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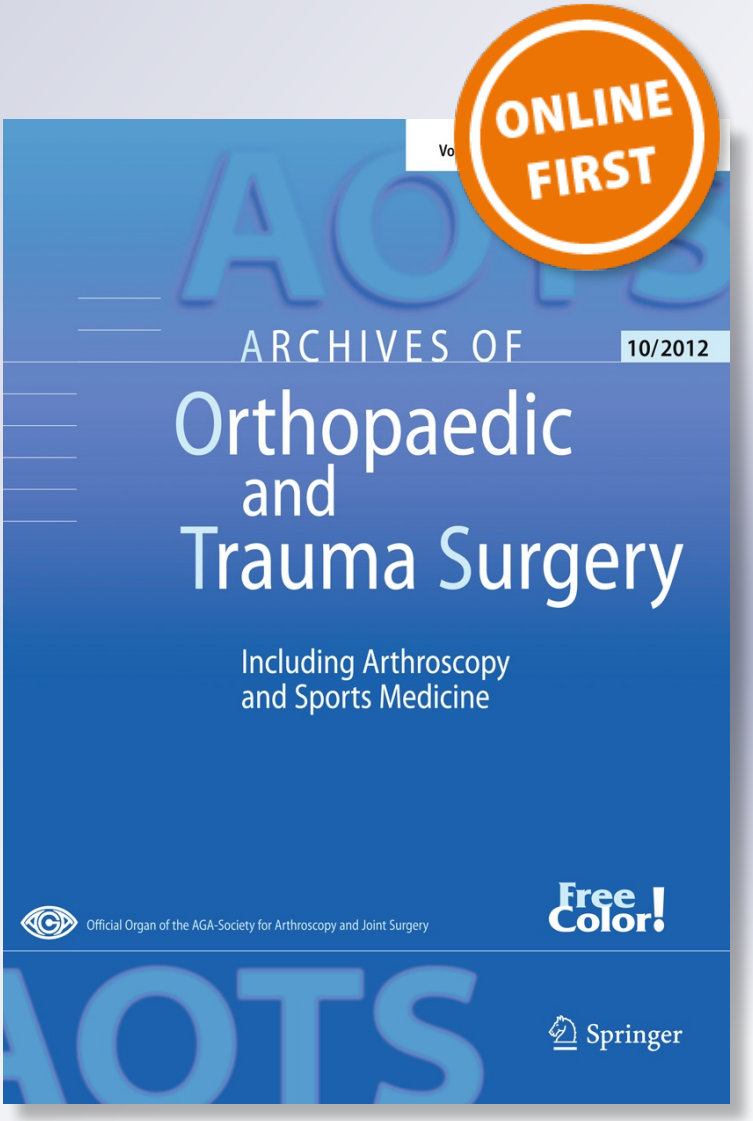

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ARTHROSCOPY AND SPORTS MEDICINE

Treatment of bone marrow edema syndrome with intravenous Ibandronate

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Abstract
Background In this pilot study, we investigated the therapeutic efficacy of intravenous Ibandronate compared to pain medication on the outcome of bone marrow edemas (BME) of the knee and talus.
Patients and methods Fifteen patients with a painful BME of the knee and 15 patients with a BME of the ankle, confirmed on MRI, were enrolled and treated with three ambulatory infusions of each 6 mg Ibandronate (group 1). A control group (group 2) of 10 patients with a BME of the knee and 10 patients with a BME of the talus was treated with pain medication and partial weight bearing. Patients were evaluated clinically at baseline and at 1, 3, 6 and 12 months after therapy start with a visual analog pain-scale (VAS) and specific joint scores (Larson knee- and Mazur ankle-score). BMEs were assessed with MRI at baseline and after 6 months in both groups.
Results In the knee group, the mean VAS pain score decreased from 8.5 at baseline to 1.2 at 12 months ($p < 0.0001$) in patients treated with Ibandronate and, respectively, from 8.1 to 4.0 in the control group ($p < 0.001$). In the ankle group, the mean VAS pain score decreased from 8.2 at baseline to 0.9 at 12 months ($p < 0.0001$) in patients treated with Ibandronate and, respectively, from 7.9 to 3.9 in the control group ($p < 0.001$). The mean Mazur ankle score increased from 51 to 91 points ($p < 0.001$) in group 1, and from 52 to 72 points in group 2 ($p < 0.01$). The mean Larson knee score increased from 54 to 89 points ($p < 0.001$) at 12 months in group 1, and from 51 to 70 points in group 2 ($p < 0.01$). For both joints, we observed a significant clinical improvement in the Ibandronate treatment group and in the control group, but functional results were significantly more improved in the Ibandronate treatment group. Only the Ibandronate treatment group showed a significant BME regression at the 6 months MRI follow-up.
Conclusions Intravenous Ibandronate therapy showed significantly better clinical results and BME regression rates on MR-imaging compared to analgesic medication in combination with partial weight bearing in the treatment of BME of the knee and talus and shortens the natural course of the disease.

