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EDITORIAL

Choosing ankle tourniquets in foot and ankle surgery: Beyond postoperative pain considerations

Samir Ghandour, Vijay Kumar Jain, Ashim Gupta

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Abstract

This editorial critically explores the use of ankle *vs* thigh tourniquets in foot and ankle surgery based on a recent study that found no significant difference in postoperative pain between the two placement techniques. Despite these findings, we argue for the preferential use of ankle tourniquets, highlighting their potential benefits in reducing venous blood stasis and minimizing soft tissue injury. This approach underscores the importance of considering long-term patient outcomes and vascular health beyond immediate postoperative pain. By integrating study findings with broader clinical considerations, we hereby advocate for a nuanced approach to tourniquet use that prioritizes patient safety and long-term recovery in conjunction with immediate postoperative pain.

Key Words: Lower extremity; Deep venous thrombosis; Recovery; Postoperative outcomes; Intraoperative decision-making

Core Tip: This editorial advocates for the selection of ankle tourniquets in foot and ankle surgery. While ankle tourniquets do not significantly reduce postoperative pain compared to thigh tourniquets, ankle tourniquets may minimize lower extremity venous stasis and soft tissue compression, especially in high-risk patients, which can enhance long-term vascular health and promote uneventful patient recovery.

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INTRODUCTION

The recent study titled "Effect of ankle versus thigh tourniquets on post-operative pain in foot and ankle surgery" presents important findings investigating tourniquet use in orthopedic procedures[1]. While the study, conducted on 201 patients undergoing foot and ankle surgery, concludes that there is no significant correlation between the site of tourniquet application (ankle *vs* thigh) and immediate postoperative pain scores, it opens the door to a broader discussion on the choice of tourniquet placement[1]. This editorial aims to delve into why, despite the study's findings, choosing an ankle tourniquet might be preferable in certain surgical scenarios, particularly to mitigate venous blood stasis in the leg and soft tissue injury, especially in procedures of longer duration and at-risk patients.

TOURNIQUET

The use of tourniquets in surgery is a long-standing practice primarily aimed at providing a bloodless field for optimal surgical visibility and reducing intraoperative blood loss[2]. However, the choice of tourniquet placement has varied, with some surgeons preferring the thigh for its ease of application and perceived patient comfort, while others opt for the ankle to localize pressure effects[3-5]. This study's finding of no significant correlation between tourniquet site and postoperative pain intensity might initially suggest that the choice of tourniquet location is inconsequential concerning pain management. Yet, this view overlooks other crucial factors, such as the potential risk of venous blood stasis, limb ischemia in patients with compromised vascular health, and associated complications[4].

Venous stasis, the stagnation of blood flow in the veins, is a known risk factor for deep vein thrombosis (DVT) and other vascular complications[6]. When a tourniquet is applied to the thigh, it exerts pressure over a larger area and encompasses major blood vessels, potentially increasing the risk of venous blood pooling and stasis in the entire leg. This is especially concerning in patients with pre-existing vascular conditions or those at higher risk for DVT. In contrast, an ankle tourniquet applied over the supramalleolar region localizes the pressure to a smaller area distal to the calf, reducing the risk of venous stasis in the leg.

Moreover, the study's methodology, while robust in its approach, does not specifically address the long-term vascular implications of tourniquet placement. The focus on immediate and short-term postoperative pain, while clinically relevant, does not encompass the broader spectrum of potential complications arising from tourniquet use, especially in patients who are immobilized for long periods of time postoperatively, with a history of DVT or suffer from peripheral vascular disease. Notably, prolonged tourniquet ischemia following thigh tourniquet use in patients with compromised extremity blood supply may lead to post-tourniquet syndrome, tissue edema, and even compartment syndrome[7]. Therefore, when interpreting the study's findings, surgeons should consider these unaddressed aspects and weigh them against the immediate postoperative pain outcomes.

It is also essential to consider the anatomical and physiological aspects of tourniquet application. With its larger circumference, the thigh often requires higher tourniquet pressures to achieve effective blood occlusion[3,4]. This increased pressure can contribute to more extensive tissue compression and potential damage[8,9]. On the other hand, the ankle, with its smaller circumference, may require lower pressures, thereby potentially reducing the overall risk of tissue injury and complications associated with high-pressure tourniquet application. Such phenomena may be better elucidated by the use of emerging computational analytical technologies, such as finite or discrete element analysis that has enabled researchers to better understand the biomechanical implications of extrinsic and intrinsic forces on anatomical structures[10]. However, to our knowledge, there is little to no computational evidence in the literature investigating the effects of tourniquet use, particularly on the ankle and thigh.

Further, the effect of ankle tourniquet placement on the rate of postoperative wound healing, surgical success, and infection rates must be studied. Some experts have recommended against the use of tourniquets for certain surgeries. For example, a study by Konrad *et al*[11] found that using a tourniquet during open reduction and internal fixation of ankle fractures increased postoperative swelling and pain, reporting a trend toward decreased range of motion in the ankle during follow-up. As a result, they do not recommend the use of a tourniquet for osteosynthesis of ankle fractures, citing the potential for increased complications such as wound healing disturbances and infections. Therefore, the evaluation of the impact of ankle tourniquets on both closed and open-foot fractures for different surgical procedures is also a critical area for future research, adding more depth to the conversation regarding the effects of tourniquet use and its placement for foot and ankle surgery.

CONCLUSION

In conclusion, while the study "Effect of ankle versus thigh tourniquets on post-operative pain in foot and ankle surgery" provides valuable insights into the relationship between tourniquet placement and postoperative pain[1]. The choice of tourniquet placement site must consider other patient-specific variables. The potential benefits of using an ankle tourniquet, particularly in reducing the risk of venous blood stasis and its complications, merit serious consideration. As with all surgical decisions, the choice of tourniquet placement should be tailored to each patient, considering both the immediate and long-term implications for patient health and recovery.

FOOTNOTES

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EDITORIAL

Evolution of treatment options for juvenile idiopathic arthritis

Tao Ren, Jia-Hui Guan, Yu Li, Nan-Nan Li, Zheng Li

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Abstract

A recent study published in *World J Clin Cases* addressed the optimal non-steroidal anti-inflammatory drugs (NSAIDs) for juvenile idiopathic arthritis (JIA). Herein, we outline the progress in drug therapy of JIA. NSAIDs have traditionally been the primary treatment for all forms of JIA. NSAIDs are symptom-relief medications, and well tolerated by patients. Additionally, the availability of selective NSAIDs further lower the gastrointestinal adverse reactions compared with traditional NSAIDs. Glucocorticoid is another kind of symptom-relief medications with potent anti-inflammatory effect. However, the frequent adverse events limit the clinical use. Both NSAIDs and glucocorticoid fail to ease or prevent joint damage, and the breakthrough comes along with the disease-modifying antirheumatic drugs (DMARDs). DMARDs can prevent disease progression and reduce joint destruction. Particularly, the emergence of biologic DMARDs (bDMARDs) has truly revolutionized the therapeutics of JIA, compared with conventional synthetic DMARDs. As a newly developed class of drugs, the places of most bDMARDs in the management of JIA remain to be well established. Nevertheless, the continuous evolution of bDMARDs raises hopes of improving long-term disease outcomes for JIA.

Key Words: Juvenile idiopathic arthritis; Treatment; Non-steroidal anti-inflammatory drug; Disease-modifying antirheumatic drug; Evolution

Core Tip: In past decades, the pharmacological treatments for juvenile idiopathic arthritis (JIA) have undergone a dramatic evolution from non-steroidal anti-inflammatory drugs to disease-modifying antirheumatic drugs (DMARDs), especially the emergence of biologic DMARDs enable patients with refractory JIA to achieve disease remission. This editorial focuses on the progress in treatment options for JIA. We hope that this editorial could provide valuable information for use of anti-JIA drugs.

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) refers to a broad term characterizing all forms of arthritis occurred in children before 16 years of age. JIA is a common autoimmune disease and a leading cause of childhood disability[1]. As a heterogeneous group of arthritis, JIA may subside with age, or, often extend chronic disease and inflammation of the joints throughout middle age in a significant proportion of patients[2,3]. Clinical manifestations of JIA include joint pain, swelling and stiffness. Moreover, it usually accompanies other systemic symptoms of flaccid fever, rash, and enlargement of liver, spleen and lymph nodes[4,5].

The goal of treatment is to control disease activity and prevent complications. Current treatment options include non-pharmacological and pharmacological interventions. Non-pharmacological interventions, such as psychological rehabilitation and exercise, are indispensable and helpful to foster the normal psychosocial and social development of the child and to keep or restore joint function and normal mobility[6,7]. Pharmacological interventions are the mainstay in the management of JIA. The therapeutic strategies have evolved markedly, owing to the availability of a growing number of specific and potent medications. Herein, we specifically discuss the progress of pharmacological treatments for JIA.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) have traditionally been the mainstay treatment for all forms of JIA. Although the era of biological targeted therapy comes, NSAIDs are still suggested as first-line therapy[8]. NSAIDs work by blocking cyclooxygenase (COX) synthesis to exert analgesic and anti-inflammatory effects[9]. They can alleviate joint pain, swelling, stiffness and fever, but have no effects on joint damage. NSAIDs are well tolerated by children with few side-effects. Moreover, the availability of COX-2 selective inhibitors further lowers the adverse reactions compared with traditional NSAIDs[10]. The most common traditional NSAIDs for JIA include naproxen and ibuprofen, while celecoxib and rofecoxib are frequently used selective NSAIDs[11]. However, the comparative effectiveness and safety between different NSAIDs remains inconclusive. Although two studies suggested the superiority of celecoxib in effectiveness and rofecoxib in safety over other NSAIDs[12,13], these findings still need to be confirmed by solid evidence. Noticeably, the duration of NSAID monotherapy for more than 2 months is discouraged if arthritis is still active[14].

GLUCOCORTICOID

Glucocorticoid is another kind of symptom-relief medication that can exert rapid and potent anti-inflammatory effect. Glucocorticoid is necessary when NSAIDs fail to provide desired efficacy. Intra-articular injection of glucocorticoid is the main treatment for monoarticular or oligoarticular JIA without systemic symptoms[15]. This topical therapy is very helpful for preventing deformities that occur after chronic arthritis. Triamcinolone hexacetonide is preferred for intra-articular injection, since it offers a more durable clinical response than the other available glucocorticoids[16]. Systemic glucocorticoid is usually restricted to systemic JIA with extra-articular manifestations[7]. Prednisone is often the drug of choice for oral administration. However, the adverse events (*e.g.*, growth retardation, infection, and osteoporosis) limit the prolonged use of glucocorticoid at large dose[17].

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Conventional synthetic disease-modifying antirheumatic drugs

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are usually used in the initial therapy of polyarthritis, and in the case of inadequate efficacy from first-line treatment for oligo-arthritis[16]. The introduction of methotrexate (MTX) was a significant milestone in csDMARDs[18]. MTX exerts long-acting anti-inflammatory effects mainly through inhibition of interleukin (IL)-1 production[19]. Owing to its sustained effectiveness and acceptable toxicity, MTX remains the first choice second-line drug for JIA that is not controlled by NSAIDs or intra-articular corticosteroid injection[20,21]. Noticeably, prolonging MTX administration for 12 months did not yield additional benefit after the achievement of disease remission by 6 months treatment[22]. The other commonly used csDMARDs include sulfasalazine, lefunomide and cyclophosphamide, and they produce anti-inflammatory effects through different mechanisms. Leflunomide is less effective than MTX[23], but it is still an effective treatment for patients with MTX intolerance[24]. In addition, sulfasalazine is often the csDMARD of choice in patients with enthesitis-related arthritis[25].

Biologic DMARDs

The pharmacological therapeutics for JIA are still evolving, in which biologic DMARDs (bDMARDs) represent the most active and revolutionary field. bDMARDs are mainly selective inhibitors targeting one of three major pro-inflammatory cytokines (TNF, IL-1β, and IL-6). The other newly developed agents include anti-T cell-specific inhibitors, CD20 monoclonal antibodies, and Janus kinase (JAK) inhibitors. They are usually given along with MTX to patients who have an inadequate response to MXT alone.

The first bDMARD introduced to the treatment of JIA is etanercept, a recombinant human TNF-α receptor antagonist. Subsequently, other anti-TNF drugs were developed, such as infliximab, adalimumab, golimumab and certolizumab. Etanercept has been demonstrated the sustained benefits in growth velocity, bone status, and quality of life, and achieving complete disease quiescence in half of the patients[26-28]. Adalimumab is found to be highly effective in patients with or without previous treatment by other biologic agents[29]. Moreover, adalimumab achieves higher response rate than infiximab which is not approved for use in JIA[30]. Golimumab fails to exert superior efficacy over placebo in a trial and it has not yet been approved for use in JIA[31]. Certolizumab is still being evaluated by an ongoing trial. Of these drugs, only etanercept and adalimumab are authorized for use in JIA by both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Other bDMARDs that have been approved to be effective in MTX-resistant JIA include IL-1 inhibitors and IL-6 inhibitors. Canakinumab, an IL-1 inhibitor, has been approved by FDA and EMA for use in systemic JIA[32], while Tocilizumab, a monoclonal antibody against IL-6 receptor, has been approved for use in both polyarticular and systemic JIA[33,34]. Unlike the key role of TNF-α in polyarticular JIA, increasing evidence suggests that the major pathogenic cytokines in active systemic JIA are IL-1 and IL-6[35,36]. Patients with the systemic subtype of JIA generally respond well to an IL-1 inhibitor or IL-6 inhibitor, whereas an anti-TNF agent could be less effective in this subtype.

Abatacept is a selective T-cell activation blocker by targeting cytotoxic T-lymphocyte-associated antigen-4. The efficacy and safety of abatacept in JIA have been evidenced by a double-blind randomized controlled withdrawal trial, and then it is approved in the United States and Europe for JIA[37]. Rituximab is a human mouse chimeric monoclonal antibody targeting B lymphocyte (CD20). It is recommended for children with JIA who remain highly or moderately active with poor prognostic factors after sequential treatment with anti-TNF drugs and abatacept[38]. Besides, some newer drugs have been developed for the treatment of JIA, mainly JAK inhibitors, *e.g.*, tofacitinib[39], baricitinib[40] and ruxolitinib [41]. Their efficacy and safety have been established in randomized controlled trials, and some of them have already been approved for use in JIA.

CONCLUSION

Huge progress has been achieved in available medications and treatment recommendations. The pharmacological treatments have undergone a dramatic evolution from NSAIDs to DMARDs, especially bDMARDs. Although treatment of JIA remains difficult, new treatments offer valuable opportunities for some patients with refractory JIA.

FOOTNOTES

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EDITORIAL

Investigating clubfoot in Saudi Arabia: Prevalence, factors, and future directions

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Abstract

This editorial discusses the significant findings and implications of the study conducted by Alomran *et al*. This retrospective study, soon to be published, provides valuable insights into the epidemiology of and risk factors associated with clubfoot in a specific Saudi population. By highlighting the study's key outcomes and discussing its broader implications for public health and clinical practices, this editorial aims to underscore the importance of continued research and targeted interventions in addressing congenital deformities such as clubfoot.

Key Words: Clubfoot prevalence; Saudi Arabia; Congenital deformities; Retrospective study; Orthopedic epidemiology

Core Tip: This editorial highlights the critical findings from the study conducted by Alomran *et al*, which examined the prevalence of and factors associated with clubfoot in the eastern province of Saudi Arabia. The study's retrospective analysis provides valuable epidemiological data and identifies key risk factors, offering insights for health-care providers and policy-makers. By addressing the significance of these findings, this editorial underscores the need for targeted interventions and continued research to improve the management and prevention of congenital deformities such as clubfoot.

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INTRODUCTION

Clubfoot, medically known as congenital talipes equinovarus, is a prevalent congenital deformity characterized by the inward and downward twisting of the foot; it strongly affects mobility and quality of life[1]. In a recent hospital-based retrospective study, Alomran *et al*[1] extensively analyzed the prevalence of and factors associated with clubfoot in the eastern province of Saudi Arabia[1]. Their research provides crucial insights into the epidemiology and determinants of this condition within a specific regional context. Their results revealed a notable occurrence of clubfoot within the region, underscoring the public health burden of this congenital deformity[1]. This analysis informs health-care providers and policymakers regarding the effective allocation of resources to develop targeted interventions for early diagnosis and treatment. Understanding the prevalence of clubfoot is crucial in ensuring timely access to specialized care and improving long-term outcomes for affected individuals. Moreover, insights from other studies highlight the complexity of clubfoot management and its influence on patient outcomes. Gelfer *et al*[2] emphasized the high rate of relapse among patients with idiopathic clubfoot and the adverse effects of this condition on clinical and quality-of-life outcomes. Similarly, genetic studies by Charng *et al*[3] and Huang *et al*[4] have highlighted the genetic basis of clubfoot, suggesting potential avenues for personalized treatment. National register data from Sweden[5] and local experiences from pediatric tertiary centers in Abha, Saudi Arabia[6], have provided additional perspectives on treatment strategies and outcomes, highlighting regional variation and the importance of tailored health care. By integrating findings from the aforementioned studies, this editorial enhances the understanding of the multifaceted nature of clubfoot, from epidemiology and genetic predisposition to clinical management and public health implications. Such insights are pivotal in shaping comprehensive strategies aimed at improving outcomes and quality of life for individuals affected by clubfoot in Saudi Arabia and beyond.

ASSOCIATED RISK FACTORS

Identifying and understanding the risk factors associated with clubfoot are imperative for developing effective preventive strategies against clubfoot. In their study, Alomran *et al*[1] identified several key factors linked to this congenital deformity in the eastern province of Saudi Arabia. These factors are genetic predispositions, maternal health conditions, and environmental influences, all of which contribute significantly to the prevalence and severity of clubfoot in the aforementioned region. Additional studies have highlighted other critical risk factors. For instance, Johansson *et al*[5] emphasized the importance of considering maternal health and prenatal care in understanding the prevalence and outcomes of clubfoot. Insights from the CoCo study conducted by Gelfer *et al*[2] highlight the challenges associated with relapse in cases of idiopathic clubfoot; they emphasized the importance of early detection and comprehensive treatment protocols to mitigate long-term complications[2]. Genetic studies, such as those by Charng *et al*[3] and Huang *et al*[4], have identified specific genes and mutations associated with clubfoot, offering potential avenues for genetic screening and personalized therapeutic approaches. These insights underscore the need for tailored intervention strategies, particularly in populations in which the prevalence of clubfoot is high. The regional analysis conducted by Alomran *et al*[1] provides a foundation for future research and public health initiatives aimed at reducing the incidence of clubfoot through targeted education and health-care interventions. Through integration of their findings into broader health-care strategies, the complex interplay of genetic, environmental, and maternal factors contributing to the prevalence of clubfoot, both in Saudi Arabia and the world, can be effectively addressed. Overall, the comprehensive analysis of associated risk factors conducted by Alomran *et al*[1] considerably enhances our epidemiological understanding of clubfoot and can inform targeted efforts to improve early detection, intervention, and overall outcomes.

CLINICAL IMPLICATIONS AND MANAGEMENT

Alomran *et al*[1] revealed a significant prevalence of clubfoot in the eastern province of Saudi Arabia: 5.3 cases per 1000 live births (42 out of 7792 births from 2015 to 2023). This finding has several critical clinical implications for managing this

congenital condition. Early detection through routine prenatal screening and postnatal examinations is essential for effectively addressing cases of clubfoot. Early identification enables timely intervention, which is crucial for minimizing the long-term complications associated with untreated clubfoot. This aligns with the findings of Gelfer *et al*[2], which emphasize the challenges of relapse and poorer clinical outcomes in idiopathic clubfoot cases. Furthermore, Alomran *et al*[1] highlighted the necessity of standardized treatment protocols and the availability of specialized care facilities. These elements are vital for ensuring optimal outcomes and reducing the burden of disability associated with clubfoot. Standardized protocols can streamline the treatment process, making it more efficient and effective, whereas specialized care facilities ensure that patients receive the best possible treatment tailored to their needs. Genetic research also contributes substantially to the management of clubfoot. The identification of genes such as *HOXD12* (homeobox D12) opens the door to personalized treatment approaches based on genetic profiles[3]. A personalized approach can lead to more targeted and effective treatment, potentially improving the prognosis of patients with clubfoot. In summary, the findings of Alomran *et al*[1] emphasize the importance of early detection, standardized treatment protocols, and specialized care facilities and the potential of personalized treatments based on genetic research. These strategies are essential for improving clinical outcomes and managing clubfoot effectively in the eastern province of Saudi Arabia and beyond.

PUBLIC HEALTH AND POLICY CONSIDERATIONS

In the context of maternal health, Suarez *et al*[7] emphasized the significance of understanding medication risks during pregnancy because medication use during pregnancy can affect the development and severity of congenital conditions such as clubfoot. This underscores the necessity for comprehensive prenatal care that includes screening for both genetic predispositions and environmental factors that could affect fetal development. Alomran *et al*[1] advocated for a holistic approach in which clinical management is improved through early detection and intervention and health-care policies are aimed at enhancing access to specialized care and implementing effective preventive strategies. By integrating the literature findings into clinical practice, health-care providers can significantly enhance the quality of life of individuals with clubfoot. Also crucial are multidisciplinary collaboration and ongoing research to optimize outcomes. Recent studies, such as that conducted by Gelfer *et al*[2], have indicated that a considerable percentage of patients with idiopathic clubfoot experience relapse, which affects clinical outcomes and quality of life[2]. This finding underscores the need for continual follow-up and adaptive treatment strategies. Johansson *et al*[5] further reported the importance of early and standardized treatment protocols, which were shown to be effective in reducing relapse rates and improving long-term outcomes. From a public health perspective, the study by Alomran *et al*[1] underscores the imperative for comprehensive health-care policies addressing congenital deformities such as clubfoot. These findings advocate for enhancing access to prenatal and postnatal care to facilitate early detection and intervention, thereby aligning with global efforts to improve outcomes for affected individuals[2,5]. By integrating standardized screening protocols into national health programs, policymakers can promote the timely identification of clubfoot, which is crucial for initiating appropriate treatment and minimizing long-term complications[8]. Furthermore, raising awareness about clubfoot among health-care providers and the general public is essential for promoting early diagnosis and improving treatment outcomes[3]. This should include educating families about available treatment options and the importance of high adherence to therapy regimens, which can mitigate the risk of relapse and enhance quality of life[9]. Additionally, insights from genetic studies, such as the identification of *HOXD12* as a disease gene[3], underscore the potential for personalized treatment approaches based on genetic profiles, thereby optimizing clinical management strategies. Overall, the effective incorporation of these strategies into public health policies will not only support the well-being of individuals with clubfoot but also contribute to the broader health-care goals of reducing disability and improving quality of life. By prioritizing early intervention, raising awareness, and integrating specialized care into health-care systems, policymakers can mitigate the societal burden of clubfoot while enabling equitable access to comprehensive health-care services.

LIMITATIONS AND IMPORTANCE OF CLUBFOOT TREATMENT

Large strides have been made in the management of clubfoot, but several limitations and challenges remain. One major issue is the variation in treatment outcomes; approximately 37% of patients with idiopathic clubfoot experience relapse, which adversely affects clinical results and quality of life[2]. This variation underscores the need for ongoing research to refine treatment strategies and elucidate the causes of relapse. Access to specialized care is another challenge. Walani *et al*[10] emphasized the global difficulties related to congenital anomalies, including clubfoot, noting that disparities in access to surgical care and follow-up treatment can lead to delayed or inadequate management. This issue highlights the necessity for more equitable distribution of resources and improved health-care infrastructure to ensure timely and effective treatment. Adherence to treatment protocols, particularly in the Ponseti method, is crucial for achieving optimal outcomes. Research indicates that noncompliance with orthotic use is a frequent problem contributing to relapse and poor outcomes[11]. Addressing adherence challenges is vital for enhancing the success of nonsurgical treatments. Despite these limitations, the importance of effective clubfoot treatment cannot be overstated. The Ponseti method remains the gold standard for initial treatment, having been demonstrated to be effective in correcting deformities and minimizing the need for surgical interventions[3,5]. However, successful outcomes depend on early diagnosis and rigorous adherence to treatment protocols. Advancements in clubfoot management are promising. Emerging research highlights the potential of personalized treatment plans based on genetic profiles to improve patient outcomes[3,4]. Additionally, innovation

regarding surgical techniques and postoperative care is expected to enhance outcomes and reduce relapse rates[12,13]. These advancements, coupled with efforts to increase access to specialized care and support adherence to treatment, will be crucial in overcoming the current challenges and achieving better outcomes for patients with clubfoot.

FUTURE RESEARCH DIRECTIONS

The study conducted by Alomran *et al*[1] opens avenues for advancing research in the field of congenital deformities, particularly clubfoot. Future investigations must delve deeper into the intricate interaction between genetic predisposition and environmental factors that contributes to the pathogenesis of clubfoot[3]. Insights gained from genetic studies underscore the potential for elucidating underlying genetic mechanisms that influence the development and severity of clubfoot[3,4]. Moreover, longitudinal studies are needed that comprehensively evaluate the long-term efficacy and outcomes of various treatment modalities for clubfoot[2,5]. Such studies are crucial for refining existing treatment protocols and developing more personalized management strategies that cater to the diverse clinical presentations and needs of patients with clubfoot[8]. Expanding research efforts to include large-scale epidemiological studies could further enhance our understanding of the global burden of clubfoot and facilitate implementation of targeted public health interventions[9]. Such initiatives are essential for informing health-care policies aiming to improve access to specialized care, optimize treatment outcomes, and ultimately reduce the socioeconomic impact of clubfoot on affected individuals and their families[6,7]. Overall, research in genetic, epidemiological, and treatment domains is pivotal for advancing the field of clubfoot management. By utilizing multidisciplinary research approaches and fostering international collaborations, future studies can contribute to the development of innovative therapeutic strategies and improve overall patient care and outcomes.

CONCLUSION

The study conducted by Alomran *et al*[1] provides crucial insights into the prevalence of and factors associated with clubfoot in the eastern province of Saudi Arabia. This editorial highlights their findings' significance and profound implications for public health and clinical practice. Understanding the prevalence of clubfoot and identifying the associated risk factors are fundamental steps in the quest to develop targeted interventions aimed at improving patient outcomes. Continued research efforts are imperative to advance the understanding of clubfoot. Future investigations should focus on exploring the genetic underpinnings of clubfoot, as highlighted by recent studies that identified *HOXD12* as a novel disease gene[3,4]. Additionally, longitudinal studies are needed to evaluate the effectiveness of various treatment modalities and to develop personalized management strategies tailored to various patient profiles[2,5]. Enhancing early detection, treatment, and prevention strategies through collaborative efforts among health-care providers, researchers, and policymakers is essential. Clubfoot's impact on affected individuals and their families can be mitigated by addressing its genetic, environmental, and clinical dimensions. Collaborative initiatives can advance the scientific knowledge and contribute to improving health outcomes and enhancing the quality of life of individuals with clubfoot worldwide.

FOOTNOTES

Author contributions: Cheng CH conceptualized the editorial and drafted the initial manuscript; Cheng CH contributed to the interpretation of the study findings and overall discussion. Designating Hao WR and Cheng TH as co-corresponding authors reflects their significant and complementary contributions to the editorial work. Hao WR played a crucial role in developing the manuscript structure, analyzing the study's implications, and ensuring the intellectual rigor of the revisions. Cheng TH, as the primary corresponding author, coordinated the editorial process, led the final revisions, and provided expertise on the broader impact of the study on public health and clinical practices. Both authors were integral to shaping the manuscript and ensuring its quality. Their joint designation as co-corresponding authors acknowledges their equal and critical contributions to the research and editorial process. All authors have read and approved the final manuscript.

