effectiveness over time of the different corrective osteotomies performed and the best devices to better stabilize the fibrodysplastic bone.

Research methods

A review of English language literature from 1987 until now was performed following the population, intervention, comparator, outcome guidelines.

Research results

Fifteen articles were included for qualitative synthesis in the study after the initial screening resulted in 184 papers.

Research conclusions

Correction of coxa vara and shepherd's crook deformity remains a demanding procedure and, especially in severe cases, more than one operation is necessary. Intramedullary nailing is often preferred to stabilize osteotomies performed in fibrodysplastic bone, while peripheral plating remains the device of choice to stabilize osteotomies performed for coxa vara.

Research perspectives

High-quality prospective randomized clinical trials are needed.

FOOTNOTES

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