Keywords Bone marrow edema · Bisphosphonate · Ibandronate · Magnetic resonance imaging

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Introduction

Bone marrow edema syndrome (BMES) is a rare, but underdiagnosed source of pain which mainly occurs around joints of the lower extremity [1–8]. Predominantly, healthy young or middle-aged patients are affected. BMES can also occur during pregnancy and was formerly named "localized

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transient osteoporosis" (LTO)[9]. Because of the rarity of BMES and its unspecific symptoms, the correct diagnosis is often delayed and an aggravating bone pain impairs function and quality of life [1, 3, 4, 7]. Radiographs help to exclude fractures, rheumatoid osteoarthritis and osteomyelitis, but show no pathologic findings in almost all patients [5–7]. In most cases, conservative therapy is initiated. In cases of prolonged pain and functional disability, an MRI is usually performed after weeks to months [3, 4, 6]. With the widespread use of MRI, as a specific diagnostic tool, the correct diagnosis can be made earlier in the disease course [3–6]. In general, BMES is considered as a self-limiting disease with remission of symptoms occurring between 6 and 24 months [2–4, 7]. Various treatment options including reduction of weight-bearing, analgesic medication, pharmacologic therapy, physiotherapy and also surgical treatment were described [3, 4, 7–11].

Recent therapeutic and imaging studies showed that BMES is a distinct clinical entity rather than an early manifestation of avascular bone necrosis (AVN) [3–5, 7, 12]. This differentiation is important for the choice of the available treatment modalities, as most invasive surgical procedures applied for the treatment of AVN, like core decompression is now considered not necessary for the treatment of a self-limiting condition, like BMES.

Several symptomatic pharmacologic therapies of BMES with anti-inflammatory drugs (NSAIDs), other analgesics or corticosteroids were shown not to affect the course of the disease [7, 8, 11, 14].

Increased bone turnover in BMES suggests a potential therapeutic target for the use of bisphosphonates [10, 21]. Bisphosphonates are inhibitors of osteoclastic activity and bone resorption with proven efficacy and approval for the treatment of osteoporosis [13, 15], corticoid-induced osteoporosis and metastatic bone disease [16–18]. In two studies, intravenous bisphosphonates were shown to be effective in the treatment of BMES of the hip [19, 20]. Ibandronate, an intravenous-administered new generation bisphosphonate, is a generally well-tolerated drug and shows even good tolerability when applied in monthly intervals like in metastatic bone disease [17, 18].

The aim of this prospective, off-label use [22], MRI-controlled pilot study was to assess the efficacy of Ibandronate, an intravenous-administered bisphosphonate for the treatment of BMES, with a special emphasis on the short-term follow-up compared to a control group that was treated with analgesic medication and partial weight bearing.

Patients and methods

We carried out a prospective, observational, off-label use study comparing bisphosphonate treatment (group 1) with a control group treated with pain medication and partial weight bearing (group 2). We included 15 patients with a BME around the knee joint and 15 patients with a BME around the ankle joint, that were treated with intravenous Ibandronate (group 1). In the control group, there were ten patients with a BME of the knee and ten patients with a BME of the talus (group 2). We included only idiopathic BME, whereas BME in combination with bone osteonecrosis were excluded.

In group 1, the treatment consisted of three ambulatory infusions with 6 mg Ibandronate (Roche AG, Germany) in 100 ml sodium chloride given over 30 min at a monthly interval. All occurring side-effects including, acute-phase reaction, flue-like symptoms, musculoskeletal pain, osteonecrosis of the jaw were noted over the study period. Patients with impaired kidney function, patients with bisphosphonate infusions due to any other cause or iloprost-infusion within the last 3 months and patients with any kind of surgery at the affected limb within 6 months of baseline were excluded. The intervention was performed as an off-label use, prospective, observational study.