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MINIREVIEWS

Impacts of radiation therapy on quality of life and pain relief in patients with bone metastases

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Abstract

Bone metastases (BM) are a common complication in advanced cancer patients, significantly contributing to morbidity and mortality due to their ability to cause pain, fractures, and spinal cord compression. Radiation therapy (RT) is vital in managing these complications by targeting metastatic lesions to ease pain, improve mobility, and reduce the risk of skeletal-related events such as fractures. Evidence supports the effectiveness of RT in pain relief, showing its ability to provide significant palliation and lessen the need for opioid painkillers, thereby enhancing the overall quality of life (QoL) for patients with BM. However, optimizing RT outcomes involves considerations such as the choice of radiation technique, dose fractionation schedules, and the integration of supportive care measures to mitigate treatment-related side effects like fatigue and skin reactions. These factors highlight the importance of personalized treatment planning tailored to individual patient needs and tumor characteristics. This mini-review aims to provide comprehensive insights into the multifaceted impacts of RT on pain management and QoL enhancement in BM patients, with implications for refining clinical practices and advancing patient care through the synthesis of findings from various studies.

Key Words: Radiation therapy; Radiotherapy; Quality of life; Pain relief; Bone metastases; Bone cancer

Core Tip: Radiation therapy (RT) significantly alleviates pain and improves quality of life in patients with bone metastases. Optimizing RT effectiveness involves personalized treatment approaches and supportive care measures to manage side effects, enhancing overall well-being and symptom control.

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INTRODUCTION

Brief overview of bone metastasis and its impact on quality of life

Cancers are a significant global problem and may lead to severe complications like bone metastasis (BM), which can cause pain and mobility issues[1,2]. Additionally, the psychological impact of cancer can be profound, resulting in anxiety and depression for many patients[3]. Metastatic bone cancer, or secondary bone cancer, denotes the proliferation of tumors originating from other tissues and disseminating (metastasizing) to bone sites[4]. According to the American Cancer Society, about 400000 new malignant BM cases are diagnosed annually[5]. The incidence rate of BM in the United States is still unknown, with estimates varying from 21000 to 400000 per annum[6]. BM ranks as the third most prevalent site for metastatic malignancies[7]. Notably, bone represents a common locus for metastases, often signaling a short prognosis for cancer patients. Indeed, BM surpasses primary bone cancers in occurrence, particularly among adults[8]. Among cancers, prostate cancer poses the highest risk for bone metastases, trailed by lung, renal, or breast cancers. The rich arterial supply to bone predisposes it to metastatic dissemination[9,10]. Generally, the presence of BM in patients predicts a poor prognosis, with median survival ranging from 6 months to 4 years, depending on the primary cancer type [8]. It can significantly impact the quality of life (QoL), causing severe pain, impaired mobility, pathological fractures, spinal cord compression, and other complications[8,11]. It negatively affects multiple domains of QoL, including physical, emotional, social, and functional well-being[11]. Pain is a significant factor impacting QoL, but other issues like reduced activities of daily living also play an essential role[11,12]. Treatment aims to relieve pain, prevent complications, and improve overall QoL. Options include pain medications, radiation therapy (RT), surgery, and bone-targeted agents like bisphosphonates[12]. In general, a multidisciplinary approach involving oncologists, pain specialists, radiologists, orthopedic surgeons, and others is recommended for optimal management[8,12].

Introduction to radiotherapy as a treatment option for bone metastasis

RT is the predominant therapeutic approach for addressing painful bone metastases in the spine and non-spine regions. Initially, conventional low-dose external beam RT was employed for this purpose; however, stereotactic body radiotherapy (SBRT) is increasingly utilized for such cases[13]. The SBRT technique employed by Correia *et al*[14] involved a variable dosing regimen (range 24-42Gy) administered in 2 to 7 separate fractions. Other studies utilized SBRT using variable dosing regimens, ranging from 15-24 Gy in a single fraction to 24 to 50 Gy delivered over 3 to 5 fractions. These studies reported local control rates of approximately 90% with a decreased incidence of adverse effects[15]. The principal aim of RT in managing BM is to alleviate pain and enhance the QoL for patients[16]. This treatment modality assumes critical importance due to the array of challenges posed by bone metastatic disease, encompassing pain, fractures, spinal cord compression, and neurological deficits[16]. Notably, RT assumes a pivotal role in pain management and overall QoL enhancement for individuals with BM[16]. In uncomplicated bone metastases, defined by the absence of pathological fractures, evidence of cord compression, or previous surgical interventions, RT has demonstrated notable efficacy, with improvements or complete pain relief observed in up to 60% of cases. Moreover, there appears to be no discernible difference in effectiveness between single or multiple-fraction RT regimens[17].

Purpose of the mini-review

Our purpose in this mini-review study was to offer a thorough investigation of the effects of RT on pain alleviation and QoL among patients with bone metastases. This involved synthesizing available evidence concerning the effectiveness of RT in managing pain associated with BM and its influence on various aspects of patient's QoL. Ultimately, our goal was to provide clinicians and researchers with valuable insights to improve the application of RT in treating bone metastases, focusing on enhancing overall well-being and symptom control for patients (Figure 1).

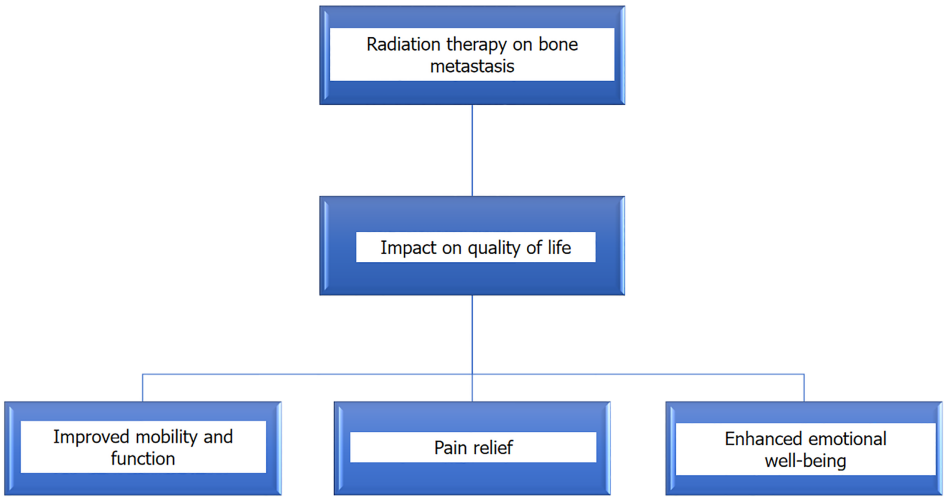

Figure 1 The impact of radiation therapy in bone metastasis patients on the quality of life.

EFFECTS OF RADIOTHERAPY ON PAIN RELIEF

Summary of studies demonstrating the efficacy of radiotherapy in reducing pain in patients with bone metastasis

Prior research has shown that conventional RT alleviates pain in approximately 60% of people suffering from painful bone metastases, with total pain reduction in about 30% of cases[18,19]. On the other hand, SBRT is a more precise RT technique delivering high doses of radiation in few fractions, primarily used for extra-cranial lesions like lung, liver, and prostate, offering enhanced accuracy compared to conventional radiotherapy (cRT)[20]. SBRT also demonstrated a pain relief rate reaching up to 50%[21]. In a study conducted by Wang *et al*[22] they revealed that patients undergoing SBRT had better pain alleviation three months after radiation than those undergoing cRT, with no increase in adverse event occurrence. Moreover, in a study on palliative RT fractionation for bone metastases, Rich *et al*[23] discovered that both single and multiple-fraction radiation treatment regimens consistently result in similar pain management and side effects. However, patients who receive single-fraction treatment are more likely to require re-treatment.

Discussion of the mechanisms by which radiotherapy alleviates pain

The exact mechanism underlying radiation-induced pain alleviation remains unexplained. Radiation's analgesic impact is thought to be due to a variety of causes, including ossification stimulation, osteoclast activity inhibition within the bone microenvironment, and cancer cell elimination, all of which lead to decreased osteolysis and, as a result, tumor burden reduction[24,25]. Some patients have immediate pain relief that lasts longer than 24 hours, indicating a decrease in inflammatory cell activity and the concentration of chemical pain mediators in the radiation-exposed area. These characteristics help to increase the analgesic efficacy of RT[26]. The fractionation regimen of RT used on individuals with BM impacts the degree of mineralization, bone density, and re-calcification at the treated location, which correlates with pain response[27,28].

Impact of pain relief on quality of life in patients with bone metastasis

Patients with bone pain frequently face increasing difficulties completing daily activities, which is accompanied by severe distress and a reduction in QoL. Despite this, few studies provide complete QoL assessments. Furthermore, existing research provides mixed results, and some show an improvement in QoL among patients who respond well to RT treatment[29-33]. Others suggest that RT's impact on QoL across various domains is inconsistent[34-36]. Nevertheless, a recent study conducted by Mendez *et al*[34] discovered that patients over 75 significantly improved overall activity, mood, and interpersonal interactions more than their younger counterparts. Furthermore, their patients experienced pain relief as early as four weeks after getting RT. This finding was associated with a statistically significant improvement in QoL across all dimensions of functional interference, except sleeping quality, consistent with Zeng *et al*[37] results. On the other hand, Khan *et al*[38] claimed that sleeping improves in the second and third month after the treatment in patients responding positively to the RT.

EFFECTS OF RADIOTHERAPY ON PHYSICAL FUNCTIONING

Review of research on how radiotherapy affects physical functioning in patients with bone metastasis

Studies have demonstrated the substantial impact of RT on the physical functioning and QoL of individuals with BM[15]. The primary goal of RT in this context is to alleviate pain and prevent skeletal-related events such as fractures, which can severely impact a patient's mobility and daily activities. while RT is beneficial for pain management and may contribute to improved physical functioning, a comprehensive approach considering all influencing factors is necessary for optimal

patient care[39].

A prospective, single-institutional study showed that RT significantly improved nine domains of QoL in patients with BM, with pain management the most notable improvement. This study underscored the effectiveness of RT in palliating painful BM and enhancing QoL[40]. Patients with bone metastases receiving palliative radiotherapy have reported improvements in their physical functioning, including general activities of daily living[11,41]. A study found that gender, performance status, and primary histology affect health-related QoL in patients with BM[42].

Discussion of improvements in mobility, daily activities, and overall physical well-being following radiotherapy

RT, particularly when integrated with complementary therapeutic modalities, enhances daily functioning, mobility, and overall physical well-being among patients with BM[43]. Its pivotal role in managing BM chiefly revolves around pain alleviation, indirectly fostering improved mobility, daily activities, and overall physical wellness. RT exhibits efficacy in providing pain relief for patients with BM originating from diverse primary cancers, including lung, breast, colon, and prostate, among others[44-48]. Augmenting RT with adjunctive interventions like Poly methyl methacrylate acetabuloplasty or pharmacological approaches such as calcitonin can increase these outcomes[49]. This body of research underscores the necessity of adopting a multidisciplinary approach to managing BM to optimize physical function and enhance the QoL for affected patients[49].

Consideration of the long-term effects on physical functioning

Although there is no investigation to provide specific results on the long-term impact of RT on physical functioning, studies suggest that by effectively managing symptoms and complications related to BM through RT and supportive care, patients may experience maintenance or improvement in physical functioning and overall QoL[41]. A primary consideration associated with RT for BM revolves around the possibility of long-term bone impairment and heightened fracture susceptibility. Radiation exposure can induce bone demineralization and debilitation, particularly within irradiated regions, consequently elevating the likelihood of pathological fractures. Such fractures can exacerbate limitations in physical functioning and mobility[50].

Combining RT with bone-targeted therapies may help mitigate the adverse effects on bone health[50]. RT may precipitate enduring musculoskeletal complications, encompassing muscle weakness, joint stiffness, and diminished range of motion. Such effects can be further compounded by the presence of underlying BM and the accompanying pain and immobility[51]. Physical activity and exercise, when possible, may help preserve musculoskeletal function and mitigate some of the adverse effects of RT and BM[51].

EFFECTS OF RADIOTHERAPY ON EMOTIONAL WELL-BEING

Examination of the psychological impact of bone metastasis and associated pain

Patients with BM usually experience psychological distress marked by anxiety, depression, and fear[52,53]. The associated pain, disability, and loss of independence often induce feelings of helplessness, social isolation, and apprehension regarding the future and end-of-life[52,54]. Studies demonstrated that BM exerts a more profound negative impact on psychological well-being compared to other metastatic sites. Multivariate logistic regression indicated that older age, female sex, malignancy, higher numeric rating scale scores, and a lower Barthel Index were associated with increased risk for psychological distress[53]. Weng Hong *et al*[55] did a study among orthopedic oncology patients and reported that 29.8% had anxiety, 16.2% had depression, and 15.2% had mixed anxiety and depression.

Review of studies showing the positive effects of radiotherapy on emotional well-being and quality of life

Few studies have looked into the psychological effects of RT. For instance, Cañón *et al*[41] revealed that responders to RT significantly improved functional psychosocial aspects (such as relations with others and life enjoyment) compared with nonresponders. These findings were consistent with Mcdonald *et al*[33], Westhoff *et al*[35], and Caissie *et al*[56] evaluated the emotional functioning of the patients by asking them about feeling tense or depressed, and they found that RT responders had an improvement in emotional functioning together with a decrease in symptoms such as insomnia at month 1.

Discussion of the role of psycho-social support in improving emotional outcomes

Providing psycho-social support for individuals coping with BM is crucial for enhancing their overall well-being and QoL. According to some studies, prognostic awareness correlates with decreased QoL and mood among patients recently diagnosed with incurable cancer[57-60]. Furthermore, some studies show that patients who go through palliative therapy along with their treatment have better outcomes than patients undergoing oncology treatment alone[61,62]. However, specific coping strategies have been examined for their potential to enhance patients' mood and QOL. For instance, acceptance has been shown to positively influence patients' psychological and emotional well-being, diverging from the adverse effects associated with denial and self-blame[63]. This insight could guide the patient's support system, including their family and medical caregivers, in creating the best environment to assist the patient in overcoming this challenge.

FACTORS INFLUENCING QUALITY OF LIFE OUTCOMES

Exploration of factors that may influence the effectiveness of radiotherapy on quality of life in patients with bone metastasis, for instance, the coronavirus disease 2019 lockdown effects on the outcomes

The pandemic of the coronavirus disease 2019 (COVID-19) challenges medical professionals to treat patients with advanced cancers, especially with RT[64]. Cancer patients are known to be fragile, so it is critical to treat patients safely and reduce the transmission risk of COVID-19[64]. Oncologists must re-organize how they approach treatment to reduce pain and improve palliation of patients[64,65]. Palliative RT can dramatically maximize the QoL of patients, even during the COVID-19 pandemic[66]. As such, guidelines recommend that patients with BM receive the 8Gy single-fraction RT during a single hospital visit[64,67]. Hypofractionated regimens for radiation are recommended to reduce the frequency of transport, the number of sessions, and complicated treatments[64].

Consideration of patient characteristics, treatment regimen, and supportive care services

Numerous factors, such as patient characteristics, treatment regimen, and supportive care services, can influence QoL outcomes[31]. Responding patients with painful BM have higher QoL scores than nonresponders after RT[31]. Elderly cancer patients show a worse QoL, including appetite and physical functioning, after RT for BM than younger patients [31,68,69]. Patients with younger ages report significant QoL[68]. More women report clinically better improvement in enjoyment of life and mood after radiation for relieving bone pain[68]. High bone pain scores are associated with poor performance status, influencing functional QoL after RT[35]. Combined hyperthermia and RT significantly improve the QoL and ease bone pain in patients with BM[70]. Nurse-led education reduces pain intensity and improves patient empowerment in cancer patients with BM undergoing RT[71].

Implications for personalized treatment approaches

Treatment recommendations for palliative RT for BM should be personalized based on individual patient characteristics to optimize patient outcomes[72-74]. Considering the patient's life expectancy, overall health, tumor progression, tumor biology, comorbidities, and clinical condition allows for the development of personalized treatment plans[72-74].

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

Summary of key findings regarding the effects of radiotherapy on quality of life in patients with bone metastasis

BM significantly impacts patients' physical, functional, and psychosocial QoL[75]. New therapies and interventions have improved patient's QoL and extended life expectancy. RT is the primary therapeutic approach for managing painful bone metastases, playing a crucial role in pain management and improving the overall QoL for individuals with BM[13,16,76].

Studies have shown the efficacy of both cRT and SBRT in relieving pain for patients with BM[22,23]. They indicated that patients undergoing SBRT experienced more pain relief three months after radiation than those undergoing cRT[22]. Radiation's impact is due to multiple factors, including ossification stimulation, osteoclast activity inhibition within the bone microenvironment, and cancer cell elimination[24,25]. These mechanisms lead to decreased osteolysis and reduced tumor burden[24,25]. Pain relief was associated with a statistically significant enhancement in QoL across various aspects of functional interference, except sleeping quality[41]. The main goal of RT is to alleviate pain and prevent skeletal-related events that can severely affect a patient's mobility and daily functioning[39]. RT is valuable for pain management and may positively enhance physical functioning[39]. Integrating RT with complementary therapeutic approaches improves physical well-being, mobility, and daily functioning in patients with BM[43]. RT can cause long-term musculoskeletal complications, including muscle weakness, joint stiffness, and limited movement, compounded by bone metastases, the accompanying pain, and immobility[51]. Research demonstrated that BM has a more profound negative impact on psychological well-being than other sites of metastasis[53]. Cañón *et al*[41] revealed that individuals who responded positively to RT experienced more improvements in their relationships with others and enjoyment of life than nonresponders.

Discussion of potential areas for further research and improvements in treatment strategies

BM, which is a severe complication of cancer, demands immediate attention as it is indicative of a limited prognosis in individuals with cancer[77,78]. Despite our knowledge being enhanced in the metastatic process, several questions remain unanswered that necessitate further research to comprehend the skeletal consequences of metastasis[78]. Future research directions in RT for BM include several critical areas[79]. These comprise response definitions, refining eligibility criteria, reirradiation, systemic therapy changes, radiation techniques, follow-up parameters, and assessment timing[79]. for instance, SBRT may improve local control and pain relief in non-spine BM individuals. However, further research is essential in areas such as volume delineation, MRI, ideal doses, and fractionation[15].

Recommendations for healthcare providers in optimizing quality of life outcomes for patients undergoing radiotherapy for bone metastasis

Therapeutic interventions have the potential to improve pain control and function and the preservation of skeletal integrity in patients with BM[80]. The approach to treatment necessitates a multidisciplinary approach[80]. Achieving successful management of BM requires collaboration among healthcare professionals such as medical oncologists,

surgical oncologists, and radiation oncologists[80]. The judgment of expert radiation oncology physicians is crucial for optimizing outcomes of RT in treating painful BM[72]. Effective RT for BM requires a personalized approach that includes various factors, such as the individual's life expectancy and the progression of tumors in different sites[73].

CONCLUSION

In conclusion, RT has been proven to be a crucial treatment for patients with BM. It significantly helps to relieve pain and improve overall QoL. This treatment approach reduces the intense discomfort often associated with metastatic bone lesions, allowing patients to experience a notable improvement in their daily functioning and well-being. While the primary goal of RT is to manage pain and control disease progression, it's equally important to consider the broader impact on patients' QoL. The physical side effects, psychological stress, and potential long-term consequences of treatment require a comprehensive and patient-centered approach. Healthcare providers should prioritize the clinical effectiveness of RT and the individual patient's experience, preferences, and overall QoL. By incorporating supportive care measures, personalized treatment plans, and ongoing assessment of QoL outcomes, we can optimize therapeutic regimens and ensure a holistic approach to caring for patients with bone metastases. Ultimately, recognizing and addressing these multifaceted needs will improve health outcomes and enhance QoL for patients undergoing RT.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Pediatric flexible flatfoot: Does obesity influence the outcomes of arthroereisis?

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Abstract

BACKGROUND

Childhood obesity has emerged in the last decades as an important public health problem worldwide. Although relationships between obesity and flatfoot have been shown, no studies have investigated the influence of obesity on arthroereisis outcomes.

AIM

To evaluate correlations between childhood overweight/obesity and clinical and radiographic outcomes after subtalar arthroereisis with self-locking implants.

METHODS

This retrospective study included one hundred and sixty-nine pediatric patients (10-14 years old) who underwent subtalar arthroereisis (PEEK PitStop® device) for severe flexible flatfoot. Exclusion criteria were additional procedures, revision of previous corrective surgeries, rigid flatfoot with severe deformity, and neurological or post-traumatic flatfoot. Preoperative/postoperative European Foot and Ankle Society (EFAS) and visual analogue scale (VAS) scores were determined; radiographic assessment was conducted on weight-bearing foot X-rays: Kite angle, first metatarsal-talus angle, Meary angle, calcaneal pitch angle and lateral

talo-calcaneal angle were analyzed.

RESULTS

EFAS and VAS scores improved post-operatively in the whole population. Only seven cases with complications were reported. Radiographic assessment revealed an improvement in all angles. Statistical analysis demonstrated that the impact of obesity was significant on arthroereisis outcomes: Relationships were reported between BMI and postoperative EFAS/VAS scores, postoperative calcaneal pitch angle, Kite angle, Meary angle and talo-first metatarsal angle.

CONCLUSION

Although arthroereisis represents a very effective and valid treatment for flatfoot both in normal weight and obese children, obesity significantly influences clinical and radiographic outcomes of arthroereisis, and obese children tend to perceive more pain and discomfort.

Key Words: Pediatric flatfoot; Obesity; Subtalar; Arthroereisis; Outcomes

Core Tip: Childhood obesity has emerged in the last decades as an important public health problem worldwide. It has been demonstrated that pediatric flatfoot is also related to obesity, showing a two-fold higher risk compared to normal weight children. While the relationship between obesity and flatfoot has been well established, only a few studies have reported the relationships between childhood obesity and arthroereisis outcomes and no studies have assessed the outcomes of self-locking implants and obesity. The aim of the present study is to evaluate correlations between childhood overweight/obesity and clinical and radiographic outcomes after subtalar arthroereisis with self-locking implants.

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INTRODUCTION

Childhood obesity has emerged in the last decades as an important public health problem worldwide. Recent data suggest that over 383 million individuals under 19 years of age may be affected in 2035, compared with over 175 million in 2020. The prevalence of obesity alone may increase from 14% to 24% of the population over the same period[1].

Childhood overweight/obesity is defined by body mass index (BMI) ≥ 25 kg/m² for overweight, and BMI ≥ 25 kg/m² for obesity, which is adjusted according to age and gender. While BMI between the 85th and 94th percentile is in the 'overweight' range, the BMI 95th percentile is in the 'obese' range[2].

Obesity is caused by excessive caloric intake; many factors may contribute including behavior, genetics, care and school environments, availability of affordable and healthy foods or beverages, and accessibility to places for physical activity[2,3].

As reported by the World Obesity Atlas in 2023, approximately 241 million children and adolescents (5-19 years old) are currently overweight or obese worldwide[1]. This scenario has been aggravated by the coronavirus disease 2019 pandemic; A recent study reported an 8.7% increase in childhood overweight and obesity during the pandemic[4]. The economic impact of childhood obesity is significant, including both the healthcare costs of treating obesity and its consequences and the impact of high BMI on economic productivity. The economic impact in the United States was $2.47 trillion, increasing from $1.96 trillion in 2020 to over $4 trillion in 2035[1].

Literature has demonstrated that childhood overweight/obesity may lead to adulthood disorders such as chronic diseases, mental health problems, diabetes, cardiovascular disease, and some types of cancer[5,6]. Moreover, children with overweight/obesity may have a higher risk of musculoskeletal disorders such as slipped capital femoral epiphysis, Blount's disease, and genu valgum, with an increased risk of fractures and musculoskeletal pain[7-11].

It has been demonstrated that pediatric flatfoot (pes planus) is also related to obesity, showing a two-fold higher risk compared to normal weight children[7,12-16]. Chen *et al*[14] found a significant difference in the prevalence of flatfoot between normal-weight (27%), overweight (31%) and obese (56%) children[14]. Cimolin *et al*[16] also reported a 70% rate of flatfoot in obese adolescents compared to 25% in the normal weight group[16].

The relationship between childhood obesity and flatfoot is still unknown. Mickle *et al*[17] asserted that higher rates of flatfoot in obese children may be explained by structural changes in the foot rather than the presence of thicker fat tissue under the midfoot region[17]. Moreover, Riddiford-Harland *et al*[18] showed that obese children have significantly greater medial midfoot fat pad thickness compared to leaner children, in non-weight and weight bearing: The authors concluded that the feet of obese children are both fat and flat[18]. These structural and morphological changes are asso-

ciated with compromised function in gait and activities[17,19].

In the treatment of pediatric flatfoot, subtalar arthroereisis has been reported as a minimally invasive, effective, and low-risk procedure[20-22]. Described firstly by Chambers[23] in 1946 and then by Lelievrè[24] in 1970, subtalar arthroereisis aims to limit subtalar eversion, to reposition the calcaneus and restore talocalcaneal divergence and talar head coverage, and not least restore the medial arch. Different devices for subtalar arthroereisis are currently used: From the first device proposed in 1974 by Subotnick[25] several implants have been introduced, differing essentially in material, shape and mechanism of action[25]. The implants were classified in 1987 by Vogler[26] into three types: Axis-altering prostheses, impact-blocking devices and self-locking implants[26].

While the relationship between obesity and flatfoot has been well established, only a few studies have reported the relationship between childhood obesity and arthroereisis outcomes. Pavone *et al*[27] reported results following calcaneostop implants[27], but no studies have investigated the outcomes of self-locking implants and obesity.

The aim of the present study is to evaluate correlations between childhood overweight/obesity and clinical and radiographic outcomes after subtalar arthroereisis with self-locking implants.

MATERIALS AND METHODS

One hundred and sixty-nine pediatric patients (10-14 years old) underwent subtalar arthroereisis between February 2020 and April 2022 at the Pediatric Orthopedics Unit of the ASST Settelaghi in Varese, the only pediatric orthopedic department in the whole Province of Varese (112000 inhabitants under 14 years old).

Surgery was indicated in patients presenting with flexible flatfoot, normal-aligned limbs and symptomatic flatfoot (foot pain during daily or sport activities, early muscle fatigue, disability in running or sport activity), severe grade (III-IV degree) or with critical malalignment of the hindfoot or a hindfoot valgus > 8°.

Exclusion criteria were introduced in order to reduce possible biases that may interfere with our purpose, which was to evaluate correlations between childhood obesity and outcomes after subtalar arthroereisis in flexible flatfoot in those aged < 10 years or > 14 years. Although there is no consensus on the age for surgery, performing subtalar arthroereisis before the age of ten may be too early, as nonsurgical management has been demonstrated to be efficient and should be pursued [28-30]; patients over 14 years were excluded because several authors have reported that the foot is defined 'mature' at the age of fourteen, with cessation of growth, closure of growth plates and stabilization of posture[31-33]. Patients undergoing additional procedures (gastrocnemius recession, hallux valgus correction, excision of accessory navicular bone, hemi-epiphysiodesis for genu varus/valgus) this criterion is crucial to reduce the effects deriving from other simultaneous procedures; revision of previous corrective surgeries for flatfeet; rigid flatfoot with severe deformity, neurological (*e.g.*, dystrophy), post-traumatic; unilateral surgery. From the original population of one hundred and sixty-nine patients, twenty-six were excluded using these criteria. Fifty-five patients were additionally lost at follow-up. Thus, eighty-eight children were finally included in this retrospective study. As bilateral surgery was performed for each patient, one hundred and seventy-two outcomes were assessed. Regular informed consent was obtained from all patients.

Thirty-one (35.2%) females and fifty-seven (64.8%) males were included in the study. Mean follow-up was 17.03 months (range 8.9-34.7).

Bilateral subtalar arthroereisis was performed in all cases using an anatomical PEEK PitStop® endorthesis (In2Bones, Memphis, TN, United States) (Figure 1). At the end of the procedure, a boot plaster was placed, and the patient was invited to walk immediately with canes. The cast was removed after three weeks, and the patient was free to walk with comfortable footwear; an exercise protocol was given to the patients to help return-to-walk. Activities with a high risk of ankle sprain (*i.e.*, running, jumping) were prohibited for the first two postoperative months: Only swimming and cycling were permitted.

Daily sport activities were allowed two months after surgery. Specific physiotherapy was indicated in the case of disability in walking or incomplete/unsatisfactory correction.

