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Review Article

Bone Marrow Edema and Zoledronic Acid - A Narrative Review

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Abstract

The objective of this study was to investigate and evaluate the effectiveness of a single dose of zoledronic acid in the treatment of bone marrow edema syndrome (BMES) in all lower extremity locations (hip, knee, foot, and ankle). A literature search was conducted on electronic databases (PubMed, Scopus, and Google Scholar) to identify clinical studies on the therapeutic use of zoledronic acid for patients with bone marrow edema syndrome. Until today, very few studies have been conducted using zoledronic acid in patients with bone marrow edema syndrome. The majority of them are retrospective. This narrative review suggests the effectiveness of a single dose of intravenously administered zoledronic acid in patients with bone marrow edema syndrome in three anatomical locations: the hip, knee, and foot/ankle. Zoledronic acid, often used in combination with partial-weight bearing, appears to reduce pain intensity, improve range of motion, and decrease lesion size in MRI imaging findings. The administration of a single dose of intravenous zoledronic acid is a reasonable therapeutic option for patients with bone marrow edema (BMES). It accelerates the time to pain resolution and simultaneously improves imaging findings in MRI. Further prospective clinical studies with a larger number of patients and longer follow-up periods are needed.

Keywords: Ankle, Bone marrow edema, Hip, Knee, Zoledronic acid

Introduction

Bone marrow edema syndrome (BMES) is a clinical-radiological condition of uncertain origin, characterized by severe, non-acute joint pain and distinctive imaging findings on magnetic resonance imaging (MRI) [accumulation of excessive fluid in bone marrow structures]. There is no history of injury, infection, or avascular necrosis[1]. This clinical condition predominantly affects middle-aged males with varying degrees of pain, primarily in the lower extremities (hip, knee, foot, and ankle). In a clinical context, musculoskeletal pain is described as occurring in a manner that is disproportionate to the findings of a physical examination. It can initially be sharp or subtle, and in some cases, it worsens over time, eventually causing significant functional impairment[2,3]. Additionally, it causes a limited range of motion, local sensitivity, and an inability to load the affected limb[4].

Regarding pathogenesis, the most prevalent theory holds that it is provoked by nerve compression or it is the consequence of a change in venous effluence, causing increased intramedullary pressure[5]. Nevertheless, original studies at the clinical and histological levels related to bone metabolism in bone marrow edema syndrome (BMES) have suggested that vitamin D deficiency has a negative impact on the bone mineralization of BMES[6,7]. Vitamin D insufficiency causes reduced calcium absorption and ultimately contributes to the release of calcium from bones in order to maintain calcium concentration in the bloodstream[8].

The radiological findings in magnetic resonance imaging (MRI) can clearly show a lower signal intensity on T1 sequences and a higher signal intensity on T2 and STIR sequences[4,5]. Due to high heterogeneity and vague

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symptoms, delays in diagnosis can lead to joint dysfunction, poor surgical outcomes, and a decline in quality of life[9]. The natural course of the disease is a self-generated decrease in symptoms and a return of MRI findings to normal, typically occurring around 6 to 12 months after their initial appearance. However, in some clinical cases, the persistence of symptoms for more than 12 months has been reported[2,10].

As far as the treatment of BMES is concerned, there are confrontations. However, the advantages of using bisphosphonates have been suggested recently and have been documented to result in a substantial decrease in pain intensity and the size of bone marrow edema, along with normalization of imaging findings in MRI[11,12]. Bisphosphonates have been suggested to have a positive impact on bone metabolism by inhibiting osteoclast function and reducing bone absorption. Thus, bisphosphonates have anti-inflammatory properties and contribute to decreasing bone pain[2,10].

Therefore, the aim of this narrative review was to investigate and evaluate the effectiveness of a single dose of zoledronic acid in treating bone marrow edema syndrome (BMES) in various locations of the lower extremities (hip, knee, foot, and ankle).

Methods

Clinical studies on the effect of zoledronic acid in the treatment of bone marrow edema were identified by conducting a literature search of electronic databases (PubMed, Scopus, and Google Scholar). The search was limited to English-language studies published until October 2023. The inclusion criteria focused on in vivo studies that examined the therapeutic effect of zoledronic acid in patients with bone marrow edema syndrome (BMES). Duplicate articles were removed, while title and abstract screening was carried out in an effort to identify potentially relevant studies. Full-text articles were evaluated, along with additional studies that were identified through the reference lists. The selected studies were critically reviewed and closely examined to determine the therapeutic effect of zoledronic acid on patients with bone marrow edema syndrome in various locations of the lower extremities (hip, knee, foot, and ankle). The outcomes assessed included pain intensity and size of damage. The findings were synthesized and presented in a narrative format, highlighting the positive impact of zoledronic acid on the treatment of bone marrow edema syndrome (BMES).