Ibandronate is a highly potent, nitrogen-containing bisphosphonate with proven efficacy in the management of metastatic bone disease, postmenopausal and corticosteroid-induced osteoporosis [15–18]. All patients were informed about the therapy spectrum of the drug and potential side effects and gave informed consent to the off-label use therapy. Patients were also informed regarding other treatment options.

The costs for the infusion therapy were paid by the health insurance of the patients and were not provided by the company holding the drug.

In group 2, the treatment consisted of pain medication with diclofenac sodium, 2 × 75 mg per day for 3 weeks and walking with crutches without weight bearing for 3 weeks and another 3 weeks of partial weight bearing with step-by-step increased weight bearing. During this time and the following period, pain medication was allowed if needed.

In all included patients, a functional impairment and pain at rest and pain during activity was present. All patients showed normal laboratory findings and normal calcium metabolism and no impaired kidney function at baseline.

Pain level was assessed with a standardized visual analog pain-scale (VAS). Patients rated their pain level by making a cross on a scale with "no pain" accounting for 0 points and "maximum pain" accounting for 10 points. The Larson score [50 points (p) function, 30p pain, 10p ROM, 10p anatomy] [23] was used for knee evaluation and the Mazur score (50p pain, 40p function, 10p ROM) [24] for evaluation of the ankle. All three scores were evaluated at baseline and 1, 3, 6 and 12 months after the start of therapy.

MRI scans of the affected joint region were obtained at baseline and 6 months after the start of therapy. All BMEs were graded on T1-, fat-suppressed T2-weighted and STIR-images and the number of affected bones was assessed. BMEs present with decreased signal intensity on T1-weighted images and with bright, increased signal intensity on T2- and STIR-images [5–7, 11]. The change of the BME-extent on MRI scans was graded by a visual assessment on STIR sequences. In sagittal and coronal sectional planes, the location and the maximum extent of the edema were determined. Four stages were differentiated [25]: stage 0: normal; stage 1: edema of up to one-third of one femoral condyle, the proximal tibia, the talus or the distal tibia; stage 2: edema of up to two-thirds of one femoral condyle, the proximal tibia, the talus or the distal tibia; stage 3: edema of one entire femoral condyle, the entire proximal tibia or the entire talus or distal tibia; stage 4: edema of both femoral condyles or a combined femoral and tibial edema; combined edema of the talus and distal tibia or a combined edema of the talus and tarsal bones. Follow-up MRI was performed with the same imaging protocol as the MRI at baseline. In addition, the presence of newly formed bone necrosis and the appearance of new BME-sites were evaluated. MRI assessment was performed in consensus by a team consisting of two experienced orthopaedic surgeons that were blinded to the clinical results.

Statistical analysis

Statistical testing was performed with Analyze-It® Software (Analyze-It version 1.73 for windows). The mean, minimum and maximum values were determined at each follow-up. The Mann–Whitney test was performed for the comparison of unpaired groups and the Wilcoxon test was used to test correlations between paired groups before and after treatment. Level of significance was set at 0.05 for all statistical methods.

Results

Baseline characteristics

In group 1, 23 men and 7 women participated in the study, at an average age of 41 years (range 18–62 years). The mean duration of symptoms before infusion therapy was 3.2 months (range 1–12 months). Twenty-one out of 30 were receiving pain medication at baseline. Mobility, limb function and quality of life in most patients were severely impaired, with eight patients (27 %) needing a walking aid at baseline.

In group 2, there were 15 men and 5 women at an average age of 44 years (range 22–57 years). The mean duration of symptoms before the start of therapy was 2.7 months (range 0.5–8 months). Patients were treated with a heterogenous mixture of partial weight bearing and/or pain medication before the start of therapy. At baseline, 12 out of 20 patients were receiving pain medication.

Results on pain

In group 1, intravenous Ibandronate treatment produced a rapid and effective pain relief for both joints (Figs. 1, 2). The mean VAS pain score decreased from 8.5 (range 5–10) points at baseline to 1.6 (range 0–5) points at 6 months ($p < 0.0001$) and to 1.2 (range 0–4) points at 12 months ($p < 0.0001$) in the knee-group (Fig. 1) and, respectively, from 8.2 (range 6–10) points at baseline to 1.9 (range 0–5) points at 6 months ($p < 0.0001$) and to 0.9 (range 0–4) points at 12 months ($p < 0.0001$) in the ankle-group (Fig. 2). Already at the 1-month follow-up, pain decreased to an average value of 4.5 in the knee-group and, respectively, to 4.1 in the ankle group (each $p < 0.01$). In group 1, at the 3-month follow-up 23 out of 30 patients (76 %) were completely pain free and all patients were able to walk without walking aid. At the 12-month follow-up, 27 patients (90 %) were completely pain free and we did