Clinical evaluation

Patients were assessed preoperatively and postoperatively at 20 days, 60 days, and at the time of the study (mean 17.03 months, range 8.9-34.7). Preoperatively, the weight, height, and BMI of each patient were also determined.

Clinical evaluation included the following: Valgus position of the heel in orthostatism, gait analysis, functional tests (Silfverskiold test, the toe rising test, Jack test), and footprint on the podoscope. Moreover, the European Foot and Ankle Society (EFAS) and visual analogue scale (VAS) scores were obtained preoperatively and postoperatively: These scores were chosen as they are universally validated, also in the Italian language[34-36]. The EFAS score concerns six items relating to activities of daily living and four relating to the performance in sports. The VAS scale is an instrument for measuring pain experienced by the patient.

Radiographic evaluation

Weight-bearing foot X-rays were obtained, analyzed and compared preoperatively and postoperatively with Synapse® software (FUJIFILM Medical Systems United States).

In the antero-posterior view, Kite angle (between lines drawn down the axes of the talus and calcaneus) and first metatarsal-talus angle (between longitudinal axes of first metatarsal and talar neck) were calculated. In the lateral projection, Meary angle (between the longitudinal axes of the talus and the first metatarsal), calcaneal pitch angle (between the calcaneal inclination axis and the supporting horizontal surface) and lateral talo-calcaneal angle (between axes of the talus and calcaneus) were analyzed.

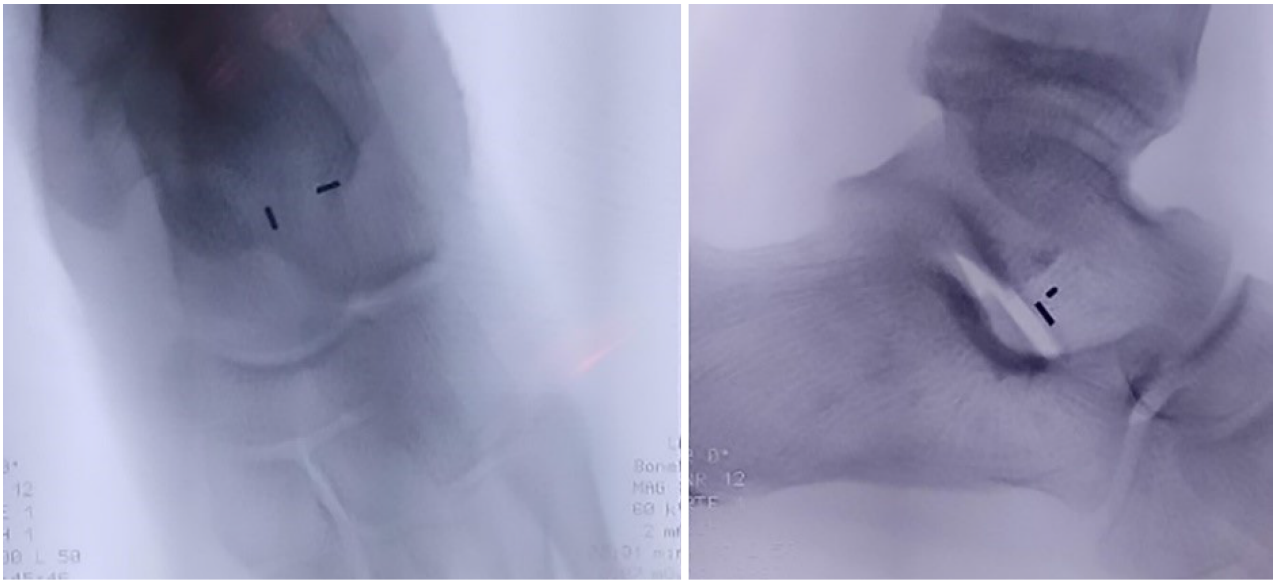

Figure 1 Postoperative X-rays of subtalar arthroereisis with the PitStop® PEEKdevice.

Statistical analysis

Data were analyzed using SPSS version 24.0 software (IBM, Armonk, NY, United States). The descriptive statistics were expressed by the use of means, SDs and frequencies. For the comparison of means, Student's *t*-tests were used with independent samples or with paired samples for the variables with normal distribution. In addition, statistical correlations between variables were identified by *t*-test; then, by means of linear regression, the trend of each parameter was analyzed as the other variables changed, obtaining R^2. Statistical significance was set at $P < 0.05$.

RESULTS

Mean age at surgery was 12.20 years (range, 10.15-14.48): Seventeen 10-year-old children (19.40%), twenty-four 11-year-old children (24.10%), twenty-two 12-year-old children (33.90%), nineteen 13-year-old children (17.80%), and six 14-year-old children (4.80%).

Mean BMI at the time of surgery was 20.69 (range: 14.08-29.34, SD: 3.44). Forty-two patients had a BMI < 18 kg/m² (23.8%), one hundred and twelve were normal weight (63.6%) and twenty-two were obese (22.6%).

The following PitStop® PEEK endorthesis sizes were used: Size 10 in four cases (2.3%), size 11 in thirty-three cases (18.8%), size 12 in seventy-two cases (40.9%), size 13 in sixty-three cases (35.8%), and size 14 in four cases (2.3%).

Clinical evaluation

EFAS and VAS scores are reported in Table 1. The mean preoperative EFAS score was 17.73 points (range, 2.00-40.00); postoperatively, the average score was 34.38 points (range, 18.00-40.00); as a result, the mean score increase was 16.65 points (range, 15.80-17.49, $P = 0.001$).

The mean preoperative VAS score was 6.38 points (range, 0.00-10.00); postoperatively, the average score was 1.98 points (range, 0.00-6.00); as a result, the mean score increase was 4.4 points (range, 4.04-4.75, $P = 0.001$).

A few complications were reported: Six cases had superficial wound dehiscence (3.4%) and only one case required implant removal by surgery after three years due to ankle sprain during national gymnastics games (1.2%). Normal weight children reported four of six dehiscences and implant removal, without any significant differences to obese patients ($P = 0.697$). Physiotherapy was indicated in thirty patients (34.1%) due to disability in walking or sports.

Radiographic evaluation

Radiographic data are reported in Table 2. The mean preoperative Kite angle was 25.11° (range, 10.00-39.00); postoperatively, the mean angle was 20.78° (range, 11.00-33.00); as a result, the average reduction was 4.33° (SD 3.52; $P = 0.001$); the mean preoperative first metatarsal-talus angle was 7.86° (range, 1.00-31.00); postoperatively, the mean angle was 4.99° (range, 0.00-15.00); as a result, the average reduction was 2.86° (SD 4.19; $P = 0.001$).

The mean preoperative Meary angle was 7.35° (range, 1.00-21.00); postoperatively, the mean angle was 3.44° (range, 0.00-18.00); as a result, the average reduction was 3.91° (SD 3.80; $P = 0.001$); the mean preoperative calcaneal pitch angle was 15.52° (range, 8.00-27.00); postoperatively, the mean angle was 18.83° (range, 7.00-33.00); as a result, the average increase was 3.31° (SD 2.38; $P = 0.001$); the mean preoperative talo-calcaneal angle was 37.52° (range, 28.00-54.00); postoperatively, the mean angle was 31.75° (range, 22.00-42.00); as a result, the average reduction was 5.77° (SD 4.55; $P = 0.001$).

Table 1 Preoperative and postoperative European Foot and Ankle Society and visual analogue scale scores

		Average	Min	Max	SD	SE	Sig ($P < 0.05$)
EFAS score	Pre	17.73	2.00	40.00	5.74	0.433	
	Post	34.38	18.00	40.00	4.08	0.308	
Δ EFAS		-16.65	-16.00	0.00	5.69	0.429	0.001
VAS score	Pre	6.38	0.00	10.00	2.48	0.187	
	Post	1.98	0.00	6.00	1.23	0.117	
Δ VAS		-4.40	0.00	-4.00	2.36	0.179	0.001

EFAS: European Foot and Ankle Society; VAS: Visual analogue scale scores.

Table 2 Preoperative and postoperative radiographic assessment

		Average	Min	Max	SD	SE	Δ value	SD	SE	Sig ($P < 0.05$)
Calcaneal pitch angle	Pre	15.52	8.00	27.00	3.18	0.240	3.31	2.38	0.179	0.001
	Post	18.83	7.00	33.00	4.37	0.330				
Talo-Calcaneal angle	Pre	37.52	28.00	54.00	4.32	0.329	-5.77	4.55	0.344	0.001
	Post	31.75	22.00	42.00	3.64	0.275				
Meary angle	Pre	7.35	1.00	21.00	4.02	0.303	-3.91	3.80	0.287	0.001
	Post	3.44	0.00	18.00	2.85	0.215				
Kite angle	Pre	25.11	10.00	39.00	5.22	0.394	-4.33	3.52	0.265	0.001
	Post	20.78	11.00	33.00	4.37	0.330				
Talo-M1 angle	Pre	7.86	1.00	31.00	4.32	0.330	-2.86	4.19	0.316	0.001
	Post	4.99	0.00	15.00	3.01	0.227				

Statistical analysis demonstrated a significant correlation between BMI < 25 kg/m² and BMI > 25 kg/m² ($P < 0.05$), and postoperative VAS: Normal weight patients 1.88 points; obese patients 2.64 points ($P = 0.001$); postoperative EFAS: Normal weight patients 31.09 points; obese patients 34.84 points ($P = 0.048$); postoperative Kite angle: Normal weight patients 20.32°, obese patients 23.95° ($P = 0.005$).

Relationships between BMI and postoperative EFAS score, postoperative VAS, postoperative calcaneal pitch angle, postoperative Kite angle, postoperative Meary angle and postoperative talo-first metatarsal angle were analyzed by linear regression: Postoperative EFAS score tended to decrease as BMI increased ($P = 0.001$; SE coefficient 2.081; R^2 corrected 0.095) (Figure 2A). Postoperative VAS score did not appear to be affected by BMI trends.

Postoperative calcaneal pitch decreased as BMI increased ($P = 0.001$; SE coefficient 2.493; R^2 corrected -0.007); the postoperative Kite angle also seemed to have a clinically agreeable behavior, as the angle tended to increase with increased BMI ($P = 0.003$; SE coefficient 1.802; R^2 corrected 0.003) (Figure 2B). Finally, the postoperative Meary angle tended to increase as the patient's BMI increased ($P = 0.001$; SE coefficient 2.563; R^2 corrected 0.067). No other statistically significant trends were detected.

DISCUSSION

Childhood obesity currently represents an important public health problem. Among other severe consequences, pediatric flatfoot has also been demonstrated to be related to obesity[7,12-15].

It has been shown that pediatric flatfoot (pes planus) is also related to obesity, with a two-fold higher risk compared to normal weight children[7,12-16]. The relationship between childhood obesity and flatfoot is still unknown. The structural and morphological changes reported in obese children with flatfeet are associated with compromised function in gait and activities[17,19].

In the treatment of pediatric flatfoot, subtalar arthroereisis has been reported as a minimally invasive, effective, and low-risk procedure[20-22].

Our study demonstrated that this surgical procedure is very effective in the treatment of symptomatic and flexible flatfoot: The EFAS score significantly increased and the VAS score significantly decreased after arthroereisis ($P < 0.001$), with general satisfaction in children and parents. Similarly, all angles measured significantly improved in the whole

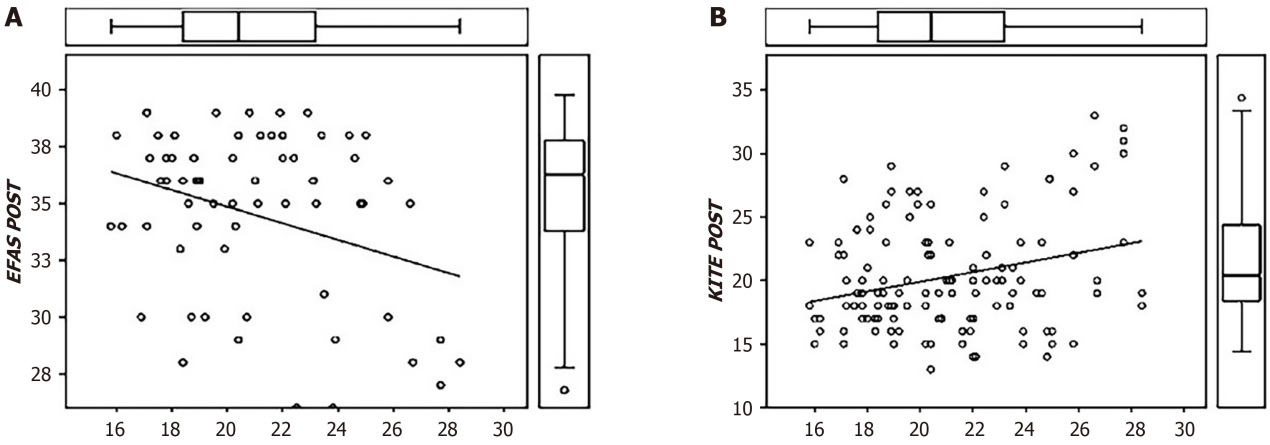

Figure 2 European Foot and Ankle Society/body mass index correlation and Kite angle/body mass index correlation. A: European Foot and Ankle Society/body mass index (EFAS)/body mass index (BMI) correlation: Postoperative EFAS score tended to decrease as BMI increased (P = 0.001; SE coefficient 2.081; R^2 corrected 0.095); B: Kite angle/BMI correlation: Postoperative Kite angle tended to increase with increased BMI (P = 0.003; SE coefficient 1.802; R^2 corrected 0.003). EFAS: European Foot and Ankle Society.

pediatric population (P = 0.0011). Our favorable results are similar to those reported in several other studies[37-44].

Regarding complications, we reported a rate of only 4.6%: The most common complication was superficial dehiscence treated with simple medications. Our results are in line with those from other studies, with complication rates ranging from 4.8% to 19.3%[20,45,46]. It is our opinion that superficial wound dehiscence is caused by the cast as sweating is frequent, leading to maceration of the skin surrounding the wound. Thus, we currently prefer not to use a cast but an ankle orthosis. The only case of implant removal was caused by an unpredictable traumatic event during gymnastics.

As demonstrated by the statistical analyses, obesity has a significant influence on both clinical and radiographic outcomes of subtalar arthroereisis: BMI over 25 kg/m² is significantly correlated with worse postoperative EFAS and VAS scores (P < 0.05). Also, postoperative angles show worse values in obese patients: Postoperatively, the calcaneal pitch, Kite angle, and Meary angle were significantly influenced (P < 0.05).

Few studies have reported the relationship between childhood obesity and the corrective potential of arthroereisis: Only Pavone reported results after calcaneo-stop implants[27], but no studies have reported the outcomes of self-locking implants.

As the goniometric improvements, with the exception of the Kite angle, were substantially similar in normal weight/overweight children, subtalar arthroereisis is effective in treating flexible flatfoot in both populations. However, the following question might arise: Is it worth performing this surgical procedure in overweight children? Based on our results, the answer is yes, and for two reasons. Firstly, the significant improvements in the postoperative EFAS score, VAS score and radiographic angles confirm that arthroereisis represents an effective and valid treatment of flatfoot even in this population; on the other hand, obese patients seem not to incur more complications than normal weight children, as complications were related to unpredictable factors.

Nevertheless, our results allow us to assert that subtalar correction due to arthroereisis requires greater effort in overweight children, resulting in poorer outcomes than normal weight patients as demonstrated by postoperative lower EFAS and higher VAS scores. Although good radiographic correction was obtained after subtalar arthroereisis, obese children tended to perceive more pain and discomfort midterm than their normal weight peers. These findings were confirmed by linear regression studies when evaluating the relationship between BMI and clinical-radiographic outcomes.

CONCLUSION

Subtalar arthroereisis is effective in treating flexible flatfoot both in normal weight and obese populations. Nonetheless, obesity significantly influences clinical and radiographic outcomes and obese children tend to perceive more pain and discomfort.

FOOTNOTES

Author contributions: Monestier L and Riva G were the patients' surgeons; Monestier L, Pelozzi A, Bozzi E, Latiff M and Marciandi L reviewed the literature and contributed to manuscript drafting; Latiff M and Pautasso A analyzed the imaging findings; Surace MF, Pilato G, D'Angelo F, Monestier L and Riva G were responsible for the revision of the manuscript for important intellectual content; All authors issued final approval for the version to be submitted.

Institutional review board statement: In compliance with Italian law, we are not required to ask for Ethic Committee approval for this type of study.

Informed consent statement: Regular informed consent was obtained from all patients. Informed written consent was obtained from the patients for publication of this report and any accompanying images.

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

Data sharing statement: The authors confirm that the data supporting the findings of this study are available within the article.

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SYSTEMATIC REVIEWS

Platelet-rich plasma for de Quervain's tenosynovitis: A systematic review and meta-analysis

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Abstract

BACKGROUND

Platelet-rich plasma (PRP) injection is used as an alternative non-operative management for de Quervain's tenosynovitis (DQT) to regenerate tendon healing.

AIM

To assess and conclude the research-based study systematically to analyse the efficacy of PRP on DQT.

METHODS

This systematic review used the Cochrane Handbook for Systematic Reviews and the guideline of preferred reporting items for systematic review and meta-analysis. A systematic literature search was applied to 11 databases. The authors assessed the study quality and risk of bias of each included study. Results of the meta-analysis were presented using mean difference (MD)/standardized mean difference (SMD) and 95% confidence interval (CI).

RESULTS

The authors evaluated 275 studies found in the literature search; 12 studies met the criteria for this review, and then the study quality and risk of bias were assessed. Pooled analysis of data from two studies involving 194 subjects with DQT showed that, compared with conservative treatment, PRP injection was associated with a greater reduction in visual analog scale pain in one month and six months after treatment (MD: -0.67, *P* value < 0.00001; MD: -1.16, *P* value < 0.00001) and the increase of Mayo's wrist score in one month and six months after treatment (SMD: 3.72, *P* value < 0.00001; SMD: 4.44, *P* value < 0.00001).

CONCLUSION
PRP can be used as an alternative non-operative treatment for DQT due to the tissue regenerative effect of PRP.

Key Words: De Quervain'S disease; De Quervain'S tenosynovitis; Platelet-rich plasma; Stenosing tenosynovitis

Core Tip: De Quervain's tenosynovitis (DQT) is a common tendon disorder characterized by wrist pain and tenderness at the first dorsal compartment of the wrist. Platelet-rich plasma (PRP) injection is currently used as an alternative non-operative management for DQT to regenerate tendon healing due to its tissue regenerative effect, which provides better pain management and stable improvement in functional outcomes in the long term. Ultrasonography-guided PRP with percutaneous needle tenotomy gives a better outcome. There are minimal side effects associated with PPR injection.

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INTRODUCTION

Tendon disorders are frequent conditions that limit daily activities and influence the quality of life[1-4]. De Quervain's tenosynovitis (DQT) is a common tendon disorder characterized by wrist pain and tenderness at the first dorsal compartment of the wrist; correlated with overworked, routine, and sustained activities that involve the tendons of abductor pollicis longus (APL) and extensor pollicis brevis (EPB)[5-14]. The incidence of DQT is 0.5% in males and 1.32% in females, and female between 30 to 50 years is the highest risk[6-9,11,12]. The diagnosis of DQT is confirmed with Finkelstein's test or Eichhoff's test and radiological examination if required[7,8,11].

Most patients respond well to non-surgical management, including activity modification, splinting, physical therapy, non-steroidal anti-inflammatory drugs (NSAIDs) medication, and corticosteroid injection[10-12]. In some cases where non-surgical management fails, primarily because of a false injection site and anatomical variation in the first dorsal compartment, a surgical release of the first dorsal compartment and decompression of the stenosed APL and EPB tendons is preferred[8,9,12,13,15]. Platelet-rich plasma (PRP) injection is currently used as an alternative non-operative management for DQT to regenerate tendon healing[9,10,12]. Gulati *et al*[6] concluded that PRP injection reduced pain and improved range of motion in DQT. PRP injection is a novel therapy used in various health disorders, including in orthopedic cases[4,16,17]. Platelet have hundreds of bioactive protein and cytokine which control cells differentiation and maturation, angiogenesis, and also synthesis of connective tissue. It supports the healing of degenerated tissue by stimulating revascularization, epithelialization, cell generation, and formation of extracellular matrix[4,18-21].

Many studies have explained PRP injection in DQT, but a systematic review focusing on PRP used for DQT is unavailable. This systematic review and meta-analysis aimed to systematically evaluate and conclude the research-based studies to report PRP's efficacy for DQT.

MATERIALS AND METHODS

This study's protocol was registered on the International Prospective Register of Systematic Reviews with register number CRD42023466818. The Cochrane Handbook for systematic reviews and the preferred reporting items for systematic review and meta-analysis (PRISMA) were used as guidelines in this systematic review-meta-analysis[22-24].

Inclusion and exclusion criteria

Inclusion criteria: Publication type: Full-text manuscripts reported the efficacy of PRP for DQT primary research study; Articles published in English; Articles published in January 2000 - December 2023; The study used humans as the subject; The objective, methodology, and outcome of the study must discuss the efficacy of PRP for DQT.

Exclusion criteria: Review; Variables that were associated with the efficacy of PRP for DQT.

Literature search

A systematic literature search was performed in these online scientific databases: ClinicalKey, Cochrane Library, EBSCOhost, Emerald Insight, Europe PMC, Google Scholar, JSTOR, ProQuest, PubMed, ScienceDirect, and Springer Link. The search used the following keywords for the title and abstract: (platelet-rich plasma OR PRP) AND (stenosing tenosynovitis OR de quervain tenosynovitis OR de quervain disease). The references of included studies were analysed to

ensure that all published studies were included.

Data collection and analysis

Articles were selected for evaluation after two authors (NNH and RSNM) had evaluated keywords from the online medical bibliographic databases. The results of the literature search were discussed with other authors (GS, JB and GTP), and any inconsistencies in results were deliberated. Three authors independently assessed selected full papers. Two authors independently evaluated selected studies for this systematic review to confirm the results (NNH and GS). The data from the included studies were presented in a summary table containing the key points of each study. The key points of each study were: First author, country, year, study design, sample, sample characteristic, outcome measure, and result.

Quality assessment

The first author evaluated the study quality and risk of bias of each included article and deliberated them with other authors. Version 2 of the Cochrane risk-of-bias tool for randomized trials (ROB 2) was performed to evaluate randomized control trial studies in which the interpretation was high risk or some concerns or low risk[25]. Newcastle–Ottawa scale for the prospective study was applied to assess the quality and risk of bias of the prospective study; the explanation of the result was: ≥ 7 points were included in the good study, 5-6 points were included in the fair study, < 5 points were included in the poor study. The Joanna Briggs Institute (JBI) critical appraisal checklist was used to evaluate the descriptive study's quality and risk of bias[25-27].

Statistical analysis

Review manager 5.4 was used to assess the overall effect size of PRP efficacy for DQT. A P value < 0.05 was considered statistically significant. Results were summarized using the mean difference (MD)/standardized mean difference (SMD) and 95% confidence interval (CI). Heterogeneity was evaluated using the I^2 (inconsistency) value; < 25%, 26%-50%, and > 50% were considered low, moderate, and high heterogeneity. Funnel plots were performed to assess the risk of publication bias[24,28].

RESULTS

Selection of articles for review

PRISMA flow diagram is presented in Figure 1. Initially, 275 peer-reviewed studies were identified from online medical research databases. After duplicates were removed, 152 studies were proceeded with the title and abstract screening. Seventeen articles were assessed for eligibility, of which 12 studies were included in the systematic review and two studies were included in the quantitative synthesis (meta-analysis).

Assessment of study validity (quality assessment and risk of bias)

All included studies were associated with the efficacy of PRP for DQT. Figure 2 provides the quality scores for randomized control trial studies, and the study had low risk. Table 1 shows quality scores for prospective studies, and the studies had 6-9 points (fair and good study). The JBI critical appraisal checklist for case reports and case series is presented in Table 2 and Table 3, and all of the studies had an overall appraisal in "included studies" for systematic review.

Study characteristic

Table 4 shows the study characteristics for the included studies. Most studies were prospective studies that discussed the efficacy of PRP in reducing pain in DQT subjects.

Meta-analysis of the included studies

The forest plots of included studies for meta-analysis of the PRP efficacy for DQT are shown in Figure 3. Pooled analysis of data from two studies involving 194 subjects with DQT showed that, compared with conservative treatment, PRP injection was associated with a greater reduction in visual analogue scale (VAS) pain in one month and six months after treatment [MD: -0.67 (95%CI: -0.96 to -0.38), P value < 0.00001 and the heterogeneity (I^2) was 9%; MD: -1.16 (95%CI: -1.41 to -0.91), P value < 0.00001 and the heterogeneity (I^2) was 0%] and the increase of Mayo's wrist score in one month and six months after treatment [SMD: 3.72 (95%CI: 3.22 to 4.22), P value < 0.00001 and the heterogeneity (I^2) was 98% (high heterogeneity); SMD: 4.44 (95%CI: 3.91 to 4.98), P value < 0.00001 and the heterogeneity (I^2) was 44% (moderate heterogeneity)]. The differences in demographic variance and occupational status influenced the heterogeneity of the included studies. Figure 4 shows the funnel plots, with the symmetry of the scatter plot in the triangle (low risk of bias).

DISCUSSION

Twelve studies had reported the efficacy of PRP as a treatment for DQT: Ten studies reported the reduction of VAS (scoring for assessing pain), four studies reported the improvement of Mayo's wrist score (scoring for assessing wrist as

Table 1 Newcastle-Ottawa scale (prospective study)

No.	Ref.	Selection				Comparability	Outcome			Total
		1	2	3	4		1	2	3	
1	Asaad *et al*[9], 2023	×		×	×		×	×	×	6
2	Deb *et al*[5], 2020	×	×	×	×	×	×	×	×	8
3	Giroti *et al*[12], 2021	×	×	×	×	××	×	×	×	9
4	Gulati and Ramesh [6], 2022	×	×	×	×	××	×	×	×	9
5	Johurul *et al*[29], 2019	×	×	×	×	××	×	×	×	9
6	Kumar *et al*[14], 2023	×	×	×	×	××	×	×	×	9
7	Ramesh *et al*[30], 2018	×		×	×		×	×	×	6
8	Sheikh *et al*[10], 2020	×	×	×	×	××	×	×	×	9

The maximum point for comparability was 2; Selection: (1) Representativeness; (2) Selection of non-exposed; (3) Ascertainment of exposure; and (4) Demonstration that outcome was not present at the beginning; Outcome: (1) Assessment of the outcome; (2) Follow-up long enough; and (3) Adequacy of follow-up.

Table 2 The Joanna Briggs Institute critical appraisal checklist for case report

No.	Major components	1	2
1	Were patient's demographic characteristics clearly described?	Y	Y
2	Was the patient's history clearly described and presented as a timeline?	Y	Y
3	Was the current clinical condition of the patient on presentation clearly described?	Y	Y
4	Were diagnostic tests or assessment methods and the results clearly described?	Y	Y
5	Was the intervention(s) or treatment procedure(s) clearly described?	Y	Y
6	Was the post-intervention clinical condition clearly described?	Y	Y
7	Were adverse events (harms) or unanticipated events identified and described?	Y	Y
8	Does the case report provide takeaway lessons?	Y	Y
	Overall appraisal	I	I

1: Chen *et al*[7], 2021, United States; 2: Peck and Ely[13], United States, 2013; I: Included, Y: Yes.

functional outcome), four studies reported the reduction of disabilities of the arm, shoulder, and hand (DASH) score (scoring for assessing disability), one study reported the improvement of Jebsen-Taylor hand function test (scoring for assessing hand as functional outcome), and two studies reported the improvement of ultrasound findings (tendon thickness, combined tendon and sheath thickness, and extensor retinaculum thickness). Pooled analysis of included studies also supported these results, in which PRP was associated with a reduction in VAS and increasing Mayo's wrist score ($P < 0.00001$). All these studies reported that PRP is an alternative treatment for DQT due to the initiation and production of growth factors like vascular endothelial growth factor, platelet-derived growth factor, transforming growth factor (TGF)-α, and TGF-β which supported the tissue regeneration through angiogenesis, chemotaxis, and cell proliferation that are activating intracellular signal transduction pathways[6-9,12,13,29-31].