Results

Hip

In a clinical study conducted by Evangelatos et al., involving 9 patients with transient osteoporosis of the hip (TOH), it was suggested that a single dose of zoledronic acid, when combined with partial weight-bearing, is safe and results in the remission of bone marrow edema, a decrease in pain intensity within 30 days, and rapid functional recovery[13].

Furthermore, in another clinical review study by Flores-Robles et al., 17 cases of bone marrow edema were identified, with the hip being the affected joint in 5 patients. The study supported the use of zoledronic acid treatment as a therapeutic option in managing BMES, as 75% of the treated patients experienced complete remission[10].

Additionally, in another prospective study by Vasiliadis et al., 54 patients with bone marrow edema were included. Of these patients, 16.7% (9 patients) had the affected joint in the hip. The study found that a single dose of zoledronic acid 5mg, combined with partial-weight bearing for 30 days, resulted in improved mobility and a reduction in edema in patients with bone marrow edema syndrome (BMES)[8]. The mean visual analogue scale (VAS) score for the hip was 6.77±0.83 at baseline and 5.11±2.14 at the 6-month follow-up[8].

Knee

In a clinical retrospective study by Muller et al., 34 patients with painful bone marrow edema lesions of the knee were treated with either bisphosphonate (ibandronate - 9 patients, alendronate - 3 patients, zoledronic acid - 12 patients) or sequential therapy (ibandronate to zoledronic acid - 7 patients) or denosumab (3 patients). The authors concluded that zoledronic acid is more effective than other antiresorptive treatments, especially when compared to ibandronate[14].

Additionally, in the retrospective review conducted by Flores-Robles et al., which involved 17 patients with bone marrow edema syndrome, the knee was the only affected joint in one patient. This patient experienced moderate pain at baseline, but it completely recovered after 12 months[10].

In a prospective study conducted in Greece, which involved 54 patients with bone marrow edema syndrome, the knee was the most commonly affected joint (32 patients - 59.2%). The authors concluded that a single dose of intravenous zoledronic acid, along with partial weight load for 30 days, can reduce pain intensity. This treatment was found to be effective in 66% of patients with bone marrow edema located in the knee, and in 33% of patients with BMES localized in the hip, foot, and ankle[8]. Consequently, the authors suggest that the knee joint shows the best results in 15 out of 32 patients (46.9%)[8].

Foot and Ankle

In a retrospective review conducted by Singh et al., 18 consecutive patients with foot and ankle bone marrow edema were included. Out of these patients, 9 were treated with a single dose of 5mg intravenous zoledronic acid and were advised to bear weight cautiously. These patients reported a remission of their pain symptoms in an average of 5.8 weeks. The total duration of treatment, including the initial 8 weeks of partial weight bearing on the affected limb only, was 13.8 weeks. The authors argued that there may be a potential

for an accelerated reaction to intravenous zoledronic acid administration[2]. Moreover, they suggested that patients who received intravenous zoledronic acid reported headaches and flushes in 11% of cases[2].

Moreover, in the retrospective review by Flores-Robles et al., it was found that the ankle joint was more often affected (9/17 patients - 53%), while in 2 cases (2/17 patients - 11.7%), the foot joint was affected. The authors suggest that zoledronic acid is effective, as more than 75% of patients were able to daily activities[10]. Furthermore, there was resolution of pain and the clinical effect was maintained for more than one year[10].

Additionally, in a prospective study conducted at a center in North Greece, the affected joint was the foot and ankle in 13 patients (24.1%)[8]. The mean visual analogue score was 7.46±0.96 at baseline and 5.15±2.03 at the 6-month follow-up[8]. The authors concluded that the administration of intravenous zoledronic acid provides improved clinical and radiological results in patients with bone marrow edema syndrome[8].

Discussion

The present narrative review provides an overview of the consequences of administering intravenous zoledronic acid to patients with bone marrow edema syndrome (BMES). Zoledronic acid appears to have a positive effect on BMES. It reduces pain intensity, improves range of motion, and decreases the size of the lesion in MRI imaging findings.