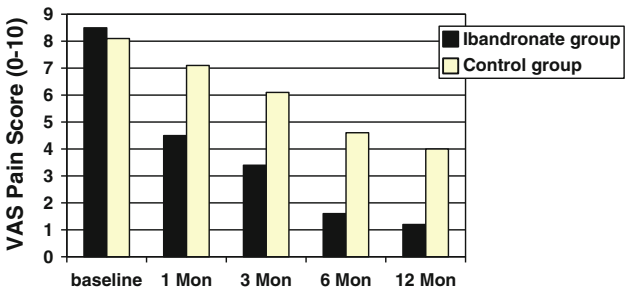


Fig. 1 Knee VAS pain-scores (mean values) for both treatment arms at each follow-up. Ibandronate treatment led to a significantly more improved result

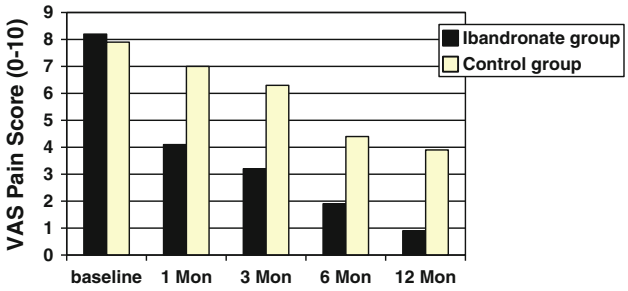


Fig. 2 Ankle VAS pain-scores (mean values) for both treatment arms at each follow-up. Ibandronate treatment led to a significantly more improved result

not observe a deterioration of results. At the 12-month follow-up, only 6 % of the patients were receiving analgesic medication. We did not observe a significantly different effect on pain reduction in the knee-group versus the ankle group.

In group 2, we observed a significantly slower pain relief (Figs. 1, 2). At the 1- and 3-month follow-up, we observed a significantly slower reduction in the pain VAS score for patients in the control group compared to the patients in the Ibandronate group. After 3 months, only 4 patients (20 %) were completely pain free and 14 patients (70 %) were still taking pain medication, and 8 patients (40 %) were still using walking aids. The mean VAS pain score decreased from 8.1 (range 5–10) points at baseline to 4.6 (range 3–8) points at 6 months ($p < 0.01$) and to 4.0 (range 2–6) points at 12 months ($p < 0.001$) in the knee-group (Fig. 1) and, respectively, from 7.9 (range 4–10) points at baseline to 4.4 (range 2–8) points at 6 months ($p < 0.01$) and to 3.9 (range 2–6) points at 12 months ($p < 0.001$) in the ankle group (Fig. 2). Overall, we observed a significantly smaller and delayed therapeutic effect in group 2 compared to group 1 for both joint locations.

Functional scores

In the Ibandronate treatment group (group 1), the mean Mazur ankle score increased from 51 (range 38–68) points at baseline to 88 (range 69–100) points at 6 months ($p < 0.001$), and to 91 (range 72–100) points at 12 months ($p < 0.001$) (Fig. 3). The average Larson knee score increased from 54 (range 41–65) points at baseline to 86 (range 67–100) points at 6 months ($p < 0.001$), and to 89 (range 71–100) points at 12 months ($p < 0.001$) (Fig. 4).

In the Ibandronate treatment group, patients rated their result as good or excellent in 93 % of the cases.

After 3 months, 28 patients (93 %) were able to return to work and to perform their activities of daily living.