Seven researches discussed about the comparison of PRP and corticosteroid (CS) as a treatment for DQT. All these studies concluded that PRP provided better outcomes than CS because PRP efficacy as an osteointegration and histopromotive agent had a long-term sustained effect with no adverse effect. In contrast, CS had a short-term effect[5,6,10-12,14,29]. According to Giroti *et al*[12], VAS reduction and DASH improvement were better after CS injection in comparison to PRP injection in the first month; however, after six months, PRP injection showed greater VAS reduction and DASH improvement in comparison to CS injection. PRP has four stages of treatment as a regenerative agent, making PRP has a late onset and long-term effect compared to CS injection. The first stage is an inflammatory stage, consisting of increased vascular permeability, initiation of angiogenesis, stimulation of tenocyte proliferation, and initiation of type III collagen synthesis in the injection site within two to three days. This inflammatory stage begins with a temporary improvement of the inflammatory response due to cyclooxygenase-2 induction, nuclear factor kappa B activation, and the secretion of pro-inflammatory cytokines. This step is continued by the production of an anti-inflammatory microenvironment through the secretion of prostaglandin E2. The second stage is the proliferative stage, where fibroblast proliferation and neo-

Table 3 The Joanna Briggs Institute critical appraisal checklist for case series

No.	Major components	1
1	Were there clear criteria for inclusion in the case series?	Y
2	Was the condition measured in a standard, reliable way for all participants included in the case series?	Y
3	Were valid methods used for identification of the condition for all participants included in the case series?	Y
4	Did the case series have consecutive inclusion of participants?	Y
5	Did the case series have complete inclusion of participants?	Y
6	Was there clear reporting of the demographics of the participants in the study?	Y
7	Was there clear reporting of clinical information of the participants?	Y
8	Were the outcomes or follow-up results of cases clearly reported?	Y
9	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Y
10	Was statistical analysis appropriate?	NA
	Overall appraisal	I

1: Mahdi Al-ardi[8], Iraq, 2017; I: Included, NA: Not available; Y: Yes.

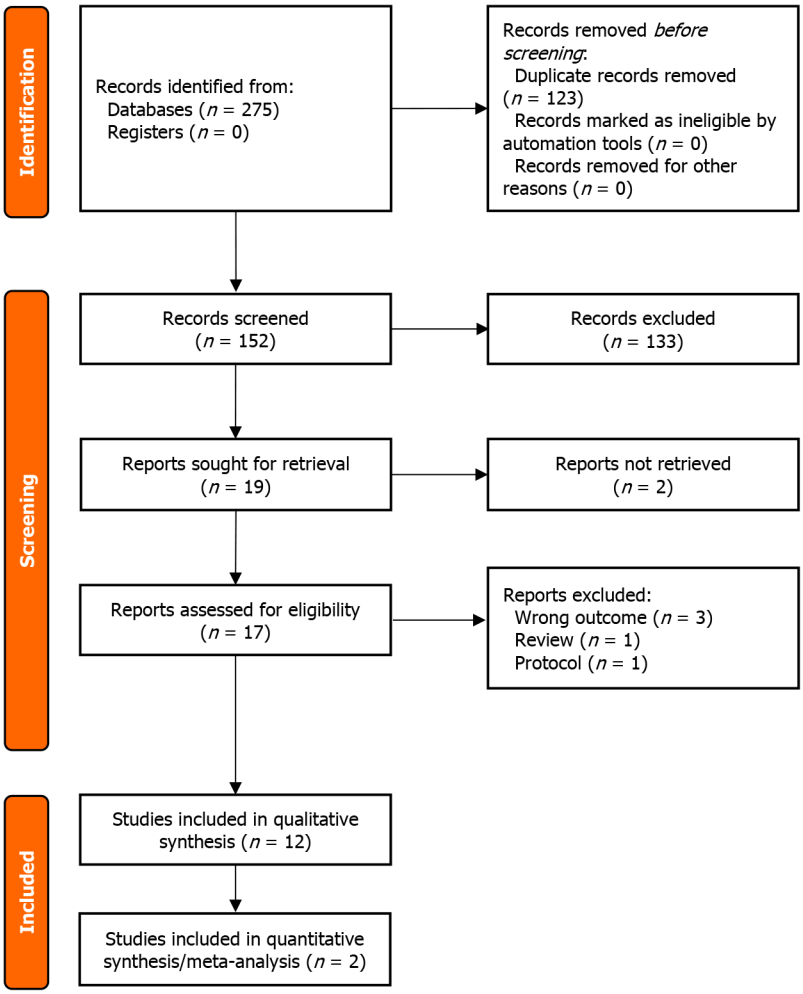

Figure 1 PRISMA flow diagram.

Table 4 Study characteristic

No.	Ref.	Study design	Sample (n)	Sample characteristic: age (year), gender (male, female)	Outcome measure	Result
1	Mahdi Al-ardi[8], 2017, Iraq	Case series	PRP: 30	Age: > 25	Pain reduction (VAS)	PRP injection reduced pain in 1, 3, and 6 months after treatment (VAS in baseline: 5.92; 1 months: 2.11; 3 months: 2.01; 6 months: 2.01; $P < 0.001$)
2	Asaad *et al* [9], 2023, Iraq	Prospective study	PRP: 12	Age: 43 (26-68); Gender: F	Pain reduction (VAS) and USG evaluation of tendon	PRP injection reduced pain significantly in 1 and 3 months after treatment (VAS in baseline: 8.66 ± 0.65; 1 months: 4.5 ± 1.97; 3 months: 1.91 ± 2.71; $P < 0.001$); decreased tendon sheath effusion significantly in 1 and 3 months after treatment (baseline: 2.07 ± 0.52; 1 months: 1.6 ± 0.75; 3 months: 0.73 ± 0.76; $P < 0.001$); decreased retinaculum thickness significantly in 1 and 3 months (baseline: 1.89 ± 0.5; 1 months: 1.3 ± 0.6; 3 months: 0.96 ± 0.56; $P < 0.001$); decreased peri-tendinous hyperemia significantly in 1 and 3 months (baseline: 58.3%; 1 months: 16.7%; 3 months: 0%; $P < 0.001$)
3	Chen *et al* [7], 2021, United States	Case report	PRP: 1	Age: 38; Gender: F	Pain reduction	The PRP injection reduced pain after 2 weeks, completely resolved it after 4 weeks, and there were no recurrent pain or weakness symptoms after 6 months
4	Deb *et al*[5], 2020, India	Prospective study	PRP: 67; Conservative: 64; CS: 69	PRP; Age: 53.96 ± 09.47; Gender: 38, 29; Conservative; Age: 51.85 ± 10.14; Gender: 43, 21; CS; Age: 57.49 ± 10.00; Gender: 33, 36	Pain reduction (VAS) and functional outcome (Mayo's wrist score)	PRP injection reduced pain significantly in 1, 6, 12 months after treatment compared to conservative and CS therapy (VAS in 1 months: 4.91 ± 1.01 *vs* 6.37 ± 2.45 *vs* 5.13 ± 2.07; 6 months: 3.96 ± 1.94 *vs* 5.01 ± 0.26 *vs* 6.09 ± 1.41; 12 months: 2.11 ± 0.28 *vs* 7.61 ± 0.72 *vs* 4.93 ± 1.95; $P < 0.001$) PRP injection improved functional outcome significantly in 1, 6, 12 months after treatment compared to conservative and CS therapy (Mayo's wrist score in 1 months: 73.61 ± 7.01 *vs* 39.71 ± 4.47 *vs* 63.45 ± 5.17, p: 0.045; 6 months: 83.47 ± 6.83 *vs* 51.43 ± 6.64 *vs* 70.94 ± 6.29, p: 0.003; 12 months: 87.24 ± 6.94 *vs* 64.78 ± 7.12 *vs* 72.01 ± 5.42, p: 0.001).
5	Giroti *et al* [12], 2021, India	Prospective study	PRP: 22 hand; CS: 28 hand	PRP; Age: 44.44 (27-60); Gender: 2, 20; CS; Age: 43.16 (31-59); Gender: 3, 24	Pain reduction (VAS) and disability reduction (DASH score)	PRP injection reduced pain in 6 months after treatment compared to CS therapy (VAS: 1.4 *vs* 2.1) PRP injection reduced disability compared to CS therapy (DASH score: 23.5 *vs* 39.7)
6	Gulati and Ramesh[6], 2022, India	Prospective study	PRP: 22; CS: 22	PRP; Age: 46.3 ± 9.7; Gender: 6, 16; CS; Age: 42.3 ± 5.8; Gender: 7, 15	Pain reduction (VAS) and disability reduction (DASH score)	PRP injection reduced pain significantly in 4, 12, and 24 weeks after treatment compared to CS therapy (VAS in 4 weeks: 5 *vs* 7; 12 weeks: 3.5 *vs* 5; 24 weeks: 1 *vs* 5; $P < 0.001$) PRP injection reduced disability significantly in 4, 12, and 24 weeks compared to CS therapy (DASH score in 4 weeks: 61.3 *vs* 93.1; 12 weeks: 40.9 *vs* 87.2; 24 weeks: 13.6 *vs* 72.7; $P < 0.001$)
7	Johurul *et al* [29], 2019, Bangladesh	Prospective study	PRP: 25; CS: 35	PRP; Age: 35 ± 2.1; Gender: 10, 15; CS; Age: 42 ± 7.3; Gender: 15, 20	Pain reduction (wrist pain)	PRP injection reduced pain significantly in 60 days after treatment compared to CS therapy (wrist pain: 1.1 ± 1.0 *vs* 2.7 ± 1.0, p: 0.0001)
8	Kumar *et al* [14], 2023, India	Prospective study	PRP: 30; CS: 30	PRP; Age: 35.83 ± 8.48; Gender: 8, 22; CS; Age: 37.80 ± 6.44; Gender: 10, 20	Pain reduction (VAS), disability reduction (DASH score), and functional outcome (Mayo's wrist score)	PRP injection reduced pain insignificantly in 3, 6, 12 months after treatment compared to CS therapy (VAS in 3 months: 1.87 ± 1.78 *vs* 2.30 ± 2.32, p: 0.420; 6 months: 0.83 ± 0.99 *vs* 1.23 ± 1.61, p: 0.251; 12 months: 0.40 ± 0.62 *vs* 0.47 ± 0.78; p: 0.715) PRP injection reduced disability insignificantly in 3, 6, 12 months after treatment compared to CS therapy (DASH score in 3 months: 5.66 ± 6.56 *vs* 6.82 ± 8.70, p: 0.633; 6 months: 2.38 ± 3.87 *vs* 3.02 ± 5.13, p: 0.587; 12 months: 0.49 ± 0.85 *vs* 1.21 ± 2.83, p: 0.183) PRP injection improved functional outcome insignificantly in 3, 6, 12 months after treatment compared to CS therapy (Mayo's wrist score in 3 months: 82.83 ± 8.68 *vs* 82.00 ± 9.34, p: 0.722; 6 months: 88.83 ± 6.91 *vs* 86.83 ± 7.13, p: 0.274; 12 months: 92.50 ± 4.10 *vs* 90.83 ± 5.88, p: 0.208)

9	Peck and Ely [13], 2013, United States	Case report	PRP: 1	Age: 74; Gender: F	Pain reduction (VAS)	PRP injection reduced pain in 3 and 6 months after treatment (VAS baseline: 38 of 100; 3 months: 10 of 100; 6 months: 14 of 100)
10	Ramesh *et al* [30], 2018, India	Prospective study	PRP: 141	Age: 41.24 (21-59); Gender: 77 , 64	Pain reduction (VAS) and functional outcome (Mayo's wrist score)	PRP injection reduced pain significantly in 6 months after treatment (VAS: 9.42 *vs* 3.92, $P < 0.001$) PRP injection improved functional outcome significantly in 6 months after treatment (Mayo's wrist score: 22.71 *vs* 71.46, $P < 0.001$)
11	Sheikh *et al* [10], 2020, Egypt	Prospective study	PRP: 20 hand; CS: 20 hand	PRP; Age: 41.45 ± 11.54; Gender: 15, 2; CS; Age: 41.30 ± 8.06; Gender: 16, 2	Pain reduction (VAS), disability reduction (qDASH score), functional outcome (JHFT), and USG evaluation of tendon	PRP injection reduced pain significantly in 6 months after treatment compared to CS therapy (VAS: 2.13 ± 2.75 *vs* 1.94 ± 3.04, p: 0.034) PRP injection reduced disability significantly in 6 months after treatment compared to CS therapy (qDASH score: 10.90 ± 10.86 *vs* 9.38 ± 13.52, p: 0.729) PRP injection improved functional outcome significantly in 6 months after treatment compared to CS therapy (JHFT: 49.56 ± 5.98 *vs* 50.39 ± 7.63, p: 0.735) PRP injection decreased tendon thickness insignificantly in 6 months after treatment compared to CS therapy (LS: 2.35 ± 0.77 *vs* 1.99 ± 0.53, p: 0.133; TS: 2.54 ± 0.67 *vs* 2.42 ± 0.57, p: 0.571); decreased tendon and sheath thickness insignificantly in 6 months after treatment compared to CS therapy (LS: 3.23 ± 0.92 *vs* 2.91 ± 0.96, p: 0.335; TS: 3.53 ± 0.87 *vs* 3.18 ± 0.63, p: 0.183); decreased extensor retinaculum thickness significantly in 6 months after treatment compared to CS therapy (0.98 ± 0.35 *vs* 0.59 ± 0.25, $P < 0.001$)
12	Shoma *et al* [11], 2023, Bangladesh	RCT	PRP: 33; Conservative: 30; CS: 31	PRP; Age: 45.6 ± 10.4; Gender: 12, 21; Conservative; Age: 42.4 ± 6.3; Gender: 7, 23; CS; Age: 46.9 ± 11.3; Gender: 9, 22	Pain reduction (VAS) and functional outcome (Mayo's wrist score)	PRP injection reduced pain significantly in 3 and 6 months after therapy compared to conservative and CS therapy (VAS: 3.5 ± 0.7 *vs* 4.4 ± 0.7 *vs* 3.9 ± 0.5, $P < 0.001$) PRP injection improved functional outcome significantly in 3 and 6 months after therapy compared to conservative and CS therapy (Mayo's wrist score: 87.9 ± 3.7 *vs* 65.2 ± 7.2 *vs* 73.7 ± 4.8, $P < 0.001$)

CS: Corticosteroid; DASH: Disabilities of the arm, shoulder, and hand; DQT: De quervain's tenosynovitis; F: Female; JHFT: Jebsen hand function test; LS: Longitudinal section; n: Number; p: Probability; PRP: Platelet-rich plasma; ROM: Range of motion; TS: Transeversal section; qDASH: Quick disabilities of the arm, shoulder, and hand; USG: Ultrasonography; VAS: Visual analogue scale.

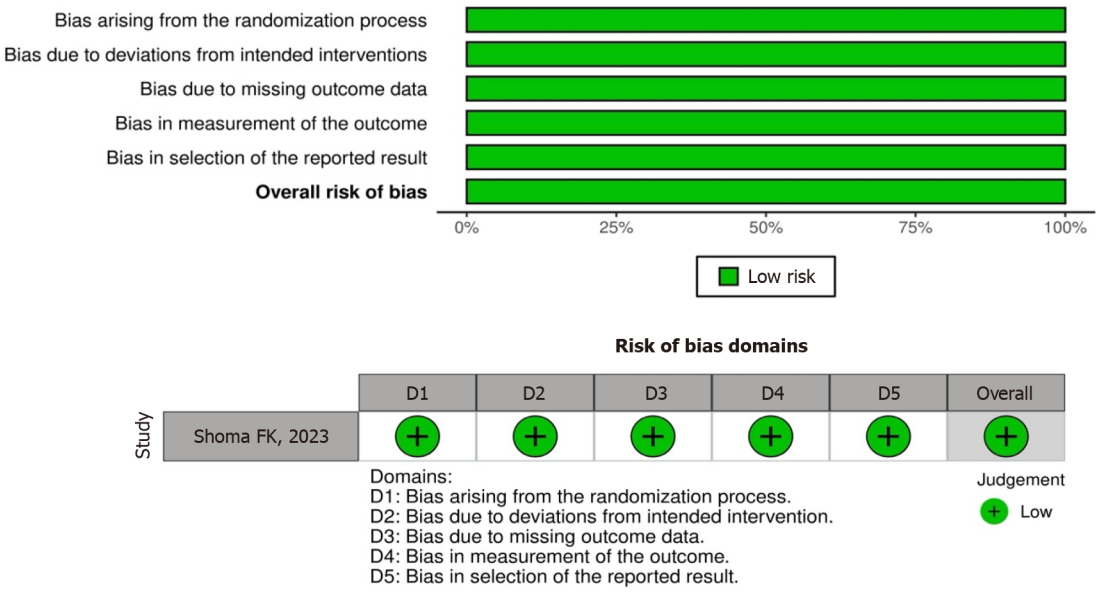

Figure 2 ROB 2: Shoma FK, 2023[11].

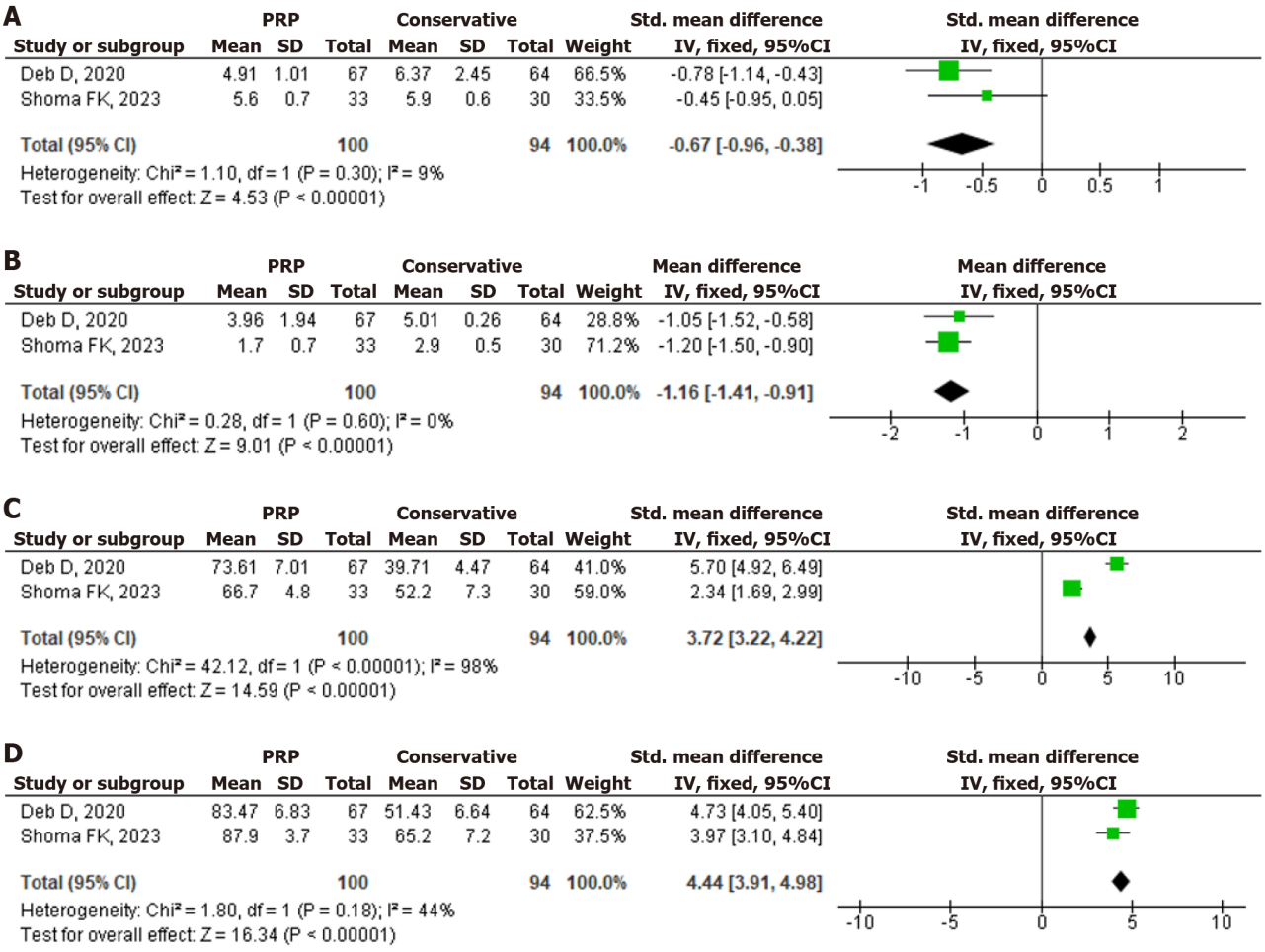

Figure 3 Forest plots of the comparison between platelet-rich plasma injection and conservative treatment. A: Visual analogue scale (VAS) pain at first month after treatment; B: VAS pain at six months after treatment; C: Mayo's wrist score at first month after treatment; D: Mayo's wrist score at six months after treatment. PRP: Platelet-rich plasma.

angiogenesis accumulate. During this stage, water content and glycosaminoglycan levels are high, which lasts from one to six weeks. The remodelling stage is the third stage (six to ten weeks), with cellularity, collagen, and glycosaminoglycan production reduced, followed by the last stage, namely the maturation stage, where production of type I collagen is occurred which lasts from ten weeks to six months (in this stage, the metabolism of tenocyte remains high)[6,32-34]. According to this finding, PRP injection provides better pain management and stable improvements in functional results in the long term. In contrast, CS injection results in rapid recovery but temporary improvement (short-term effect)[29,33,35,36].

For PRP preparation, most studies used 10-30 cc of blood from the patient's vein with an aseptic procedure and combined with an anticoagulant (citrate phosphate dextrose adenine-1). After that, the blood was placed into a PRP kit and centrifuge twice: The first time was four minutes at 3200 rpm, and the second time was three minutes at 3300 rpm to separate erythrocyte, platelet-poor plasma, and PRP. Then, 1.5-4 cc of PRP was collected. Prior to injection, 10% of calcium chloride solution was combined with autologous PRP in a ratio of 1: 10. First, the PRP injection was administered under local anaesthesia and injected along the inflamed tendon sheath of APL and EPB tendons; then, an antiseptic dressing was applied at the injection site after the procedure. The patient was observed for 10-15 minutes to monitor any adverse effects from the procedure and the patient was discharged with a recommendation to take a rest the next day, refrained from weight bearing and repetitive movements on the treated wrist for at least one week and the usage of wrist splint for 48-72 hours, the usage of cold compress or paracetamol for analgesia if necessary, and avoided the usage of NSAID[5-9,13,14,29,30].

Six studies discussed the usage of ultrasonography (USG) to guide the PRP injection to increase the accuracy of injection due to the anatomical variation of the first dorsal compartment of the wrist[5,7,9,10,13,30]. USG-guided PRP injection accurately directs the injection into the disorder area in cases of sub-compartmentalization, reduces the risk of subsequent tear, and prevents injection-associated complications, including superficial radial nerve injury[9,10]. Four studies used percutaneous needle tenotomy before the injection to create intra-tendinous micro tears and induce faster healing[9,37]. The fundamental theory of needle tenotomy is associated with the neovascularization and inflammatory response induced by perforation, which promotes tendon healing[38-41].

The dosage of PRP ranged from 1.5-4 cc from the included studies, with no differences in results in this dosage range[5-13,29,30]. However, with USG guided, the smaller volume of PRP injection (1.5 cc) can be effective in achieving good

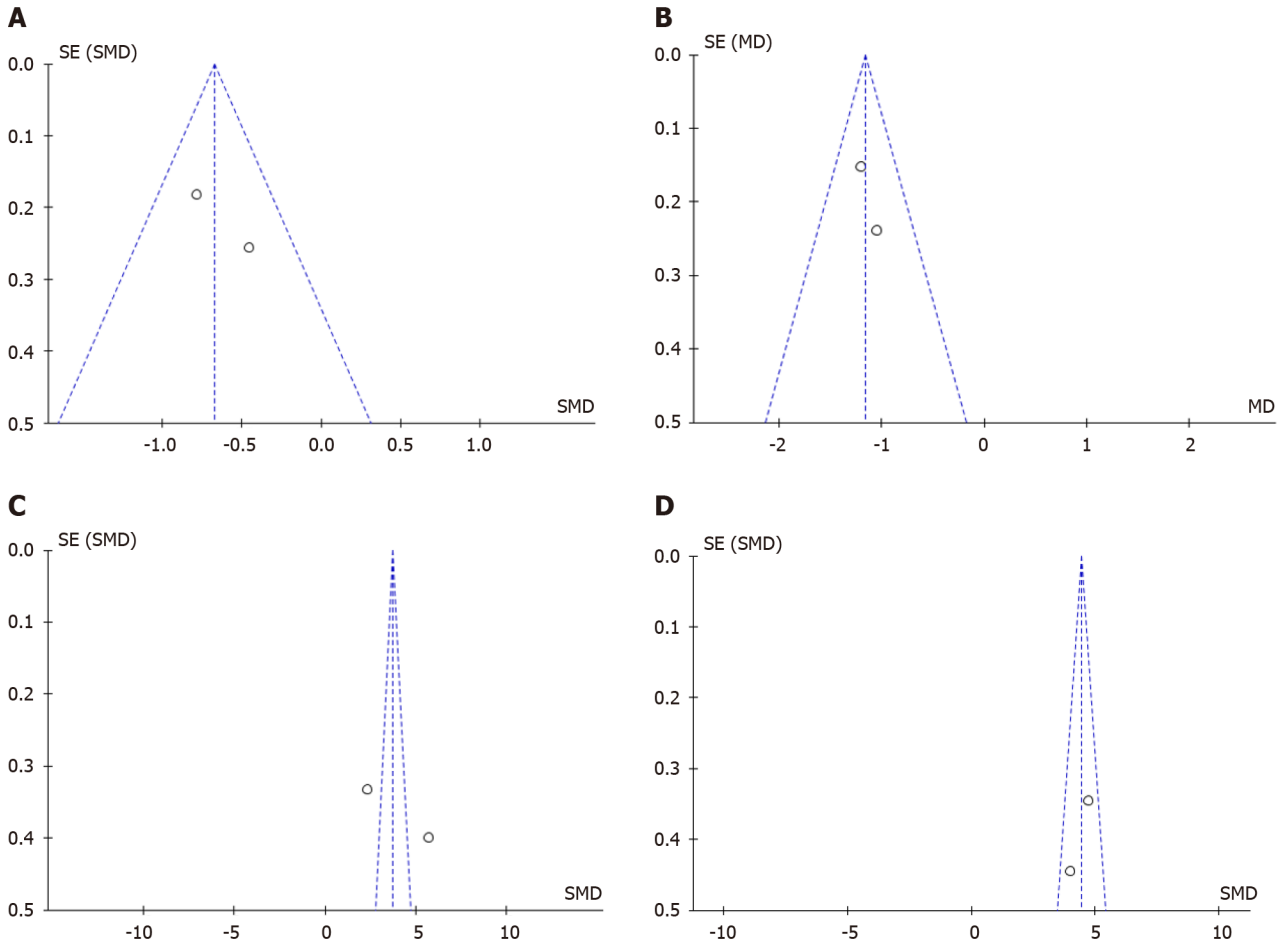

Figure 4 Funnel plots of the comparison between platelet-rich plasma injection and conservative treatment. A: Visual analogue scale (VAS) pain at first month after treatment; B: VAS pain at six months after treatment; C: Mayo's wrist score at first month after treatment; D: Mayo's wrist score at six months after treatment.

outcomes compared to PRP injection without USG guided due to the accuracy of injection location[8,29]. Most studies used single dose of PRP injection, but three studies used multiple doses of PRP injection, with the treatment interval being four weeks[5,6]. The interval between doses was required because of the initiation of fibroblast proliferation and neo-angiogenesis[30,42].