A lot of studies have analyzed and documented the clinical and radiographic findings of bone marrow edema syndrome (BMES). They supported a clear superiority of the male gender[1,3-4,14]. The majority of defects were located in the lower extremities, with the proximal femur (head and neck) being the most frequent anatomical location in most studies, followed by the knee and foot/ankle[1-2,15-16]. Despite these findings, a recent prospective study from Greece suggested a higher prevalence of females, with a male-to-female ratio of 1:1.84[8]. Furthermore, in this study, the majority of the lesions were located in the knee (32 cases - 59.3%). The foot/ankle was the second most common location, followed by the hip[8]. A potential reason could be attributed to the fact that prior studies are concentrated in specific anatomical locations[10,15-16]. Additionally, a study by Cahir and Toms supported the finding that the knee is the most frequently affected joint[17].

Until today, very few studies have been conducted on the use of bisphosphonates in bone marrow edema syndrome. The majority of them are retrospective. A small number of patients have been administered bisphosphonates such as alendronate, ibandronate, or zoledronic acid[10,15-16]. The present narrative review involved searching the literature for all clinical studies (retrospective and prospective) that used a single dose of intravenously administered zoledronic acid in patients with bone marrow edema syndrome in three anatomical locations: hip, knee, and foot/ankle. Zoledronic acid has some important advantages: it is administered once per year, has no serious adverse events, and is cost-effective. The most common side effects are headache, flashes, fever, and a flu-like syndrome, which can last up to 72 hours after the intravenous administration of the drug.

Various studies have suggested the effectiveness of zoledronic acid in achieving complete remission of the disease. Despite these factors, the effectiveness of the treatment may be delayed. It may take up to 4 weeks for the intensity of the pain to decrease and 14 to 52 weeks for the pain to completely resolve[2,10,14]. Especially, in a retrospective observational clinical study by Muller et al., 12 patients with bone marrow edema syndrome located in the knee were treated with a single dose of intravenous infusion of zoledronic acid. An absolute remission of the symptoms was recorded in 11 patients (92%) 4 weeks after the drug administration[14].

Although intravenous infusion of zoledronic acid has shown promising results, therapies that combine ibandronate and vitamin D have demonstrated complete pain remission and significant improvement in functional recovery and mobility within the first 15 days of infusion in professional athletes[3]. Furthermore, a clinical retrospective study by Singh et al. supported the finding that combining partial weight-bearing with the infusion of zoledronic acid in patients with bone marrow edema in the foot/ankle accelerates recovery time compared to partial weight-loading alone[2]. Additionally, in a prospective study conducted at a Greek hospital, it was found that the intravenous administration of zoledronic acid, combined with partial weight-loading for 30 days, can decrease the intensity of pain[8].

In the same study from Greece, a significant decrease in initial MRI edema was recorded in only 20 patients (37%) overall. The best results were observed in the knee joint, with 15 out of 32 patients (46.9%) showing improvement[8]. In contrast, the retrospective review by Flores-Robles et al. suggested that three months after the infusion of zoledronic acid, the edema in MRI findings had disappeared in 62.5% of the patients. Additionally, a decrease of more than 50% in the initial edema was recorded in 3 patients (37.5%)[10]. In agreement with the previous study in clinical research by Simon et al., a nearly complete remission of bone marrow edema was observed 13 months after the intravenous administration of bisphosphonates in professional athletes[3]. A potential reason for this is that standardization of MRI imaging findings occurred approximately 3 to 18 months after their initial appearance[10,12].

This is one of the very few narrative reviews that investigated the efficacy of intravenous infusion of zoledronic acid in patients with bone marrow edema syndrome, regardless of the affected joint in the lower limbs (hip, knee, foot/ankle). By conducting a comprehensive literature search up until October 2023, all relevant studies were critically analyzed and their findings were systematically recorded.

Conclusions

The present narrative review supports that the administration of a single dose of intravenous zoledronic acid as a reasonable therapeutic option. It reduces the time for the patient to be back in his every day activities, and his work, as it deteriorates pain and improves mobility and weight bearing. The MRI shows a significant improvement for patients with bone marrow edema syndrome (BMES) after the intravenous administration. However, further prospective clinical studies with a larger number of patients and longer follow-up are necessary in order to document the favorable results of intravenously administered zoledronic acid.

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