There was no complication associated with PRP injection in DQT treatment, however Asaad *et al*[9] reported two patients that experienced with mild vasovagal sign following the procedure due to the adverse event of lidocaine or pain at the time of procedure. According to Chen *et al*[7], the skin discoloration or atrophy caused by CS injection that has persisted for more than one year had utterly resolved after six weeks of PRP injection; this was probably due to the effect of PRP in tissue regeneration.

Despite PRP is a safe treatment with minimal side effects, some disadvantages and contraindications need to be considered. Adverse effects at the injection site (formation of scar tissue and calcification, infection, allergic reaction), no established and consistent method for preparing and administering PRP (ideal duration, method, frequency, volume and concentration of these components for maximizing beneficial effects are still unclear) are disadvantages for PRP treatment. While, critical thrombocytopenia, platelet dysfunction, hemodynamic instability, systemic infection, local inflammation at the injection site, and patients who are unwilling to accept risk are absolute contraindications for PRP treatment[43,44]. The relative contraindications of PRP treatments are the usage of NSAID within two days, glucocorticoid injection at the treatment site within a month, systemic glucocorticoid consumption within two weeks, recent fever or illness, malignancy especially bone or haematolymphoid malignancy, anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (less than 150000 platelets per microliter), and smokers[45-47].

Strengths and limitations of the study

This systematic review consisted of 12 studies that discussed PPR efficacy for DQT. The majority of the studies were prospective studies that discussed the efficacy of PRP in reducing pain in DQT.

The limitations of this systematic review were that the majority of studies were observational studies, the baseline characteristics were varied, the demography variance and confounding variables in the human study were unknown, the sample size in some studies were small, the difference of PRP preparation and technique between included studies, there was limited follow-up time, and this systematic review only reviewed English-language articles.

Future implication

The current systematic review can be a scientific publication for physicians, researchers, and all readers associated with the efficacy of PRP for DQT. Further research is needed with a larger sample size, diverse demographic variances, longer follow-up time, and standardization of PRP preparation and injection technique.

CONCLUSION

PRP can be used as an alternative non-operative treatment for DQT who did not respond to traditional therapy due to its tissue regenerative effect. USG-guided PRP with percutaneous needle tenotomy gives better outcome in DQT. Further research is needed related to standardization of PRP preparation and PRP injection technique.

FOOTNOTES

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SYSTEMATIC REVIEWS

Conservative management of spinal pathology with autologous conditioned serum: A systematic review of the literature

Christian J Rajkovic, Matthew L Merckling, Alyssa W Lee, Galadu Subah, Aryan Malhotra, Zachary D Thomas, Sabrina L Zeller, John V Wainwright, Merritt D Kinon

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Abstract

BACKGROUND

Chronic inflammatory pain is associated with increased expression of interleukin (IL)-1, an inflammatory cytokine, and activity on its receptor (IL-1R). In response, the body produces IL-1R antagonist (IL-1Ra) to reduce this signaling. Autologous conditioned serum (ACS) is the only biologic therapy for spinal pathologies that enhances the action of endogenous IL-1Ra reserves to improve symptoms. This systematic review investigates the effectiveness of ACS in treating pain and disability caused by spinal pathologies.

AIM

To evaluate the use of ACS as a conservative management option for spinal pathology.

METHODS

A systematic review of PubMed/Medline was performed to identify studies investigating administration of ACS for treatment of any spinal pathology.

RESULTS

Six articles were included, comprising 684 patients treated with epidural (n = 133) or transforaminal (n = 551) ACS injections. Patients had an average age of 54.0 years with slight female predominance (53.2%). The lumbar spine was most commonly treated, with 567 patients (82.9%) receiving injections for lumbar radiculopathy (n = 67), degenerative disc disease (DDD) (n = 372), or spinal stenosis (n = 128); cervical injections were performed in 109 patients (15.9%). Mean (SD) follow-up was 21.7 (4.8) weeks from first ACS injection. All studies investigating mechanical lumbar and lumbar or cervical radicular pain reported significant pain reduction at final follow-up compared to baseline. ACS achieved comparable or su-

perior results to lumbar epidural steroid injections. Adverse events were reported in 21 patients (3.1%), with no serious adverse events.

CONCLUSION
ACS injection is a safe and effective intervention for pain reduction in many spinal pathologies, including cervical and lumbar radiculopathies.

Key Words: Spine; Autologous conditioned serum; Orthokine; Regenokine; Epidural steroid injection; Interleukin-1; Interleukin-1 receptor antagonist

Core Tip: Injections of autologous conditioned serum (ACS) are an emerging conservative management strategy for reducing inflammation and pain in various osteoarthritic conditions. This therapy extracts and amplifies the novel anti-inflammatory molecule, interleukin-1 receptor antagonist, in a patient's serum for autologous treatment of inflammation. This study systematically reviews the literature for articles investigating the effectiveness of ACS in improving pain, disability, and quality of life in patients with spinal pathology.

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INTRODUCTION

Interleukin (IL)-1 is a known potentiator of osteoarthritis through biochemical enhancement of acute and chronic inflammation, thus precipitating tissue necrosis and the development of pain. Through stimulation of the IL-1 receptor (IL-1R), IL-1 induces pathological catabolic activity *via* the upregulation of cytokines, such as IL-6 and tumor necrosis factor α (TNF-α), and proteolytic enzymes, such as matrix metalloproteinases and ADAMTS-4[1]. IL-1 has also been reported to upregulate nociceptive pathways that induce hyperalgesia and neuropathic pain[2]. In pathologies of the spine, such as chronic radiculopathy, disc degeneration, and spinal stenosis, chronic inflammatory pain is associated with enhanced expression of IL-1 and activity of IL-1 on IL-1R[3-5]. To maintain balance between inflammatory stimuli and the subsequent host response, the body produces IL-1R antagonist (IL-1Ra), the only cytokine inhibitor naturally produced by the body, to reduce signaling at IL-1R[6,7]. Upregulation of IL-1Ra has been shown to inhibit necrosis of cartilage, muscle, and nervous tissue of the spine. At concentrations between ten and one thousand times in excess of normal serum, IL-1Ra can completely block IL-1R and IL-1 signaling[8,9].

Current recombinant biologics, such as Anakinra™, rilonacept, and canakinumab, manipulate the IL-1 signaling cascade for treatment of various autoimmune, inflammatory, and malignant spine and non-spine diseases[7,10]. However, autologous conditioned serum (ACS) is the only biologic therapy for spine pathology that enhances the action of patients' endogenous IL-1Ra reserves to reduce inflammation and improve symptoms[7,10]. Referred to as Orthokine™ and Regenokine™ in the United Kingdom and the United States, respectively, ACS was originally described by Dr. Peter Wehling, a German spine surgeon, in 1997 as a method of manipulating extracted patient serum to amplify production of IL-1Ra[10]. In this process, the patient's venous blood is incubated at 37 °C for several hours in the presence of borosilicate glass beads, which induce de novo production of IL-1Ra from serum monocytes and platelets to a concentration approximately ten times the serum concentration. This increased saturation of IL-1Ra functions to antagonize the inflammatory process of IL-1, thus preventing tissue destruction seen in chronic inflammation and improving the patient's pain response in a clinically meaningful manner[11]. IL-1 has been shown in the literature to sensitize affected nerve roots to hyperalgesia in cases of spinal radiculopathy[12]. In addition to IL-1Ra, other cytokines, including IL-10, IL-6, and TNF-α, and growth factors, such as fibroblast growth factor 2 (FGF-2), vascular endothelial growth factor, and hepatocyte growth factor (HGF), are also present in increased concentration following conditioning[8,10]. ACS is then either stored for later use or immediately injected into the affected area. In spinal injections, the typical dosing regimen is three injections per week over three weeks, and this regimen can be repeated as often as necessary if the therapy remains effective at relieving pain[8]. Spinal injections are typically performed twice a week over six weeks in one of two fashions, around the epidural space similar to an epidural steroid injection (ESI) or transforaminally around the spinal nerve root[13]. The purpose of this systematic review is to investigate the effectiveness of ACS in treating neurologic deficit, disability, and pain caused by spinal pathology.

MATERIALS AND METHODS

A systematic review of the literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Figure 1). PubMed/Medline was interrogated for clinical studies investigating the administration of ACS for the treatment of any spinal pathology. This systematic review was not prospectively registered.

Eligibility criteria

Articles included in this review met the following inclusion criteria: (1) Article discusses spinal pathology; (2) Article applies an intervention of ACS administration; and (3) Pain, disability, or quality of life outcome is reported. Studies were excluded if they met any of the following exclusion criteria: (1) Unavailable in English; (2) Abstracts and unpublished studies; (3) Reviews; (4) Articles describing non-spinal pathology; and (5) Articles describing non-ACS IL-1 therapies.

Information sources and search strategy

Using PRISMA guidelines, PubMed/Medline database was queried on November 3, 2023 using search terms inclusive for spinal pathology and anti-IL-1R therapy including: "autologous conditioned serum", "regenokine", "orthokine", "IL-1 receptor antagonist", "IL-1Ra", and "anti IL-1". No limits were imposed on the year of publication. Full search terms used can be found in Supplementary material 1. No limits were placed on the year of publication of queried articles, and all articles included were peer-reviewed, published, and accessed without requiring contact with corresponding authors.

Selection process

Articles were queried by author Rajkovic CJ, and seven authors (Rajkovic CJ, Merckling M, Lee AW, Subah G, Malhotra A, Thomas ZD, Zeller SL) independently screened each title, abstract, and manuscript for inclusion and exclusion criteria. Duplicate articles were screened and removed from the query. Bibliographies of the included articles were also screened using our inclusion and exclusion criteria for additional relevant studies. The screening results were confirmed by two additional reviewers (Rajkovic CJ and Zeller SL).

Data collection process, data items, and statistical analysis

Two authors (Rajkovic CJ and Merckling M) independently extracted and recorded all data into two separate Google spreadsheets. Source articles were used to cross-check and verify the data in each spreadsheet. The following information was extracted from each article: The spinal pathology treated, the study design, the baseline characteristics of each cohort, the dosing regimen and route of administration of the ACS treatment, and any comparable interventions for conservative management of spinal pathology. For articles where the age or sex of the ACS cohort was only reported as a pooled statistic with other cohorts, the pooled statistic was used to estimate the overall age or sex distribution of the ACS cohort. Primary outcomes investigated included patient pain, disability, and quality of life scores. Secondary outcomes investigated included reported adverse events and analgesic use. Data that was only reported graphically was extracted using webplotdigitizer (https://automeris.io/WebPlotDigitizer/) software to estimate mean and standard deviation values. All statistical comparisons for reported outcomes were extracted from individual included studies, and no meta-analysis was performed between studies. The statistical methods of this study were reviewed by Dr. Elizabeth Drugge from New York Medical College.

Study risk of bias assessment

Two reviewers (Subah G and Zeller SL) independently assessed the risk of bias of the studies included in this systematic review using the Joanna Briggs Institute critical appraisal checklist for both cohort studies and randomized control trials (RCT)[14]. This process involved considering 11 and 13 questions about cohort studies and RCT, respectively, to assess risk of bias. Studies with a score < 50% of questions answered "yes" were considered as high risk, a score between 50% and 69% as moderate risk, and a score ≥ 70% as low risk (Table 1).

RESULTS

Baseline characteristics of included studies

Our search query retrieved 385 articles from PubMed/Medline, and 376 articles were excluded on initial screening for the following reasons: Not spinal pathology (n = 198), no IL-1Ra treatment (n = 124), basic science study (n = 44), review article (n = 4), not English (n = 3), letter to the editor (n = 2), and retracted article (n = 1). Of the remaining nine articles, three investigated anakinra treatment and were excluded. Six articles were finally included from 2007 to 2023, comprising 684 distinct patients who were treated with ACS for spinal pathology and 72 patients who were treated with comparative steroid injections. The mean (SD) follow-up for these patients was 21.7 (4.8) weeks following their first ACS injection. All ACS injections were performed either interlaminarly (n = 61 patients) or transforaminally (n = 623 patients). The included articles consisted of two pilot studies, two prospective cohort studies, one retrospective cohort study, and one RCT. Each study's design, baseline clinical characteristics of the patient cohort, and investigated outcomes are summarized in Table 2. Among patients treated with ACS in the included articles, the average age was 54.0 years (n = 684 patients, range: 17-93), the average BMI was 26.4 kg/m^2 (n = 120 patients), and 53.2% of patients were female. Pre-existing comorbidities were only reported by Godek *et al*[13], including two patients with diabetes, four patients with peripheral vascular

Table 1 Risk of bias assessment

Manuscript type	Ref.	Related questions													Total	Risk of bias
Randomized control trial		Was true randomization used for assignment of participants to treatment groups?	Was allocation to treatment groups concealed?	Were treatment groups similar at the baseline?	Were participants blind to treatment assignment?	Were those delivering the treatment blind to treatment assignment?	Were treatment groups treated identically other than the intervention of interest?	Were outcome assessors blind to treatment assignment?	Were outcomes measured in the same way for treatment groups?	Were outcomes measured in a reliable way?	Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Were participants analyzed in the groups to which they were randomized?	Was appropriate statistical analysis used?	Was the trial design appropriate and any deviations from the standard randomized control trial design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?		
	Godek *et al* [13]	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	85%	Low
Cohort studies		Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Was follow-up complete, and if not, were the reasons for loss to follow-up described and explored?	Were strategies to address incomplete follow-up utilized?	Was appropriate statistical analysis used?	N/A	N/A		
	Becker *et al* [15]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	100%	Low
	Goni *et al* [16]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N/A	N/A	73%	Low
	HS *et al*[17]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	100%	Low
	Godek *et al* [19]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N/A	N/A	82%	Low

	Godek *et al* [18]	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N/A	N/A	73%	Low

Table 2 Designs and conclusions of included studies

Ref.	Study design	Sample size	Age (mean)	BMI (mean)	Female	Pathology	Intervention (s)	Latest follow-up	Outcomes measured	Conclusion
Becker *et al* [15]	Randomized prospective cohort study	ACS: *n* = 32, 5 mg Triamcinolone: *n* = 27, 10 mg Triamcinolone: *n* = 25	53.9 (range: 29-81)	Not reported	38.10%	Lumbar radiculopathy	3 weekly transforaminal injections of ACS, 5 mg triamcinolone, or 10 mg triamcinolone	20 weeks post-final injection	VAS, ODI	Epidural ACS injection for unilateral lumbar radiculopathy significantly improved patient pain and disability compared to baseline to an extent potentially superior to ESI. No statistically significant difference in symptom improvement was observed between 5 mg and 10 mg epidural injection of triamcinolone
Goni *et al*[16]	Pilot study	ACS: *n* = 20; MPS: *n* = 20	ACS: 42.25; MPS: 46.80	Not reported	ACS: 40%; MPS: 45%	Cervical radiculopathy	A single 2-3 mL transforaminal injection of ACS or MPS	6 months post-injection	VAS, NDI, NPDS, PCS, MCS	Patients with cervical radiculopathy treated with epidural ACS injection experienced sustained improvement of pain, disability and quality of life. ACS produced as good or better improvement of symptoms with longer duration of relief compared to epidural methylprednisolone
HS *et al*[17]	Prospective study	ACS: *n* = 20	37.15	24.92 kg/m^2	Not reported	Lumbar radiculopathy	A single 2 mL transforaminal injection of ACS	6 months post-injection	VAS, SLRT, ODI, PCS, MCS	Epidural ACS injection can modify the disease course of unilateral lumbar radiculopathy by significantly improving pain, disability, and quality of life
Godek *et al* [19]	Pilot study	ACS: *n* = 15	38.8	Not reported	40%	Lumbar radiculopathy	1-2 weekly transforaminal injections of 3-4 mL ACS	6 months post-injection	VAS, ODI, SLRT, OLST, Analgesic use	ACS is a promising option for significantly improving pain and disability in patients with single-level lumbar radiculopathy. No radicular damage or sever adverse events were reported
Godek *et al* [18]	Retrospective study	ACS: *n* = 497	57.1 ± 16.5 (range: 17-93)	Not reported	57.70%	Cervical DDD (transforaminal injection): *n* = 89. Thoracic Spine DDD (transforaminal injection): *n* = 8. Lumbar Spine DDD (transforaminal injection): *n* = 271. Lumbar Spine DDD (interlaminar injection): *n* = 1. Lumbar Spine Stenosis (transforaminal injection): *n* = 118.	Cervical: 4 doses of 3-4 mL transforaminal ACS injections. Thoracic: 6 doses of 3-4 mL transforaminal ACS injections. Lumbar: 4-6 doses of 4 mL ACS injected transforaminally or interlaminarly	6 months post-final injection	Modified McNabb scale	ACS injection was well tolerated with very few and limited cases of adverse events. ACS injection produced satisfactory improvement in Modified McNabb Scale scores for patients with cervical or lumbar discopathy. Unsatisfactory results predominated in cases of lumbar spinal stenosis

						Lumbar Spine Stenosis (interlaminar injection): n = 10				
Godek *et al* [13]	Randomized control trial	ACS: n = 100	46.29 + 13.61	26.67 ± 4.49	51%	Lumbar Radiculopathy due to DDD (interlaminar injection): n = 50. Lumbar Radiculopathy due to DDD (transforaminal injection): n = 50	2 weekly interlaminar or transforaminal injections of 8 mL ACS	24 weeks post-final injection	NRS, ODI, RMQ, EQ-5D-5 L mobility, EQ-5D-5 L self-care, EQ-5D-5 L usual activities, EQ-5D-5 L pain/discomfort, EQ-5D-5 L anxiety/depression, EQ-5D-5 L-based LSS, EQ-5D-5 L VAS, EQ-5D-5 L Index	Epidural and transforaminal ACS injections both significantly improve patient outcomes compared to baseline. Treatment with transforaminal ACS injection produced statistically superior improvement in EQ-5D-5 L scores compared to epidural ACS injection

BMI: Body mass index; ACS: Autologous conditioned serum; VAS: Visual acuity scale; ODI: Oswestry disability index; ESI: Epidural steroid injection; MPS: Methylprednisolone; NDI: Neck disability index; NPDS: Neck pain disability scale; PCS: Physical component score; MCS: Mental component score; SLRT: Straight leg raise test; OLST: One leg standing test; DDD: Degenerative disk disease; RMQ: Roland Morris questionnaire; EQ-5D-5 L: Euro quality of life-five dimensions-five levels; LSS: Level sum score.

disease, and two patients with bone metabolism disorders in the RCT of 100 subjects. At baseline, patients were described to have moderate-severe pain of at least six weeks duration in three studies[15–17] and any chronic radicular symptoms in the remaining three studies[13,18,19]. Patients were opioid or steroid-naive for at least six months in three of the six included studies[15,17,19], and oral nonsteroidal anti-inflammatory drugs were allowed during the treatment period for four of the six included studies[15–17,19]. The lumbar spine was the most common spinal segment treated, with 567 patients (82.9%) receiving ACS injections for either lumbar radiculopathy (n = 67 patients), lumbar DDD (n = 372 patients), or lumbar stenosis (n = 128 patients). Cervical ACS injections were performed in 109 patients (15.9%) for either cervical radiculopathy (n = 20 patients) or DDD (n = 89 patients), and only eight patients received thoracic ACS injections (1.2%) in our systematic review, exclusively for thoracic DDD. Radiographic severity at presentation was only evaluated in one study with Godek *et al*[19] reporting an average disc herniation size of 5.3 ± 2.4 mm. Risk of bias assessment was low for all included studies.

Efficacy in pain management

All included articles investigated pain relief following injection with ACS as a primary outcome. Specific metrics used to report pain included the visual acuity scale (VAS; four studies; Figure 2), numerical ranking scale (NRS; one study), and modified McNab scores (one study). All studies investigating ACS treatment of lumbar pathology reported significant pain reduction at final follow-up compared to baseline. Godek *et al*[19] reported a significant reduction in VAS score compared to baseline at both one month and three months (P = 0.002 and P < 0.0001, respectively) following transforaminal ACS injection for lumbar radiculopathy. Similarly, Becker *et al*[15] and HS *et al*[17] reported a significant reduction in baseline VAS scores at the end of 22 weeks and 24 weeks, respectively, for patients receiving transforaminal ACS injections for lumbar radiculopathy (P < 0.001 for both studies). Godek *et al*[13] observed a significant reduction in NRS scores at 24 weeks post-injection compared to baseline for both interlaminar and transforaminal injections in their RCT (6.1 *vs* 2.8, P < 0.0001 for interlaminar ACS injection; 6.1 *vs* 2.8, P < 0.0001 for transforaminal ACS injection). Among patients who received transforaminal ACS injections for cervical radiculopathy in a study by Goni *et al*[16], a 73.24% improvement (71.0 mm to 19.0 mm) in reported VAS scores was observed at six months following injection (P-value not reported).

Comparing ACS injection with ESI for treatment of lumbar pain, Becker *et al*[15] observed no significant difference in reported VAS scores between patients receiving ACS or 10 mg triamcinolone ESI at 22 weeks following their first injection (95%CI: -23.5, 4.9). When comparing ACS injection to a 5 mg triamcinolone ESI, the authors found that patients receiving

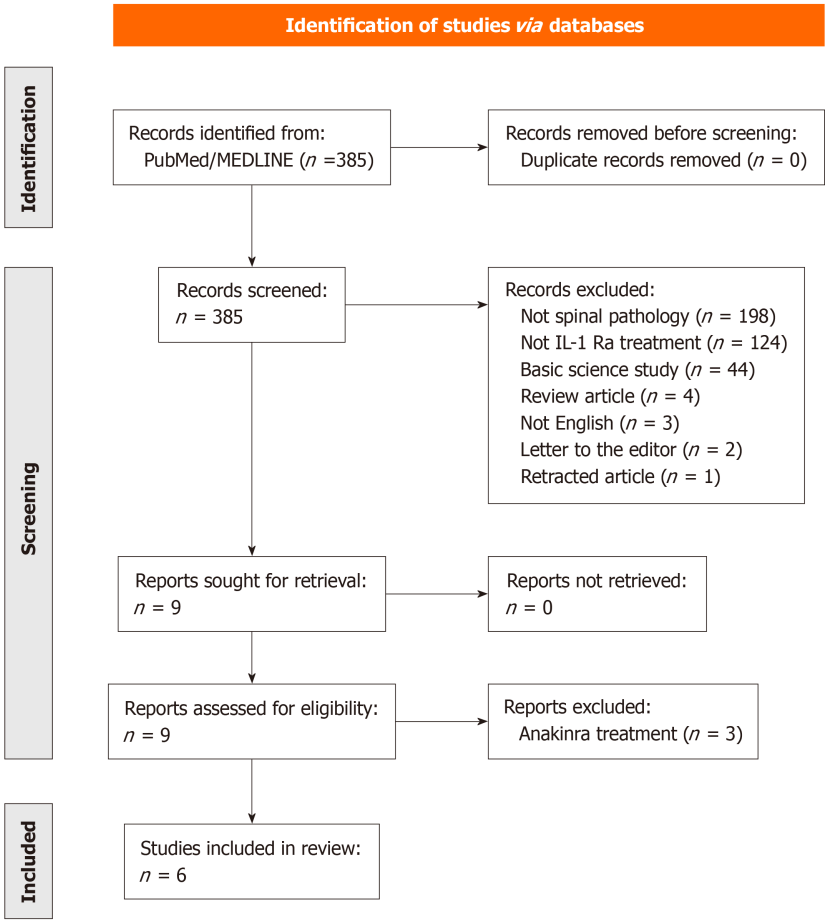

Figure 1 The preferred reporting items for systematic reviews and meta-analyses flowchart of search results.

ACS injection reported significantly lower mean (SD) VAS scores [23.3 (24.8) mm *vs* 36.8 (28.3) mm; $P = 0.046$]. Goni *et al* [16] reached a similar conclusion observing that patients receiving epidural ACS for cervical radiculopathy reported significantly lower VAS scores at their six-month follow-up than patients receiving methylprednisolone ESI (19.0 mm *vs* 27.5 mm; $P = 0.027$).

The modified McNab scores used by Godek *et al*[18] assessed both pain and disability using the following scoring system: (1) Excellent (no pain or mobility restriction and full level of activity); (2) Good (occasional pain and return to previous activity level); (3) Fair (improvement of pain with continued disability and reduced activity level); and (4) Poor (no pain improvement with continued disability and/or necessitated surgical intervention)[18]. For ease of comparison between different spinal pathologies, the authors defined a score of A or B as a satisfactory outcome. In cases of cervical and lumbar DDD, a satisfactory outcome at six-month follow-up was achieved in 61.8% and 56.5% of patients, respectively. These patients also had remarkably low rates of deterioration following initial improvement, with only 4.07% and 3.69% of patients showing a worsening of symptoms for cervical and lumbar DDD, respectively. In cases of thoracic DDD and lumbar spinal stenosis treated with transforaminal ACS injection, outcomes were less favorable with only 37.5% and 33.9% of patients achieving a satisfactory outcome. Patients with lumbar stenosis who were treated with interlaminar ACS injection fared better than those treated with transforaminal injection, achieving a 90% satisfactory outcome rate at six-month follow-up. However, this result was not statistically significant from baseline McNab scores because of a ten-patient cohort size.

Improvement of disability

All included studies investigated disability following injection with ACS as a primary outcome. Disability metrics included the Oswestry Disability Index (ODI; four studies; Figure 3), the Roland Morris Questionnaire (one study), the neck disability index (NDI; one study), and the neck pain and disability scale (NPDS; one study). Similar to pain response following ACS injection, Godek *et al*[19], Godek *et al*[13], Becker *et al*[15], and HS *et al*[17] reported significantly improved ODI scores at 12 weeks ($P = 0.005$), 24 weeks ($P < 0.0001$), 22 weeks ($P < 0.001$), and 24 weeks ($P < 0.001$), respectively. To assess patient disability due to cervical radiculopathy, Goni *et al*[16] documented both NDI and NPDS scores at baseline and 24 weeks following cervical transforaminal ACS injection and demonstrated a 74.47% and 73.76% improvement in average scores, respectively (*P*-value not reported).

The efficacy of ACS injection compared to ESI was less conclusive regarding disability outcomes. While Goni *et al*[16] observed that patients receiving cervical ACS injection reported significantly lower NDI and NPDS scores (NDI 15.9 *vs* 30.4, $P < 0.001$; NPDS 18.55 *vs* 31.1, $P < 0.001$) than patients receiving methylprednisolone ESI at 24 weeks, Becker *et al*[15]

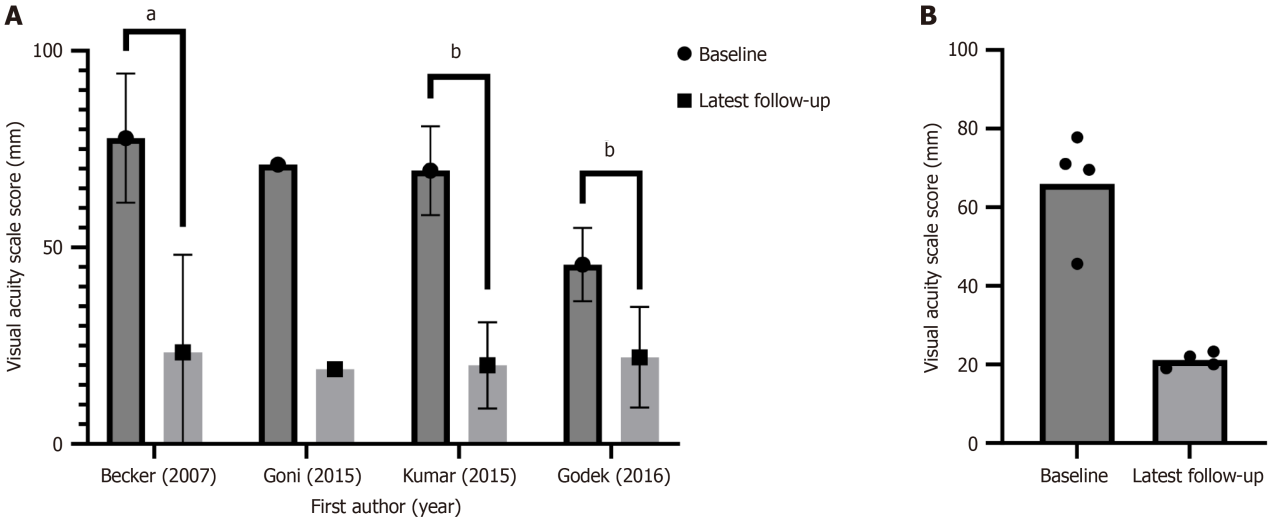

Figure 2 Patient visual acuity scale scores at baseline and at latest follow-up. A: The mean and standard deviation visual acuity scale (VAS) scores are depicted at baseline and latest follow-up after autologous conditioned serum injection for each of four included studies Becker *et al*[15]: n = 32, Goni *et al*[16]: n = 20, HS *et al*[17]: n = 20, Godek *et al*[19]: n = 15. Goni *et al*[16] did not report standard deviations for reported VAS scores or conduct pairwise comparison between baseline and follow-up VAS scores; B: The combined mean VAS scores are depicted at baseline and follow-up as reported by Becker *et al*[15], Goni *et al*[16], HS *et al*[17], and Godek *et al*[19]. $^{a}P < 0.05$; $^{b}P < 0.01$.

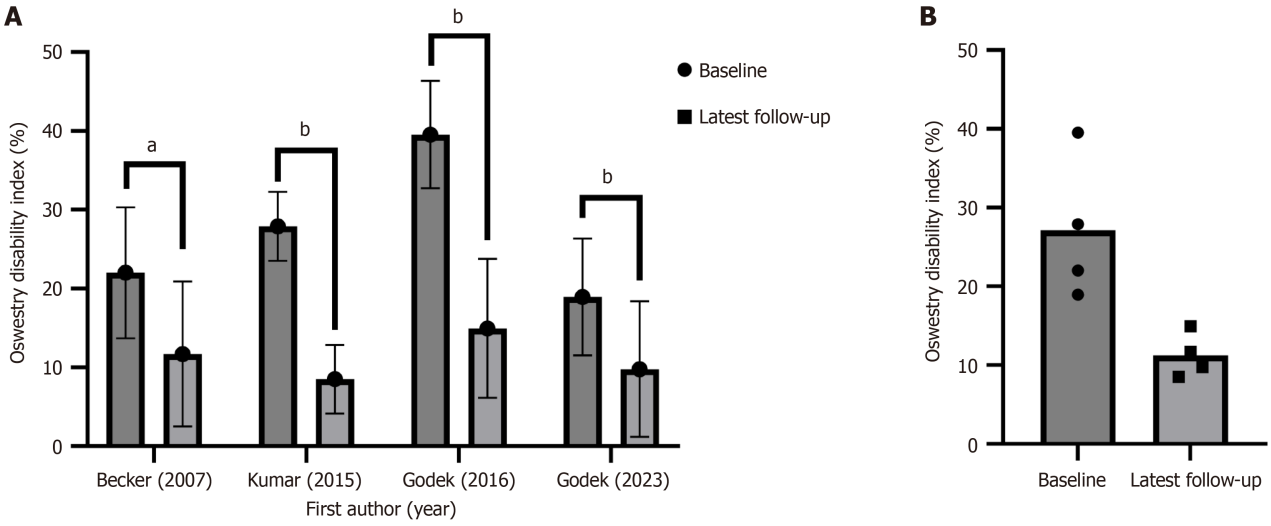

Figure 3 Patient Oswestry disability index at baseline and at latest follow-up. A: The mean and standard deviation Oswestry disability index (ODI) are depicted at baseline and latest follow-up after autologous conditioned serum injection for each of four included studies Becker *et al*[15]: n = 32, HS *et al*[17]: n = 20, Godek *et al*[19]: n = 15. Godek *et al*[13]: n = 100; B: The combined mean ODI scores are depicted at baseline and follow-up as reported by Becker *et al*[15], HS *et al*[17], Godek *et al*[19], and Godek *et al*[13]. $^{a}P < 0.05$; $^{b}P < 0.01$.

found no significant difference between ODI scores (P = 0.95) of patients receiving epidural ACS, 5 mg triamcinolone ESI, or 10 mg triamcinolone ESI for lumbar radiculopathy at 22 weeks.

Quality of life improvement

Quality of life was assessed using the Euro quality of life-five dimensions-five levels (EQ-5D-5 L) index (one study), the EQ-5D-5 L VAS (one study), the physical health component score (PCS) of the short form-36 (SF-36) questionnaire (two studies), and the mental health component score (MCS) of the SF-36 questionnaire (two studies). Comparing scores at baseline and 24 weeks post-injection, the RCT by Godek *et al*[13] observed a significantly improved EQ-5D-5 L index for patients receiving interlaminar (0.805 *vs* 0.913, P = 0.0001) and transforaminal (0.754 *vs* 0.895, P = 0.0001) ACS injections. Similarly, improvement from baseline to 24 weeks was also observed in EQ-5D-5 L VAS scores for interlaminar (66.14 *vs* 74.25, P = 0.0474) and transforaminal (60.14 *vs* 77.62, P < 0.0001) ACS injections. ACS injections were also shown to improve the average PCS of patients with cervical radiculopathy (27.35 at baseline to 49.08 at 24 weeks, P-value not reported) and lumbar radiculopathy (27.25 at baseline to 49.32 at 24 weeks, P < 0.001) in studies by Goni *et al*[16] and HS *et al*[17], respectively. Similarly, these two studies reported an improvement in MCS at 24 weeks for cases of cervical radiculopathy (36.22 at baseline to 47.12 at 24 weeks, P-value not reported) and lumbar radiculopathy (36.59 at baseline to

47.51 at 24 weeks, $P < 0.001$). Epidural ACS injections were also shown to outperform methylprednisolone ESI in improving PCS (49.08 *vs* 44.39, $P = 0.004$) and MCS (47.12 *vs* 42.42, $P < 0.001$) at 24 weeks following injection for cervical radiculopathy.

Adverse events

Adverse events of any kind were reported in 21 of the 684 patients (3.1%) included in this systematic review following ACS injection. No serious adverse events directly attributable to ACS injection, including infection, muscle atrophy, or hematoma, occurred in any of the patients in this review. The most severe adverse events reported were due to natural progression of disease, specifically four patients who eventually required emergency surgery due to persistent pain and foot paresis while receiving ACS therapy[18,19]. Further, three of the six studies included protocols for the treatment of persistent pain with over-the-counter analgesics taken as needed. The remaining adverse events were self-limited and resolved within 48 hours. These included headache ($n = 4$), dizziness ($n = 4$), syncope ($n = 1$), sweating ($n = 3$), tachycardia ($n = 2$), back stiffness ($n = 1$), and neck stiffness ($n = 2$). Godek *et al*[18] reported a mild complication rate of approximately 10% in its pooled cohort of osteoarthritis treatment, limited to mild myalgia, chills, weakness, and fevers resolving within 48 hours of injection[18]. In studies that compared ACS to ESI, the adverse event rates were similar between groups, with Becker *et al*[15] reporting one adverse event in each of its ACS and triamcinolone ESI treatment groups, and Goni *et al*[16] reporting 8 adverse events in its ACS treatment group and 11 adverse events in its methylprednisolone ESI treatment group ($P = 0.53$).

DISCUSSION

Despite the 200 billion dollars spent annually on its management, spine pain remains a leading cause of disability and the most common cause to seek emergency care[20]. Therefore, the need for continued advancements in managing chronic spine symptomatology is clear. While surgical intervention may be indicated in select patients depending on the nature and severity of their conditions, nonoperative treatment remains the first-line management for most mechanical and radicular pain generated by the spine[21]. In this review, all studies investigating ACS for mechanical lumbar, lumbar radicular, and cervical radicular pain unanimously reported significant pain reduction compared to baseline. Pain relief was sustained through final follow-up, ranging between 3 and 6 months from treatment.

Disrupting the inflammation-pain cycle of chronic spine pathologies is a mainstay of nonoperative treatment strategies, and ACS represents a particularly intriguing option for the treatment of spine-related pain due to its anti-inflammatory properties. ACS has been widely marketed for the treatment of knee osteoarthritis as Orthokine™ in Europe and Regenokine™ in the United States, and several clinical trials have demonstrated its effectiveness in relieving arthritic pain through the anti-inflammatory effects of IL-1Ra, its active ingredient[22–24]. Further, ACS contains several other anti-inflammatory factors such as IL-4, IL-10, IL-13, FGF-2, HGF, and TGF-β1, which may further inhibit inflammation-induced hyperalgesia[25,26]. In cases of radiculopathy, standard injection protocol for ACS is done *via* fluoroscopic guidance to the nerve root for transforaminal injections or following an interlaminar approach for epidural injections[8]. The proposed physiologic mechanism by which ACS is thought to relieve symptoms of radiculopathy concerns the inflammatory pathogenesis of back pain. In particular, several studies have correlated significant differences in pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α with severity of presentation of lower back pain[27]. Therefore, the antagonism of these factors with IL-1Ra and the previously described anti-inflammatory contents of ACS show promise as therapeutic components to alleviate the symptoms of spinal radiculopathy[17]. The sustained pain relief noted by several studies suggests the efficacy of ACS for these conditions, especially when considering these results in studies that used ESI as a comparator therapy[23].

ESIs serve both diagnostic and therapeutic purposes in spinal pain management, including identifying the anatomic locus of pain, providing short- or long-term pain relief, or delaying the need for surgical intervention; however, there is no definitive consensus on the exact indications of ESI treatment[28]. Further, patients experience variable responses with regard to the extent and duration of pain relief following ESI[29]. Patients are also limited to 2-3 ESIs annually to avoid the complication of increased degenerative changes secondary to increased osteoclast-driven bone turnover seen with repetitive corticosteroid treatment. Despite these limitations, ESI is a mainstay in the nonoperative management of many spine conditions and served as a comparison to ACS in several of the reviewed studies. ACS produced better long-term reduction in lumbar radicular symptoms when compared to 5 mg triamcinolone ESI, although no significant difference was appreciated compared to the 10 mg triamcinolone dose[15]. In the context of cervical radiculopathy, ACS treatment outperformed the methylprednisolone ESI regarding pain relief, further suggesting the comparable if not superior efficacy of ACS injection compared to ESI for pain relief[16]. In addition, ACS injections do not have the same limitation on dosing frequency that is observed with ESI and can be repeated as many times as necessary if symptom relief continues[8]. The only contraindications to receiving ACS therapy are ongoing infections, fever, diarrhea, vaccinations within the last 4 weeks, and comorbid cancer due to the altered cytokine profile of blood samples of patients with these conditions[18]. Cost is also an important factor when comparing ACS to ESI with a complete regiment of ACS therapy costing between $1000 and $3000 often out-of-pocket compared to a lumbar ESI costing an average of $601[30,31].

Of note, not all etiologies of spinal pain achieved significant relief with ACS. Godek *et al*[18] reported an improvement of radicular symptoms when DDD was the underlying pathology, but significant relief was not achieved in those with radicular pain secondary to spinal stenosis. This limitation has also been observed in ESI for lumbar stenosis and is thought to be due to the addition of fluid volume to an already compressed spinal canal along with a lipomatosis effect stimulated by the steroid[32]. In the remainder of our review, three studies only investigated radiculopathy due to DDD,

and two studies did not clarify underlying pathology, making the evaluation of ACS for the treatment of spinal stenosis difficult to assess.

In addition to pain relief, all included studies assessed improvement in disability. All studies reported significant improvement in disability when compared to baseline as measured by various disability indices; however, there were variable findings across studies when comparing ACS to ESI. In patients with cervical radiculopathy, NDI and NPDS scores were significantly less following ACS injections than following methylprednisolone ESI injections[16]; however, no significant difference in ODI scores was observed between ACS and either 5 or 10 mg triamcinolone ESI for lumbar radiculopathy at 22 weeks[15]. The comparison of disability reduction after ACS *vs* ESI is inconclusive as the studies utilized variable ESI medications and different disability measures. Thus, additional studies are needed to make this comparison.

All studies reporting quality of life measures demonstrated significant improvement following ACS injections when assessed by several different subjective tools. This benefit was seen specifically for patients suffering from cervical or lumbar radiculopathy. The improvement in MCS is particularly relevant considering the well documented association between radicular pain and declining mental health outcomes[33]. The inclusion of this outcome was an important factor in assessing the utility of ACS treatment for patients living with chronic radicular pain.

Another potential benefit of ACS is the minimization of steroid treatment in diabetic patients concerned with blood glucose management. While long-term diabetes management assessed through hemoglobin A1C levels has been shown to be unaffected by ESI treatment, a transient increase in blood glucose levels for several days following ESI has been well-documented[34]. ACS represents an alternative treatment option for chronic spine conditions in this patient population, who may benefit from the avoidance of hyperglycemia in the days following treatment.

Finally, ACS has a favorable safety profile, with an overall adverse event rate of 3.1%, and no serious adverse events attributable to ACS were identified in this review. Self-limited adverse events reported in the studies, such as headache, dizziness, and syncope, have also been well documented among ESIs[35] and are most likely related to the penetrating nature of injections rather than the injectate. The safety of ACS was shown to be comparable to that of ESI, and this review derived no indication of ACS injection carrying a higher risk profile than other forms of epidural injections.

This study is a systematic review and is thus limited by the heterogeneity of data in the included articles and the lack of compatibility between cohorts at baseline. As a result, a meta-analysis was not performed to compare data given the different pathologies and outcomes reported by each study. One limitation of this study is the limited reporting of pre-existing comorbidities that may have influenced outcomes of treatment with only one cited study including this information. Future studies may benefit from analyzing the effect of comorbidities on response to ACS. Various metrics were used across studies to evaluate pain, disability, and quality of life changes to treatment which precluded a meta-analysis of the outcomes. Further, some studies included the use of oral analgesics and variable injection sites, both of which may have played a role in outcomes. Large scale, multi-center clinical trials are needed to supplement the current literature on the effectiveness of ACS for the treatment of spinal pathology with significant follow-up and comparison to controls and standard of care conservative treatments such as ESI. Currently, a prospective protocol has been published for ultrasound-guided injection of ACS for the treatment of cervical pain with anticipated completion of the trial in early 2025[36].

CONCLUSION

While further research is needed for the evaluation of ACS in various spinal conditions and its comparison to ESI, its risk to benefit profile has shown promise for nonoperative management of spine conditions. ACS therapy for mechanical and radicular symptoms has demonstrated value when compared to ESI. Examined studies showed improved long term relief, ability to repeat treatments without risk of bone destruction, and elimination of excessive corticosteroid treatments in diabetic patients. ESI continues to be a useful treatment option due to its cost effectiveness relative to ACS and its ability to serve as a diagnostic tool, however the future of spine care can benefit from the inclusion of ACS in the treatment algorithm of nonoperative management. Future research is needed to compare and recommend specific ACS treatment protocols with long term outcome data focused on clinical outcomes. Examination of cost effectiveness, avoidance of surgical intervention, and subjective quality of life measures should be included in these future studies.

FOOTNOTES

Author contributions: Rajkovic CJ was responsible for designing the review protocol, writing the protocol and report, conducting the search, screening potentially eligible studies, extracting and analyzing data, interpreting results, writing the manuscript, updating reference lists, and creating figures and tables; Merckling ML was responsible for screening potentially eligible studies, extracting and analyzing data, interpreting results, and writing the manuscript; Lee AW was responsible for screening potentially eligible studies and creating the PRISMA figure; Malhotra A, Thomas ZD was responsible for screening potentially eligible studies; Subah G, Zeller SL, Wainwright JV and Kinon MD was responsible for designing the review protocol, screening potentially eligible studies, assessing bias in included studies, writing the manuscript, and providing feedback.

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SYSTEMATIC REVIEWS

Pain management in acute musculoskeletal injury: Effect of opioid *vs* nonopioid medications

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Abstract

BACKGROUND

The use of opioids for pain is linked to an increased risk of developing opioid use disorder, and has resulted in the emergence of the opioid crisis over the last few years.

AIM

The systematic review question is "How does the use of opioid medications in pain management, compared with non-opioid medications, affect pain intensity over the short, intermediate, and long-term in adults with acute traumatic pain?".

METHODS

The protocol was prospectively registered on the International Prospective Register of Systematic Reviews: CRD42021279639. Medline and Google Scholar were electronically searched for controlled peer-reviewed studies published in full, with the PICO framework: P: Adult patients with traumatic injuries, I: Opioid medications, C: Non-opioid medi-cations, O: A minimum clinically important

difference (MCID) in pain.

RESULTS

After full-text screening, we included 14 studies in the qualitative synthesis. Of these 14 studies, 12 were randomized clinical trials (RCTs) and 2 were pseudo-RCTs with a total of 2347 patients enrolled. There was heterogeneity in both medication utilized and outcome in these studies; only two studies were homogeneous regarding the type of study conducted, the opioid used, its comparator, and the outcome explored. The MCID was evaluated in 8 studies, while in 6 studies, any measured pain reduction was considered as an outcome. In 11 cases, the setting of care was the Emergency Department; in 2 cases, care occurred out-of-hospital; and in one case, the setting was not well-specified. The included studies were found to have a low-moderate risk of bias.

CONCLUSION

Non-opioids can be considered an alternative to opioids for short-term pain management of acute musculoskeletal injury. Intravenous ketamine may cause more adverse events than other routes of administration.

Key Words: Acute musculoskeletal injury; Acute traumatic pain; Non-opioid analgesia; Non-opioid pain control; Opioid-sparing analgesia; Opioid crisis; Opioid disorder; Systematic review

Core Tip: Opioid use is linked to an increased risk of developing opioid use disorder. This systematic review question is "How does the use of opioid medications in pain management, compared with non-opioid medications, affect pain intensity over the short, intermediate, and long-term in adults with acute traumatic pain?". The search was performed using Medline and Google Scholar. We included 14 studies in the final synthesis [12 were randomized clinical trials (RCTs) and 2 were pseudo-RCTs]. Most retrieved studies on the use of non-opioids concluded that non-opioid drugs are non-inferior to opioids for the control of acute pain in acute musculoskeletal injury.

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INTRODUCTION

In the late 90s, the pharmaceutical industry assured the medical community that opioids prescribed for pain relief would not result in addiction. In turn, medical doctors increased their rates of opioid prescription, with the well-intentioned belief that they were effectively treating pain with little risk of harm. Increased awareness of the addictive quality of these medications has led to a reduction in the prescription of opiates in recent years. However, paradoxically, although the prescription rate has been reduced, deaths from overdoses associated with opioids continue to increase[1]. Opioid overdose deaths in the United States have increased significantly over the past decade. In California, opioid overdose death rates increased by more than threefold between 2018 and 2021[2]. By 2021, unintentional opioid toxicity caused 1 out of every 22 deaths in the United States[3]. The Centers for Disease Control and Prevention (CDC) released its most recent Clinical Practice Guideline for Prescribing Opioids for Pain in 2022 that addresses the prescription of opioids for acute pain in many common minor traumatic orthopedic conditions such as sprains and strains[4]. However, the CDC guideline does not provide non-opioid recommendations for more catastrophic traumatic conditions such as fractures necessitating surgery or hospitalization.

The question being addressed in this systematic review is "How does the use of opioid medications in pain management, compared with non-opioid medications, affect pain intensity over the short, intermediate, and long-term in adults with acute traumatic pain?". The results can be applied by orthopedic practices and other specialties (*e.g.* emergency physicians and anaesthesiologists) to adequately and appropriately utilize non-opioid medications for the management of acute pain following musculoskeletal injury.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the updated guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[5].

The protocol was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO): CRD42021279639 on November 18, 2021 after searching the main electronic registers (the Cochrane

database of systematic reviews, the JBI database of systematic reviews, and implementation reports and PROSPERO) to exclude existing systematic reviews on the same subject.

Study search

The participants, intervention, comparison, outcomes, study design method was utilized to conduct the search strategy (Table 1). The databases utilized were Medline through PubMed and Google Scholar *via* Publish or Perish software[6].

Table 1 Participants, intervention, comparison, outcomes, study design method for selecting clinical studies for the systematic reviews

Participants	Intervention	Comparison	Outcomes	Study design
Adult patients with catastrophic orthopedic trauma	Opioid medications	Non-opioid medications	A minimum clinically important difference in pain	Randomized controlled trials and observational studies

The search strategy used Boolean operators to combine selected keywords in detail (Supplementary Table 1). A first comprehensive search was performed, which began at the inception of the search strategy and ceased in December 2021. The search was re-run, updating the data collection definitively until May 15, 2024.

Study selection

After searching, we eliminated duplicate studies utilizing Endnote VX9 (Clarivate Analytics, Philadelphia, PA, United States), a citation management software. Randomized clinical trials (RCTs) and non-RCTs with a control group, were considered eligible studies. Two authors (Barletta and Visconti) evaluated the eligible studies independently through initial screening based on the title and abstract, without any restrictions. The authors (Barletta and Visconti) conducted full-text screening of the selected articles to ensure their suitability for final inclusion. Any disagreements about study eligibility or data extraction was resolved by a third author (McCaffery). Two independent reviewers (Barletta and Visconti) reviewed the entire text of the selected citations and documented the reason for excluding full-text studies that did not meet the inclusion criteria; McCaffery performed a final check as well. Each step of the search is represented in the PRISMA flow diagram (Figure 1).

Definition and outcome

For this study, catastrophic orthopedic trauma was defined as any trauma that necessitated surgery or hospitalization. We excluded trauma that necessitated access to and evaluation in the emergency department (ED) but did not require surgery or hospitalization, such as whiplash or sprained ankle. The primary outcome was a minimum clinically important difference (MCID) in pain intensity. The secondary outcome was a reduction in pain as defined by the authors of the primary studies. Patients with a trauma-related pain diagnosis were evaluated for all outcomes.

Data extraction and quality assessment

The Cochrane data collection form for intervention reviews in RCT and non-RCT studies was used by two authors (McCaffery and Nasto) to extract data independently from the included studies. The quality of the methodology and risk of bias were evaluated by the authors (McCaffery and Nasto) using the Cochrane Collaboration Revised Assessment Tool [7].

RESULTS

Overall, 58958 papers were retrieved: 13471 on Medline and 45487 on Google Scholar, and 13269 duplicates were identified and excluded. The flowchart (Figure 1) shows that 45689 titles were identified as potentially relevant and screened. After screening the title and abstract, we excluded 45652 papers. We excluded 23 papers from the full-text evaluation of the remaining 37 papers because of 4 main reasons (Figure 1). Fourteen studies (12 were RCT and 2 were pseudo-RCT) were included in the qualitative synthesis (Table 2) after full-text screening. The MCID in pain intensity was evaluated in 8 studies, while in 6 studies, any measured pain reduction was considered as an outcome. In 11 cases, the setting of care was the ED; in 2 cases, care occurred out-of-hospital; and in one case, the setting was not well-specified (Table 2). The included studies were found to have a low-moderate risk of bias (Supplementary Table 2).

The first published study on the topic, written by Soave *et al*[8], dates back more than 40 years. In this double-blind, randomized, parallel-group study, the analgesic activity of indoprofen and pentazocine was evaluated in 60 patients with severe pain due to fractures. Twenty patients received indoprofen 400 mg intravenous (IV), 20 patients received pentazocine 30 mg IV, and 20 patients received placebo. The intensity of pain was assessed prior to medication administration and at 0.5 hour, 1 hour, 2 hours, 4 hours, and 6 hours following administration. The evaluation of efficacy was based on the visual analogue scale (VAS). The analgesic effects of indoprofen were found to be significantly superior to those of pentazocine, and both drugs had good tolerability[8].

Chang *et al*[9] investigated, in an RCT, the effectiveness of 4 oral analgesics in patients who had acute, moderate-to-severe extremity pain and were admitted to the ED. Patients received one of the following regimens: ibuprofen (IBP) (400 mg)/acetaminophen (APAP) (1000 mg); oxycodone (OXY) (5 mg)/APAP (325 mg); hydrocodone (HYCOD) (5 mg)/

Table 2 Characteristics of the studies included in the qualitative synthesis

Ref.	Country/year	Injury	Opioid(s)-ROA	Nonopioid(s)-ROA	Patients /study type	Outcome (minimum clinically important difference)	Evaluation time	Efficacy result	Safety results
Soave *et al*[8]	Italy/1983	Severe pain due to fractures	Pentazocine-IV	Indoprofen-IV	The 40/pseudo-RCT	Any reduction on VAS	The 0 minute, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours	Pain relief in Pentazocine group	No differences
Chang *et al*[9]	United States/2017	Acute extremity pain	OXY/APAP-PO, HYCOD/APAP-PO, COD/APAP-PO	IBP/APAP-PO	416/RCT	Reduction of 1.3 on the NRS	2 hours	No differences	ADR in opioid
Bijur *et al*[10]	United States/2021	Acute musculo-skeletal pain	OXY/APAP-PO, HYCOD/APAP-PO, COD/APAP-PO	IBP/APAP-PO	600/RCT	Any reduction on NRS	The 0 hour, 1 hour or 2 hours	No differences	ADR in opioid
Buccelletti *et al* [11]	Italy/2014	Acute musculo-skeletal traumatic pain	COD/APAP-PO	Ketorolac-PO	134/pseudo-RCT	Any reduction on NRS	The 0 minute, 30 minutes, 2 hours	Pain relief in COD/APAP group	Not available
Craig *et al*[12]	United Kingdom/2012	Severe traumatic limb pain	MORPH-IV	APAP-IV	55/RCT	≥ 13 mm reduction on VAS	The 0 minute, 5 minutes, 15 minutes, 30 minutes, 60 minutes	No differences	ADR in opioid
Jalili *et al*[13]	Iran/2016	Severe traumatic limb pain	MORPH-IV	APAP-IV	60/RCT	Any reduction on NRS	The 0 minute, 15 minutes, 30 minutes	Pain relief in APAP group	No differences
Farahmand *et al*[14]	Iran/2018	Severe traumatic limb pain	MORPH-IV	Lidocaine-IV	50/RCT	Reduction of 1.3 on the NRS	The 0 minute, 15 minutes, 30 minutes, 45 minutes, 60 minutes	No differences	Heart rate/respiratory rate reduction in opioid
Gurnani *et al* [15]	India/1996	Acute musculo-skeletal traumatic pain	MORPH-IV	KET-subcutaneous	40/RCT	Any reduction on VAS	The 0 minute, 15 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours	Pain relief in KET group	ADR in opioid
Shimonovich *et al*[16]	Israel/2016	Moderate-severe acute traumatic pain	MORPH-IV/MORPH-IM	KET-IN	90/RCT	≥ 15 mm reduction and max pain reduction on VAS	Time to onset in min	No differences	No differences
Tongbua *et al* [17]	Thailand/2022	Moderate-severe Musculo-skeletal pain	MORPH-IV	KET-IN	74/RCT	Reduction of 1.3 on the NRS	The 0 minute, 15 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes and 120 minutes	No differences	No differences
Kampan *et al* [18]	Thailand/2024	Moderate-severe Musculo-skeletal pain (≥ 65)	MORPH-IV	KET-IN	92/RCT	Reduction of 1.3 on the NRS	The 0 minute, 30 minutes	No differences	ADR in opioid
Esfahani *et al* [19]	Iran/2021	Severe traumatic limb pain	MORPH-IV	KET-IV	76/RCT	Any reduction on NRS	The 0 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes	No differences	ADR in KET
Le Cornec *et al* [20]	France/2024	Out-of-hospital traumatic pain	MORPH-IV	KET-IV	251/RCT	Reduction of 1.3 on the NRS	The 0 minute, 30 minutes	No differences	ADR in KET

Lim *et al*[21]	Singapore/ 2021	Out-of-hospital traumatic pain	Tramadol-IM	MTX-inhalation	369/RCT	≥ 3-point reduction in NRS	The 0 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes	Pain relief in MTX group	ADR in MTX

APAP: Acetaminophen; ADR: Adverse drug reaction; COD: Codeine; HYCOD: Hydrocodone; IBP: Ibuprofen; IN: Intranasal; KET: Ketamine; MORPH: Morphine; MTX: Methoxyflurane; NRS: Numerical rating scale; OXY: Oxycodone; RCT: Randomized controlled trial; ROA: routes of administration; PO: *Per os*; IV: Intravenous; VAS: Visual analogue scale.

APAP (300 mg); or codeine (COD) (30 mg)/APAP (300 mg). The pain intensity was assessed using an 11-point numerical rating scale (NRS), ranging from the number 0, which indicates no pain, to the number 10, which indicates the most severe pain. The primary outcome was the difference in pain reduction between the groups at 2 hours after administration of medication. According to the NRS, the MCID was 1.3. There were no significant or clinical differences in pain reduction at 2 hours observed between IBP and APAP treatment or 3 different opioid and APAP combination analgesics. The use of opioids resulted in a higher prevalence of nausea and vomiting in patients[9].

Bijur *et al*[10] compared the efficacy and adverse effects of five oral analgesics in an RCT comprising 600 patients presenting to the ED with acute musculoskeletal pain. Patients received one of the following regimens: IBP (400 mg)/APAP (1000 mg), IBP (800 mg)/APAP (1000 mg), COD (30 mg)/APAP (300 mg), HYCOD (5 mg)/APAP (300 mg), or OXY (5 mg)/APAP (325 mg). The main outcome was a difference in pain on NRS before drug administration (defined as the baseline) as compared with that at 1-hour post-baseline. At 1-hour and 2-hours post-baseline, both rescue medication and adverse effects were included in secondary outcomes. The authors concluded that no analgesic was more effective after 1-hours or 2-hours following baseline, while patients treated with opioids experienced a significant increase in nausea and vomiting[10].

In a cross-sectional, observational, prospective, cohort study (pseudo-randomized), Buccelletti *et al*[11] evaluated two oral analgesics in 134 patients presenting to the ED with acute traumatic musculoskeletal pain. The oral analgesics provided were APAP/COD at the dosage of 1000 mg/60 mg and ketorolac administered at the dosage of 15 mg. Seventy-six of the patients received ketorolac and 58 received APAP/COD. The NRS was recorded at 30 minutes and at 2 hours after the administration of the analgesic therapy. Patients with fractures and muscular pain were found to experience significantly higher analgesic relief when given the combination of APAP and COD compared with those who received ketorolac[11].

Craig *et al*[12] evaluated the effectiveness of 1 g IV APAP compared to 10 mg IV morphine (MORPH) in an RCT of 55 patients with moderate-to-severe traumatic limb pain. Using a VAS, the pain score was assessed at 0 minute, 5 minutes, 15 minutes, 30 minutes, and 60 minutes following administration of medication as the primary outcome measure. The frequency of adverse reactions and the need for rescue analgesia were also documented. There were no significant differences in analgesic effect of APAP and MORPH at any time interval. The rescue analgesia administered did not significantly differ between the two groups. However, the MORPH group experienced significantly more adverse reactions compared with the non-opioid group[12].

Jalili *et al*[13] evaluated, in an RCT, the effectiveness of APAP (1000 mg) relative to MORPH (0.1 mg/kg) in patients with acute limb trauma and a reported NRS of > 3/10. The primary outcome measure was the change in pain score of the NRS at 0 minute, 15 minutes and 30 minutes after medication administration. The frequency of adverse reactions and the need for rescue analgesia were also documented at 0 minute and 30 minutes after administration of medication. There were no significant differences in analgesic effect for APAP and MORPH at any time interval. The rescue analgesia administered did not differ significantly between the two groups. The MORPH group experienced significantly more adverse reactions. The authors found that the APAP group experienced significantly more pain relief than the MORPH group. The difference in the use of rescue analgesia between the APAP and MORPH groups was significant: The APAP

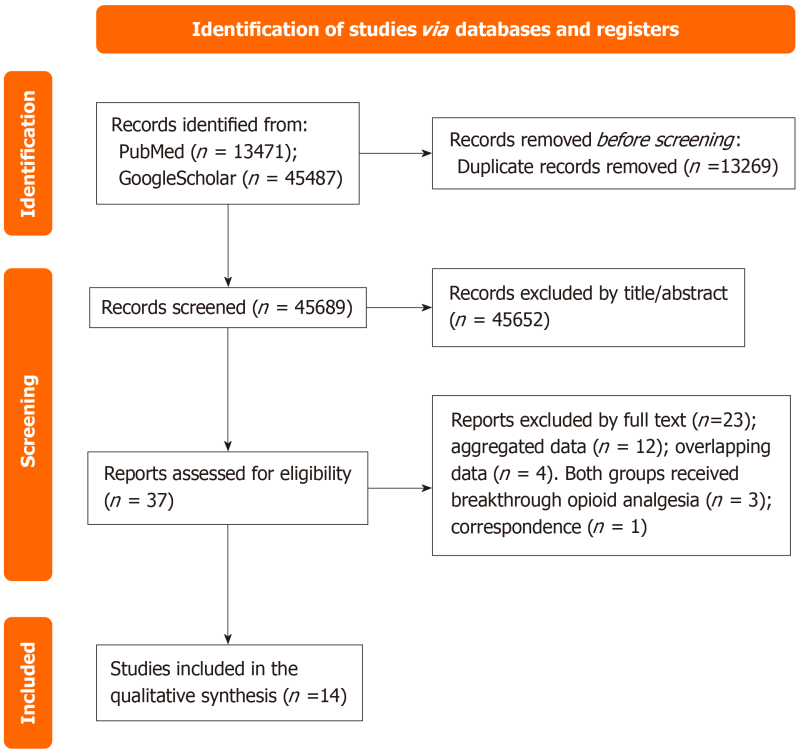

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection.

group had 4 patients who need rescue analgesia, while the MORPH group had 15 patients who need rescue analgesia. There was no significant difference in the number of patients who experienced adverse effects between the two groups [13].

Farahmand *et al*[14] enrolled 50 patients with acute limb trauma in an RCT designed to compare intravenous lidocaine and MORPH for superiority in pain management (25 in each group). Lidocaine (1.5 mg/kg) was administered *via* IV to one group and MORPH (0.1 mg/kg) was administered *via* IV to the other group. At 15 minutes, 30 minutes, 45 minutes, and 60 minutes, the patients' reported pain scores and adverse effects were documented, with their satisfaction with the pain control being assessed 2 hours later. According to the NRS, the MCID was 1.3. There were no clinically or statistically significant differences between two groups, although the pain score decreased significantly in both groups. In the MORPH group, compared with the group receiving lidocaine, the heart rate and the respiratory rate exhibited a statistically significant decrease. In both groups, only one subject reported adverse effects, *i.e.*, nausea and vomiting[14].

Gurnani *et al*[15] compared the effectiveness of pain control between ketamine (KET) and MORPH in a pilot study of 40 ASA-I adults after acute musculoskeletal trauma. In 20 patients, an initial loading dose of KET (0.25 mg/kg) was given slowly *via* IV followed by low-dose KET *via* Subcutaneous (0.1 mg/kg/hour). In the control group, 20 patients received MORPH (0.1 mg/kg intravenously, every four hours). The VAS was used to assess pain at 0 minute, 1 minute, 2 minutes, 4 minutes, 8 minutes, 12 minutes, 15 minutes, and 24 hours. Vital parameters and patient acceptability for supplementary analgesia, drowsiness score, and early mobilization were also assessed. The authors found that KET infusion provided better pain relief than intermittent MORPH, with no need for additional analgesia for the patients in the KET group. Compared with patients in the MORPH group, it was easier to physically move the patients receiving KET. The drowsiness score showed that patients were more awake and alert after receiving KET infusion. In the MORPH group, there was a high rate of nausea and vomiting[15].

Shimonovich *et al*[16] evaluated the efficacy and adverse effects of intranasal (IN) KET compared with those of IV and IM MORPH in an RCT. Ninety patients with moderate-to-severe acute traumatic pain (> 80 mm on 100 mm VAS) were randomly assigned either 1.0 mg/kg IN KET, 0.1 mg/kg IV MORPH, or 0.15 mg/kg IM MORPH. The drug was given, and pain relief and adverse events were assessed for an hour. The 'time-to-onset' was used to determine effectiveness—which was defined as a 15 mm reduction in pain on VAS—and also the duration and level of maximum pain relief. Clinically, IN KET had similar results to MORPH in terms of efficacy (onset of reduction of pain and maximum reduction time) and safety[16].

Tongbua *et al*[17] evaluated the pain-relieving effectiveness and safety of IN KET relative to IV MORPH in patients aged 65 years or older attending the ED with acute moderate-to-severe pain (score higher than 5 on an 11-point NRS). A decrease in NRS pain scores was the primary outcome, after 30 minutes of treatment; both rescue medication and the incidence of adverse effects were included in the secondary outcomes. The number of patients enrolled was 72, with 37 in the IN-KET group and 37 in the IV-MORPH group. At 30 minutes, the mean pain score for both groups did not differ significantly. Nausea and vomiting were present in one patient in the IN- KET group and in two patients of the IV-MORPH group, and only one patient in the IV-MORPH group subsequently received treatment with an anti-emetic drug [17].

Kampan *et al*[18] investigated the analgesic efficacy of nebulized KET relative to IV MORPH in older patients (aged 65 years and older) admitted to the ED with acute moderate-to-severe musculoskeletal pain (defined as a pain score of 5 or more on NRS). The outcomes were a decrease in NRS 30 minutes after treatment with nebulized KET or IV MORPH, as well as in the frequency of adverse events and the need for rescue therapy. The authors enrolled 92 patients, divided equally into each group. The nebulized KET and IV MORPH groups showed no significant difference in mean NRS at 30 minutes. The groups did not exhibit a difference in their rates of rescue therapy. The incidence of nausea in the MORPH group was significantly higher than in the KET group. None of the patients in the KET group reported nausea, whereas in the MORPH group, 8 patients experienced nausea[18].

An RCT conducted by Esfahani *et al*[19] compared the efficacy and safety of KET relative to MORPH in the reduction of pain associated with isolated traumatic limb injuries in patients referred to the ED. The number of patients enrolled was 73, with the KET group receiving 0.1 mg/kg of KET and the MORPH group receiving 0.05 mg/kg of MORPH. NRS and adverse drug reactions (ADRs) were recorded at baseline and every 5 minutes, for 30 minutes in total. At each assessed timepoint, the KET group had a significantly lower mean pain score than the MORPH group. Additionally, the KET group had significantly higher overall ADRs than the MORPH group[19].

The Intravenous Sub-dissociative-Dose Ketamine Versus Morphine for Prehospital Analgesia study is a recently published multicenter RCT assessing the non-inferiority of KET (dosed initially at 20 mg and followed by 10 mg every 5 minutes) compared with MORPH sulfate (2 mg or 3 mg administered every 5 minutes) to alleviate pain in adults with out-of-hospital traumatic pain (NRS > 5). A total of 251 patients were enrolled (KET being administered to 128 patients and MORPH administered to 123 patients). The primary outcome was the difference in NRS measured before medication administration (defined as the patient's baseline pain level) and after 30 minutes, with an MCID of 1.3. KET and MORPH showed no difference in pain reduction in patients with out-of-hospital traumatic pain. More adverse events were observed in the KET group, although no patient was required to withdraw from the study and no intervention was needed to manage ADRs[20].

Another study regarding the treatment of out-of-hospital traumatic pain (NRS > 3) conducted by Lim *et al*[21] compared inhalational methoxyflurane and intramuscular tramadol in an RCT enrolling 343 patients (methoxyflurane, 167 and tramadol, 176). The main outcomes: (1) Decreased pain, as assessed by the decrease in NRS at 5 minutes, 10 minutes, 15 minutes, and 20 minutes following administration of medication; (2) The amount of time taken to administer treatment from arriving at the scene; and (3) The amount of time required for effective analgesia to start (a drop of 3 points in NRS). The occurrence of adverse events was among the numerous secondary outcomes. Although methoxyflurane had better efficacy, speed of onset, and administration than tramadol, it was also associated with more numerous minor adverse events[21].

DISCUSSION

Most studies on the use of non-opioids have concluded that these drugs are non-inferior to opioids for the control of acute pain associated with acute musculoskeletal injury. Therefore, the use of non-opioids can be considered as an alternative to opioids for pain management in acute musculoskeletal injuries. Only two studies[8,11] (those that represented the only non-RCT included in the qualitative synthesis) report opioids to have higher efficacy than the control/non-opioid in pain management. The results are unanimous in the traditional RCT studies that were conducted.

The major limitation of our systematic review is the heterogeneity of the studies regarding the measured outcomes and the opioids and non-opioids that were utilized. This heterogeneity made it infeasible to conduct a meta-analysis. Only the studies of Tongbua *et al*[17] and Kampan *et al*[18] are homogeneous in regard to the type of study conducted, the opioid used (IV MORPH), its comparator (IN KET), and the outcome explored. A meta-analysis of the two studies, that together comprised 166 patients (Tongbua 74, Kampan 92), was not conducted because the studies' results were similar in terms of drug efficacy, and we concluded that it did not provide any additional information.

Another limitation of our systematic review is that the outcomes of the included studies were focused on the immediate, short-term response to medication. Thus, the data have limited applicability for use in consideration of longitudinal treatment of pain or discussion of long-term medication effects. The other limitation is that most of the studies were conducted in the ED. Therefore, we can only state that the use of non-opioids can be considered as an alternative to opioids in the ED for short-term pain management in acute musculoskeletal injuries.

Of all the discussed non-opioid drugs, intravenous KET and methoxyflurane were associated with higher adverse events than opioids. Specifically, only intravenous KET was linked with more adverse events than MORPH[19,22], while inhaled or subcutaneous KET did not elicit more adverse events than MORPH. KET is commonly used as an analgesic in emergency medicine[20], and, according to the literature, intravenous administration of KET could cause more adverse events than other routes of administration (ROA).

In the latest 2022 Clinical Practice Guideline for Prescribing Opioids for Pain of the CDC, non-opioid therapies are recommended for many common minor orthopedic acute pain conditions such as sprains, strains, tendonitis, and bursitis [4]. Our systematic review shows that treatment with non-opioid medications can be effective even in major trauma.

CONCLUSION

The findings of this systematic review should be treated with discretion, owing to the heterogeneity of the studies included in the qualitative synthesis. Overall, for short-term pain management of acute musculoskeletal injuries in the ED,

non-opioid medications may provide a viable substitute for opioids. IV administration of KET may cause more adverse events than other ROA. There is a need for additional high-quality RCTs that provide consistency in the target population, interventional components, methodology in reporting outcomes, follow-up periods, and full cost analysis.

FOOTNOTES

Author contributions: Fiore M designed the study and wrote the manuscript; Barletta F and Visconti A evaluated the eligible studies *via* initial screening; Gargano F prepared the manuscript; McCaffery E performed the English language check; and Nasto LA, Pola E, and Pace MC supervised the research; all authors have read and approved the final manuscript.

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CASE REPORT

Lateral femoral neck stress fractures: A case report

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Abstract

BACKGROUND

Sport-induced injuries particularly affect young, healthy, and active individuals. Running, a popular and accessible sport, can cause a wide range of injuries, including stress fractures. Stress fractures can occur during high-intensity training or competitions, especially among well-trained amateurs and professional athletes. Adequate diagnosis can be complicated by the typically young age, unremarkable medical history, and vital condition of the patient. Stress fractures present insidiously, and this is specifically the case with stress fractures of the femoral neck. Timely intervention is crucial to prevent progressive displacement, as this can damage the blood supply to the femoral head.

CASE SUMMARY

A 30-year-old male runner presented to our outpatient clinic with persistent pain 3 weeks after running a marathon. X-ray showed a complete lateral fracture of the left femoral neck, which was treated surgically with a dynamic hip screw.

CONCLUSION

It is essential for healthcare providers to be vigilant for the subtle symptoms of stress fractures to ensure timely treatment. Early recognition prevents complication and leads to a better prognosis.

Key Words: Stress fractures; Atypical; Femoral Neck; Marathon; Diagnosis; Case report

Core Tip: Sports-induced injuries primarily affect young, healthy, and active individuals. Stress fractures occur during high-intensity training, particularly among well-trained amateurs and professional athletes. Young age and a lack of medical history complicate the diagnosis of insidious femoral neck stress fractures. Failure to diagnose and initiate treatment leads to fracture progression, impacting vascular supply and overall outcome. Avascular necrosis requires more invasive and extensive treatment and increases the risk of complications and permanent disability.

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INTRODUCTION

Diagnosing (atypical) stress fractures of the femoral neck is complex due to their unfamiliarity and insidious presentation, often resulting in progressive displacement and delayed treatment. Timely diagnosis and intervention are crucial. In this article we discuss the diagnosis, treatment options and complications of lateral femoral neck stress fractures. Using a case from our clinic, we provide an overview of literature and the published cases of lateral femoral neck fractures.

Stress fractures are thought to occur due to repetitive loading that exceeds the bone's regenerative capacity, most commonly affecting young, active individuals[1,2]. This condition is prevalent among marathon runners and endurance athletes, due to the repeated mechanical stress from prolonged and cumulative exertion[1,2]. While stress fractures occur in various locations—particularly in the tibia and metatarsals[2,3]—they are especially concerning when located at the femoral neck, due to the severe implications and treatment complexity. Stress fractures of the femoral neck are rare, and comprise only 2.5%-5% of all stress fractures[4]. The etiology of femoral neck stress fractures remains unclear, but the prevailing hypothesis suggests that repetitive forces on the hip joint cause micro-stress and bone fatigue, leading to a failure of structural integrity[1,2]. If undiagnosed and, therefore, untreated, these fractures can progress to a complete fracture, with consequences often exacerbated by their subtle presentation and risk of progressive displacement, potentially resulting in severe outcomes like fracture dislocation requiring prosthetic replacement.

It is important to distinguish stress fractures from acute fractures. Stress fractures develop gradually over time due to repetitive physical load or overuse, as a result of cumulative micro-damage to the bone[1,2]. Unlike acute fractures, stress fractures may initially present with mild, progressive pain during activity, which can worsen over time if not treated. Acute fractures of the hip occur suddenly due to a significant external force, such as a fall, car accident, or direct trauma [5-7]. These fractures are typically severe, immediate, and often result in a complete break of the bone. Patients usually experience intense pain and are unable to bear weight on the affected limb, requiring prompt medical intervention, often surgical, to stabilize the fracture[5-7]. These fractures predominantly affect older adults, especially those with compromised bone quality due to osteoporosis, but can also occur in younger individuals subjected to significant trauma.

Diagnosing (atypical) femoral neck stress fractures is challenging due to their insidious presentation. Patients often present with vague persistent groin or hip pain, initially mild and easily overlooked[8-10]. Pain typically worsens with physical activity and subsides with rest, often misinterpreted as muscle strain. Despite pain, walking is usually possible [8-10]. Clinical examination most often reveals full passive range of motion, with pain elicited only at extreme hip positions[10]. Active range of motion is often not complete due to the same pain. Early-stage stress fractures are frequently missed on standard radiographs, with initial sensitivity ranging from 15%-35%, which may improve to 30%-70% after 2-10 weeks[10]. Magnetic resonance imaging (MRI) is the most reliable diagnostic tool, showing bone edema at the fracture site, but MRIs are often only performed if symptoms are chronic[8]. Diagnosis is, therefore, often delayed, averaging 14 weeks[11], increasing the risk of fracture displacement, impacting blood flow to the femoral head, and subsequent avascular necrosis. Prompt and accurate diagnosis is crucial to prevent further complications, emphasizing the vital role of care providers in early detection and timely referral for additional investigation and treatment.

CASE PRESENTATION

Chief complaints

A 30-year-old male runner presented to our outpatient clinic at the department of Sports Medicine with persistent pain in the left groin, with the inability to fully bear weight. Initial symptoms began during a marathon, manifesting as transient muscle weakness and left groin pain after a ski trip. Symptoms progressed when he resumed his training program. As an experienced runner, he had trained regularly over the past year following a standardized program (building up to a

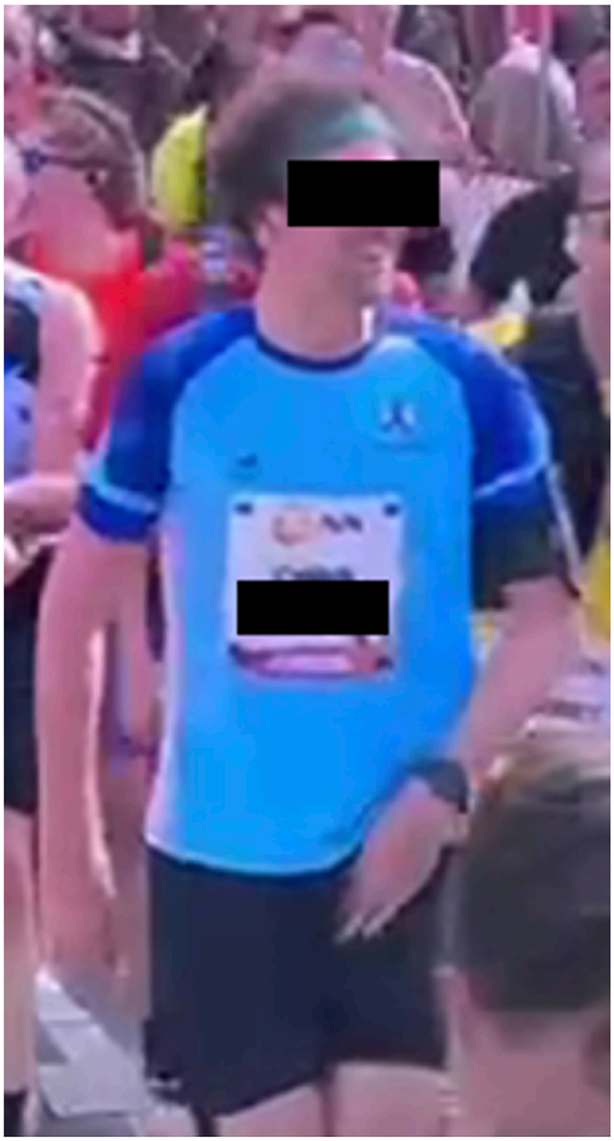

Figure 1 Clinical presentation. Presentation at the time of completing the Marathon, with the fracture already present, where loading on the affected side was possible, but limited by pain. Particularly notable is the patient's self-localization.

mileage of 40-50 km a week, with 80% endurance and 20% intensive training) with no previous episodes of groin or hip pain. No recent changes in training intensity or quality were noted, aside from the skiing trip. His caloric intake was normal for his weight and activity level, with gradual intentional weight loss of 8 kg over the past 2 years. The patient had halted training and consulted a sports physician, who made the clinical diagnosis of left psoas muscle strain. During the subsequent 4 weeks, with medication for pain relief, rest, and graded training, the patient was able to resume activity without further issues or pain.

During the marathon, the patient ran pain-free for 37 km at his trained pace. At 37 km, he began experiencing progressive groin pain, becoming unable to fully bear weight on his left leg by 40 km. Despite the pain, the patient was able to finish the marathon in 4.5 hours (Figure 1). He subsequently visited his general practitioner on day 3 post-marathon due to increasing groin pain, tenderness over the greater trochanter, and inability to fully bear weight despite pain medication. The general practitioner diagnosed acute inflammation of the prior psoas muscle strain and advised increased pain medication and rest. During the following 3 weeks, the pain gradually reduced, but was still significant, and mobilization with support became possible. Due to the persistent pain, he (re-) consulted his general practitioner and a physiotherapist, eventually presenting to the outpatient clinic of the Sports Medicine department 3 weeks post-marathon.

At this point, the patient could not bear weight on his left leg without pain, although the pain had moderately improved.

History of present illness

The patient was not on any medication, and had an unremarkable social and occupational history.

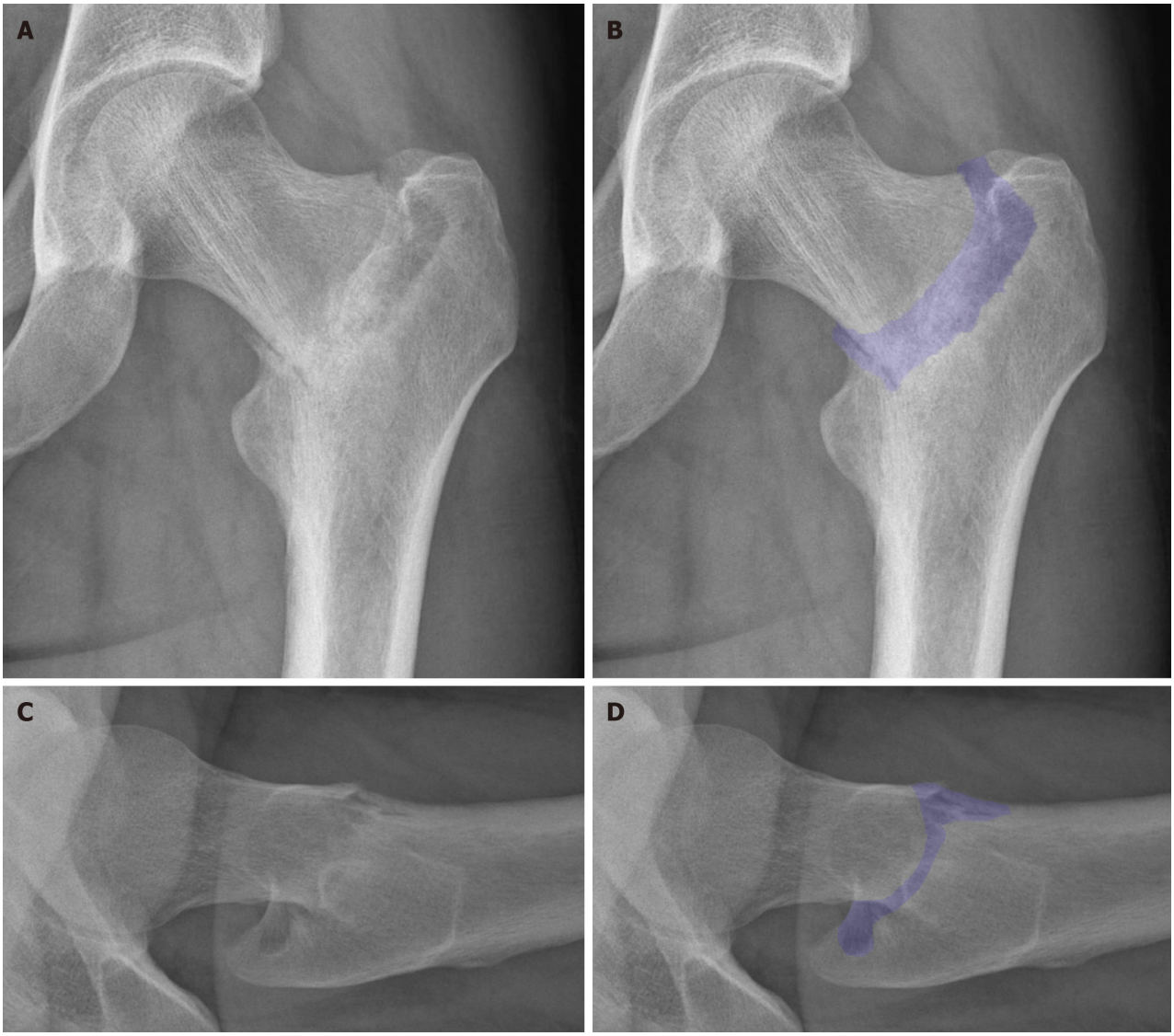

Figure 2 X-ray at presentation, coronal and lateral views. This coronal X-ray of the left hip shows a complete lateral fracture of the left femoral neck, with shortening due to varus alignment of the fracture. The lateral X-ray of the left hip shows the external rotation and notably the fracture on the anterior side. A: Coronal X-ray without overlay; B: Coronal X-ray including an overlay, highlighting the fracture; C: Lateral X-ray without overlay; D: Lateral X-ray including an overlay, highlighting the fracture.

History of past illness
The patient had no prior medical history.

Personal and family history
The patient had no relevant family history regarding osteoporosis or bone disease, with only his grandmother having sustained a femoral fracture at the age of 81 after a fall.

Physical examination
Physical examination revealed no visible abnormalities. Passive movement of the affected side was nearly complete, with mild pain at full flexion. Active hip flexion was limited by pain from 90°, and isolated straight leg raising was impossible against resistance. Sensory, motor, and circulatory function were intact.

Laboratory examinations
Not performed at the time of initial diagnosis.

Imaging examinations
The subsequent X-ray showed a complete lateral fracture of the left femoral neck (Figure 2). A subsequent computed tomography scan (Figure 3) revealed no pre-existing bone pathology, but confirmed significant impaction and malalignment. The three-dimensional reconstruction (Figure 4) showed 24.6° external rotation and 16.0 mm shortening of the affected femur and the anatomical anteversion was neutralized due to the fracture.

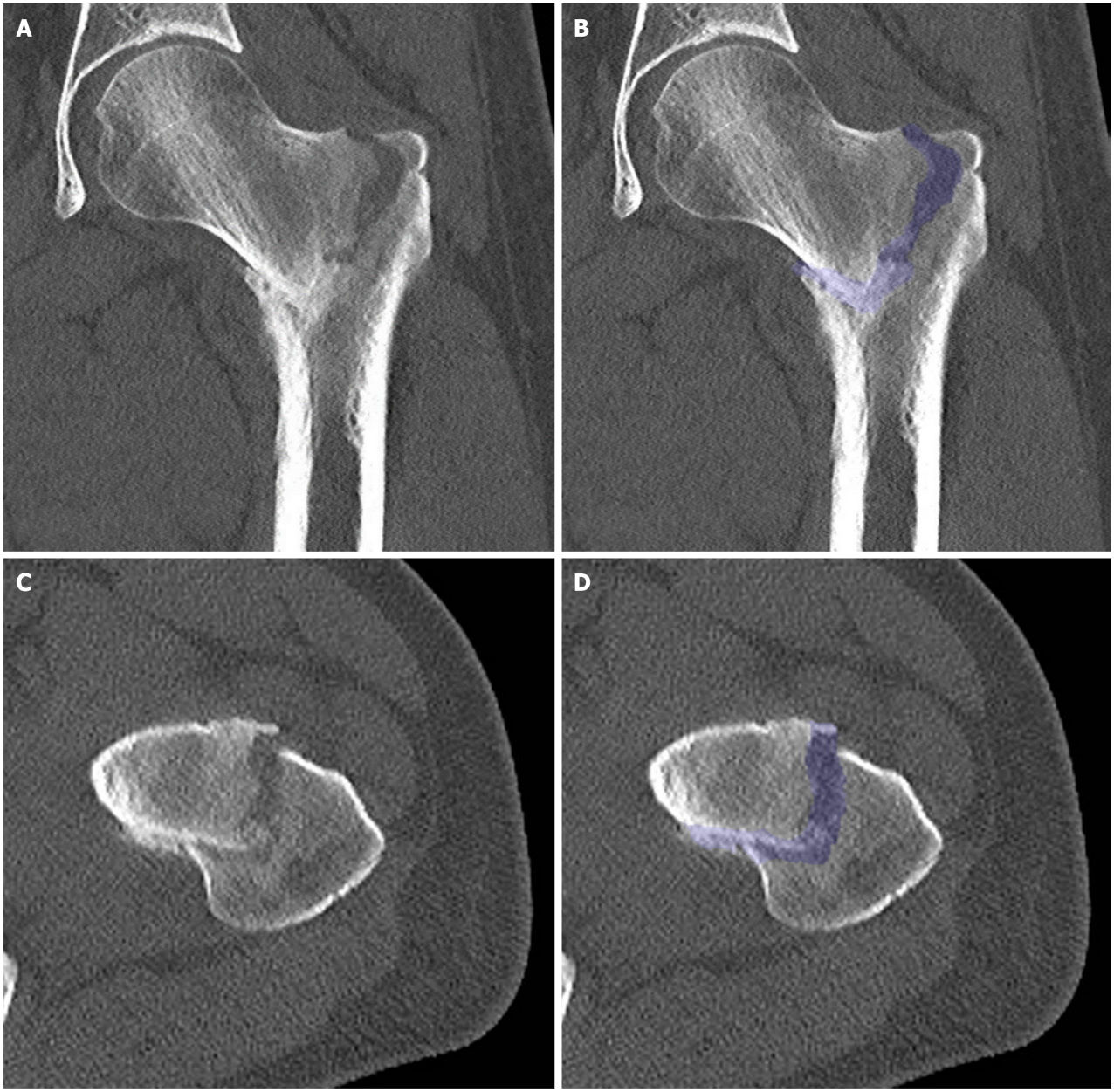

Figure 3 Computed tomography scan at presentation. A: Coronal section without overlay; B: Coronal section including an overlay, highlighting the fracture; C: Transverse section without overlay; D: Transverse section with an overlay, highlighting the fracture. Additional imaging with computed tomography did not reveal evidence of pre-existing bone pathology, but confirmed significant impaction and malalignment. Furthermore, there were multiple signs of osteopenia in the left leg, most likely due to disuse over the preceding 3 weeks. Additionally, there was thickening of the periosteum on the medial side halfway down the femur, possibly due to altered force distribution. In the transverse section, external rotation is notably observed.

FINAL DIAGNOSIS

Based on the duration and progression of symptoms, the hypothesis was that a stress fracture had initially healed due to rest in the 4 weeks preceding the marathon, but had progressed to a complete fracture during the marathon. However, an atypical femur fracture directly related to the marathon was a viable alternative.

TREATMENT

The patient underwent surgical fixation with a dynamic hip screw the day after outpatient clinic presentation. Despite the delay in presentation, anatomical alignment was successfully achieved. At the start of surgery, repositioning was acquired with traction. Afterwards, a cannulated screw (short threads were intentionally used) was placed first, to acquire more traction on the cranial side, thereby inducing more valgus alignment. The dynamic hip screw was then placed, and a four-hole plate was used due to the nature of the fracture and the unavailability of histopathology at that time. The postoperative course was uneventful, and the patient was discharged the day after surgery following initial

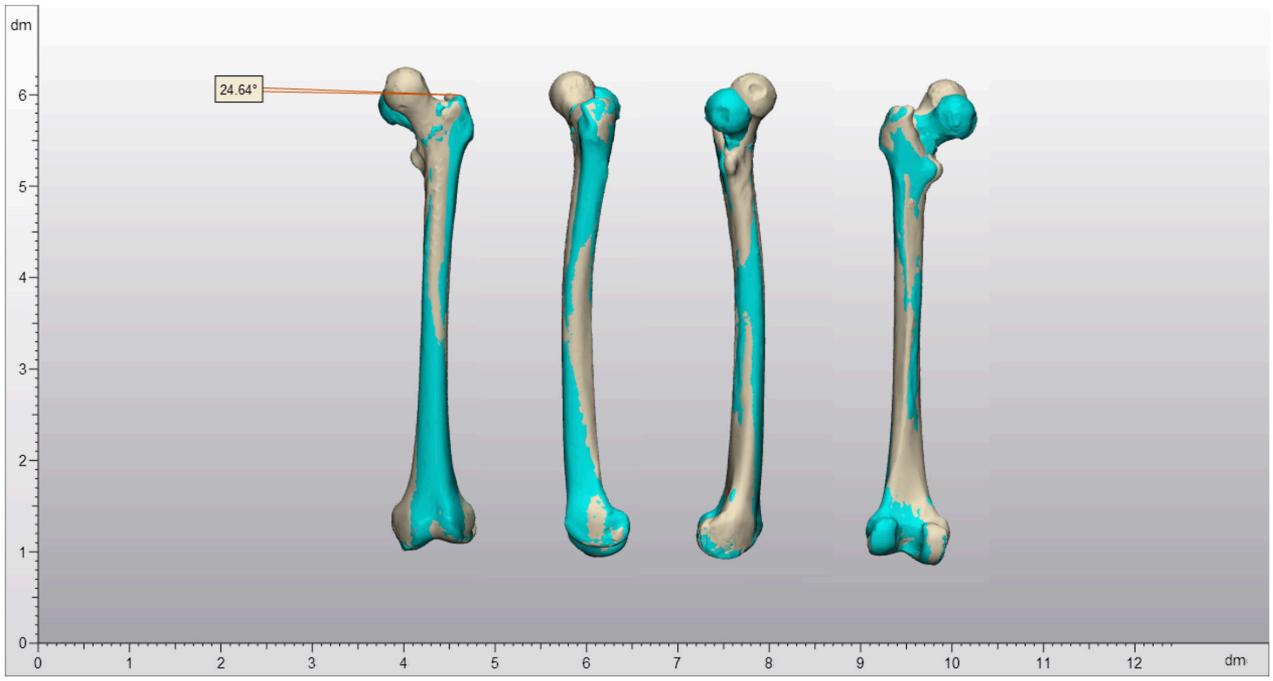

Figure 4 3D reconstruction of the fracture and malalignment at presentation. This 3D reconstruction illustrates the malalignment: 24.6° of external rotation and 16.0 mm shortening due to varus alignment at the fracture site. From left to right: Images from anterior, lateral, medial, and posterior perspectives. The sand-colored reconstruction represents the contralateral side; cyan, the affected side.

mobilization under physiotherapy supervision and a weightbearing X-ray (Figure 5).

OUTCOME AND FOLLOW-UP

Given the insufficiency fracture, the atypical lateral fracture pattern, delayed presentation, and a potential underlying bone mineral pathology, partial (50%) weightbearing was advised for 6 weeks, with 10% in the first 2 weeks. Histopathology revealed no signs of bone disease or malignancy. During outpatient follow-up, the patient made satisfactory progress under physiotherapy supervision, and a 6-week radiograph showed no change in alignment (Figure 6).

After this, the patient initiated full weightbearing under supervision of a physiotherapist. He resumed work within a week post-surgery, initially working from home for 2 weeks. The endocrinologist was consulted to exclude any metabolic predisposition, finding no underlying cause for the fracture. No abnormal measurements were found for vitamin D, calcium and phosphorus metabolism, parathyroid hormone and type I procollagen carboxy terminal propeptide, and amino terminal propeptide. However, initial examination at 6 weeks post-surgery, 9 weeks post-injury, did show disuse osteopenia of the affected leg, with heightened urinary electrolyte excretion, due to excess intake, as the rest of the body was unaffected and showed normal bone mass on DEXA-examination.

At follow-up at 3 months post-surgery, our patient had improved significantly, partly due to extensive rehabilitation therapy by a specialized physical therapist, and was able to do all his daily activities, including his work as a clinical resident, without any pain or limitations. Under strict supervision, he aims to resume his physical activities, such as tennis and running (Figure 7).

DISCUSSION

Based on the cases presented in Table 1, a common theme emerges despite varying individual factors. Obviously, these atypical stress fractures typically occur following significant increases in mileage, often during marathon training or after initiation of running regimens. Predisposing factors such as medical histories or causative agents (*e.g.*, the female athletic triad or osteoporosis) are generally absent. Absence of these predisposing factors are most likely due to publication bias, as cases where stress fractures are the result of osteoporosis, make relatively unremarkable cases. All the cases had complete fractures with varying degrees of displacement, with almost all managed surgically with a dynamic hip screw to stabilize the fracture site, after which partial weightbearing was initiated. Post-treatment outcomes show successful recovery trajectories, with patients achieving pain-free mobility and returning to physical activities gradually over weeks to months. However, there is no consistency in reporting whether patients returned to their pre-fracture level of activity, for instance long-lasting running regimens.

Table 1 Overview of published cases of atypical femoral basicervical/lateral stress fractures

Ref.	Case description	Cause of injury	Predisposing factors	Diagnosis	Treatment	Outcome
Biz *et al* [13]	33-year-old female	Marathon training	Previous history of anorexia with amenorrhea	Left femoral lateral fracture, incomplete in the posterior-distal part	DHS + 30 days of partial weightbearing	At 12-month follow-up, she was completely pain-free and demonstrated full range of motion
Biz *et al* [13]	48-year-old female	Initiated running	None	Complete and displaced left femoral neck base stress fracture	DHS + 30 days of no weightbearing. Subsequently increasing load over 20 days to complete load	At 3-month follow-up, she was able to walk, pain-free and had started stationary cycling and swimming
Cichy *et al* [9]	23-year-old male marathon runner	Marathon	None	Complete, minimally displaced basicervical fracture of the right femoral neck	DHS + 6 weeks of partial weightbearing	No avascular necrosis, lights sports
Clough *et al*[10]	55-year-old male	Marathon training	None	Displaced lateral fracture of the right femoral neck, which had collapsed into varus, with a neck-shaft angle of 110°	DHS	Not mentioned
Ejnisman *et al*[14]	56-year-old female	No clear causative agent	None	Complete fracture of the base of the femoral neck with subtle displacement	3x CHS	Full recovery after 6 months
Kerr *et al* [12]	32-year-old male	Marathon	None	Lateral fracture of the femoral neck with varus displacement and a neck-shaft angle of 90°	DHS + 6 months of partial weightbearing	Full weightbearing, lights sports at 8 months
Scott *et al* [15]	50-year-old male marathon runner	Increased his running mileage	None	Slightly displaced fracture through the base of the neck of the right proximal femur	3x CHS + 6 weeks of partial weightbearing	Full weightbearing, light sports at 12 weeks

CHS: Cannulated hip screw; DHS: Dynamic hip screw.

Stress fractures occur when repetitive loading surpasses the body's ability to regenerate, and are common in young and active individuals[1,2]. This condition is particularly prevalent among marathon runners and other endurance athletes due to the repeated mechanical stress from prolonged and cumulative exertion[1,2]. The hypothesis of etiology of stress fractures is that repetitive forces on the hip joint cause micro-stress and fatigue, leading to a failure of structural integrity[1,2]. If undiagnosed and untreated, these fractures can progress and displace, potentially leading to severe complications such as avascular necrosis. Diagnosing an (atypical) femoral neck stress fracture presents challenges due to its subtle onset; patients typically report persistent, vague groin or hip pain that initially is mild and often misdiagnosed [8-10]. Pain worsens with activity, but improves or resolves with rest, mimicking symptoms of muscle overuse. Initial radiographs often miss early fractures, exhibiting low sensitivity; initially ranging from 15%-35%, increasing to 30%-70% after 2-10 weeks[10]. MRI represents the current golden standard, but is often employed only after prolonged complaints and, therefore, the diagnosis is frequently delayed by an average 14-week interval[11].

Delayed diagnosis increases the risk of progressive displacement of the fracture, leading to reduced blood supply and increasing the risk of avascular necrosis[10-12]. Complications such as displacement of an initially well-aligned fracture, varus deformity, avascular necrosis, and non-union are not very common, but unfortunately delayed diagnoses are frequent[10-12]. The degree of fracture displacement is the most critical factor affecting the patient's prognosis[11]. Regarding medial column fractures, progressive displacement leads to a 60% reduction in sports activity levels and a 30% incidence of avascular necrosis[10,11]. No information is available regarding these important predictors of long-term functioning for lateral column fractures. Therefore, a quick and accurate diagnosis is crucial to prevent further complications. General practitioners and other primary care providers play an essential role in early detection. By being alert to the symptoms of stress fractures, physicians can refer patients for further investigation and treatment in a timely manner, significantly improving the prognosis.

Femoral neck stress fractures can be treated conservatively or surgically, depending on the severity and stability of the fracture. Conservative treatment is only justifiable for an incomplete fracture on the medial side, *i.e.* the compression side [8]. This approach involves rest and non-weightbearing mobilization of the affected leg, followed by a gradual increase in weightbearing over 12 weeks[8]. However, if the fracture is on the lateral side, there is a high risk of progression, necessitating primary surgical treatment, most preferably with cannulated hip screws or a dynamic hip screw[8]. Surgical fixation should be considered in all cases, even for incomplete medial fractures, as it allows for immediate postoperative weightbearing. Prolonged immobilization is unacceptable for the typically young patient group[3,8].

Displaced fractures or fractures that have existed for a longer time, with a high risk of non-union and avascular necrosis, require surgical intervention[3,8]. The preferred method is surgical fixation, often by means of a dynamic hips

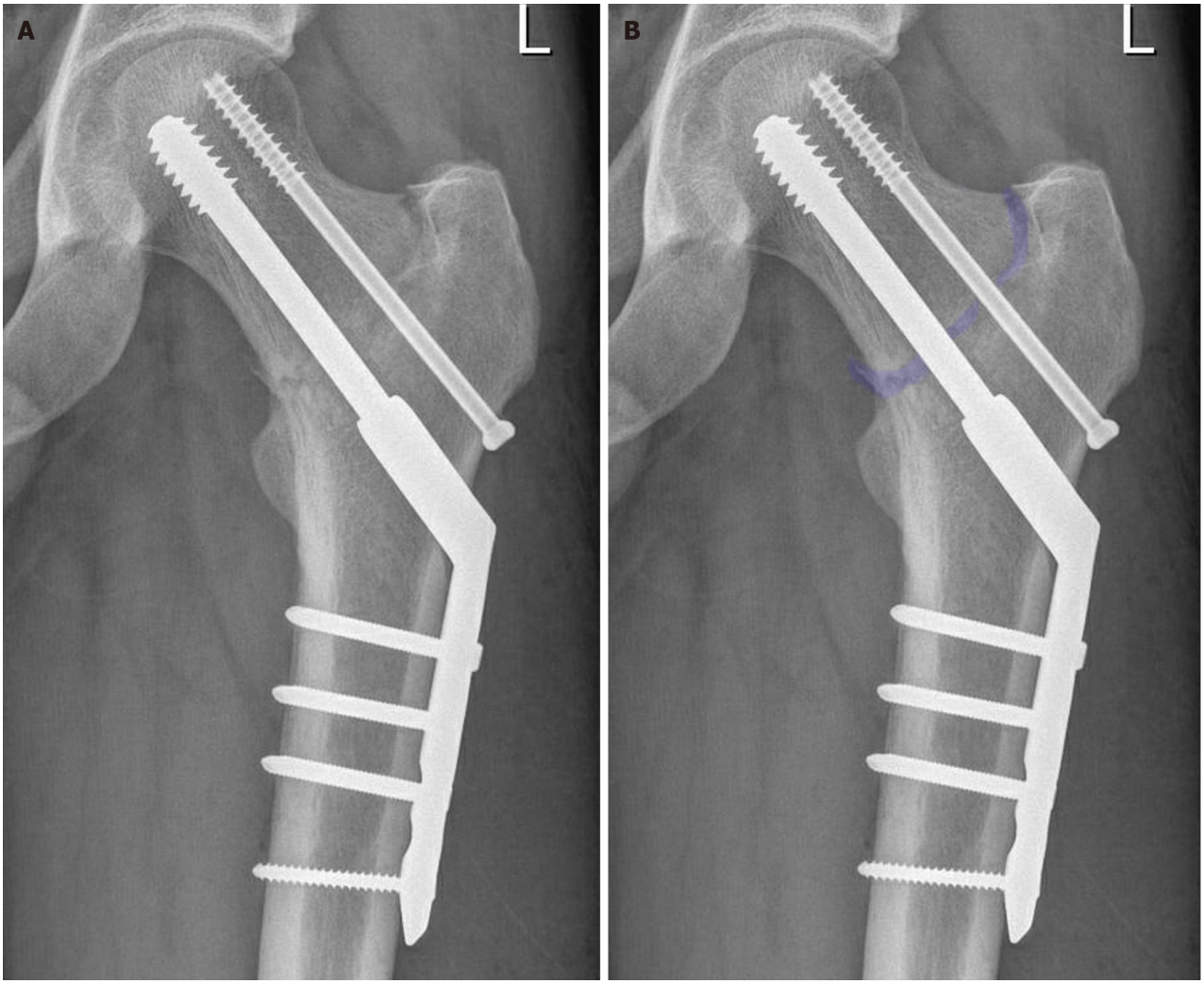

Figure 5 Position after bearing weight on postoperative day 1, coronal view. The position post-operation and loading on day 1 was anatomically correct, with notably good results on the medial side, despite the delayed presentation. Due to uncertainty regarding underlying pathology, a four-hole dynamic hip screw including an anti-rotation screw was chosen. A: Corresponds to the picture without overlay; B: Includes an overlay, highlighting the fracture.

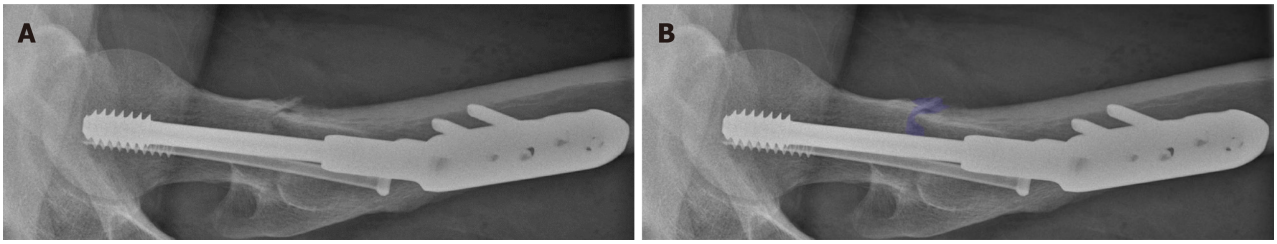

Figure 6 Position after bearing weight on postoperative day 1, lateral view. The position post-operation and loading on day 1 was anatomically correct, with notably good results on the medial side, despite the delayed presentation. A: Corresponds to the picture without overlay; B: Includes an overlay, highlighting the fracture.

screw or cannulated hip screws, aiming to restore anatomy and maintain adequate blood supply to the femoral head[8,11,12]. Surgical fixation of (incomplete) lateral, medial, or displaced fractures, can be performed with specific fixation methods depending on the degree of displacement, angle of the fracture, and patient-related factors. These methods vary from cannulated hip screws, dynamic hip screws, and intramedullary pens, to complete hip replacement surgery.

Recovery after surgery varies significantly depending on the duration, alignment, and severity of the fracture[8,11,12]. Conservatively treated, non-displaced fractures have a better prognosis and a shorter recovery period. Displaced fractures and cases with avascular necrosis often require long-term rehabilitation and can result in permanent limitations, both during sport and daily activities[8]. Therefore, timely and adequate treatment is vital to ensure the best possible outcome for the patient.

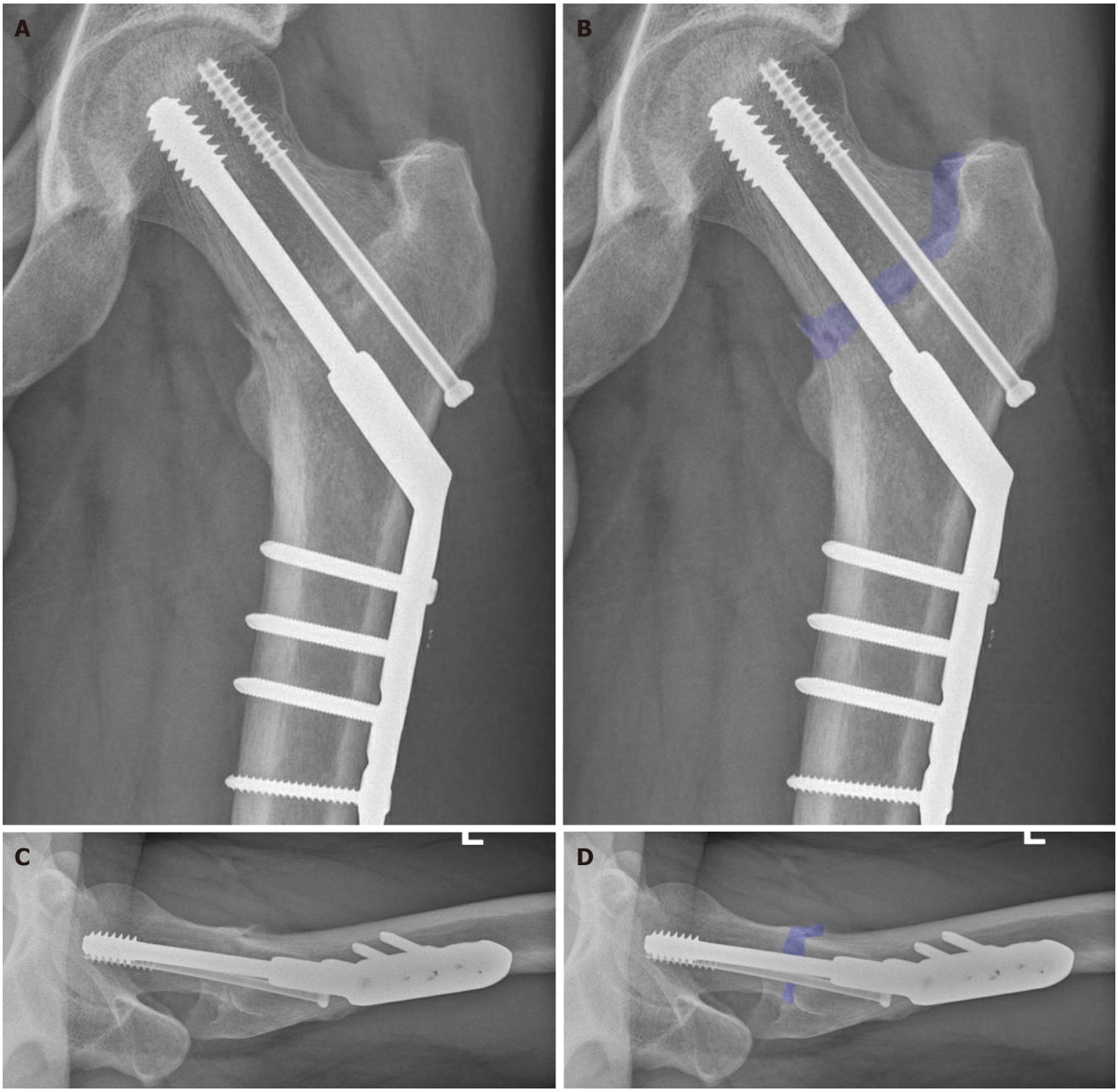

Figure 7 Position of osteosynthesis material at outpatient clinic follow-up. A: Coronal X-ray without overlay; B: Coronal X-ray including an overlay, highlighting the fracture; C: Lateral X-ray without overlay; D: Lateral X-ray including an overlay, highlighting the fracture. During the outpatient clinic follow-up, the patient was almost free of complaints and the alignment was consistent with before. At this time, there were no convincing signs of bone remodeling, which is also not expected with this atypical fracture.

In our case, the initial presentation during marathon training was particularly insidious, given the rapid transient nature and absence of symptoms during other sport activities. Initial additional diagnostics would not have revealed a stress fracture, which would have only been detected by MRI as an area of bone edema[8]. During the second presentation, when there was a complete lateral fracture, timely radiographic diagnosis would have resulted in earlier surgical fixation, significantly lowering the risk of non-union, complications, and making a return to pre-existing functioning more likely[9,10,12]. However, timely detection of a femoral neck (stress) fracture is extremely challenging due to the non-specific clinical symptoms. The symptoms can be easily misinterpreted, and a prolonged diagnosis period is common[8,11,13-15], due to the low incidence of stress fractures, the vitality of young patients, and atypical symptoms, leading to muscle overuse being be more likely. Consequently, insufficient action is often taken. Increased alertness and a lower threshold for additional diagnostics in the presence of persistent and/or atypical hip or groin pain in active patients results in earlier identification and appropriate treatment.

CONCLUSION

It is essential for healthcare providers, specifically those in primary care and emergency departments, to be vigilant for

the subtle symptoms of stress fractures to ensure timely diagnosis and treatment. Early recognition and intervention can prevent complications such as avascular necrosis and permanent disabilities, leading to a better prognosis with recovery to pre-existing levels of functioning.

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FOOTNOTES

Author contributions: Oudmaijer CAJ wrote the manuscript; Paulino Pereira NR, Visser D, Veltman ES, and van Linschoten R extensively revised the manuscript; Wakker AM was responsible for the graphical representation and 3D reconstruction, and revised the entire manuscript; Oudmaijer CAJ, Veltman ES, and van Linschoten R wrote and made the decision to submit the final report.

Informed consent statement: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The first author approached the patient to request his cooperation and permission to set up this case report. The necessary consent forms were provided to the patient by the first author and were subsequently signed by the first author in his role as the patient.

Conflict-of-interest statement: There are no financial and/or other competing interests for the (principal) investigator(s) of the trial to declare.

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