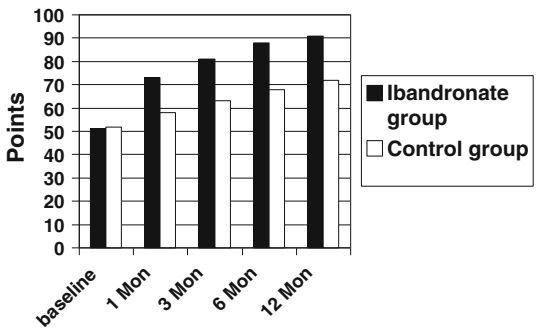


Fig. 3 Mazur ankle scores showing significant better functional results in the Ibandronate treatment group

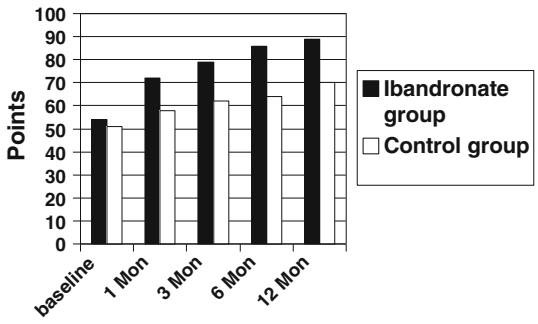


Fig. 4 Larson knee scores showing significant better functional results in the Ibandronate treatment group

In group 2, the mean Mazur ankle score increased from 52 (range 35–64) points at baseline to 68 (range 49–79) points at 6 months ($p < 0.05$), and to 72 (range 50–87) points at 12 months ($p < 0.01$) (Fig. 3). The average Larson knee score increased from 51 (range 38–62) points at baseline to 64 (range 48–74) points at 6 months ($p < 0.05$), and to 70 (range 50–81) points at 12 months ($p < 0.01$) (Fig. 4).

Functional results for both joints showed a significantly better improvement in the Ibandronate treatment group (group 1) compared to the control group (group 2) at 1, 3, 6 and 12 months.

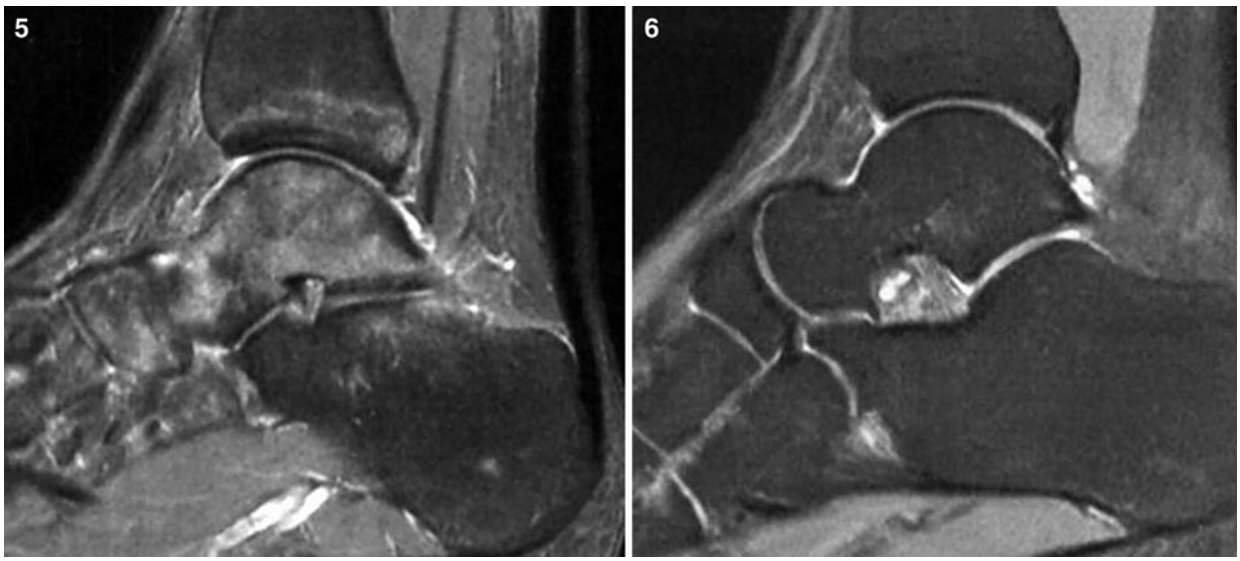
MRI results

Comparison of the MRI before the treatment and after 6 months (average 5.6; range 4.3–7.5 months) showed a significant reduction of the mean BME-extent from stage 2.9 (range 1–4) to stage 0.8 (range 0–2) in the Ibandronate treatment group (group 1) ($p < 0.001$) (Figs. 5, 6, 7, 8, 9, 10). In the control group (group 2), the mean BME-extent showed a non-significant reduction from stage 2.8 (range 1–4) before treatment to stage 2.2 (range 1–3) after 6 months ($p > 0.05$). In none of the cases we observed a newly formed avascular bone necrosis in the former BME areas at the time of the follow-up MRI in both groups.

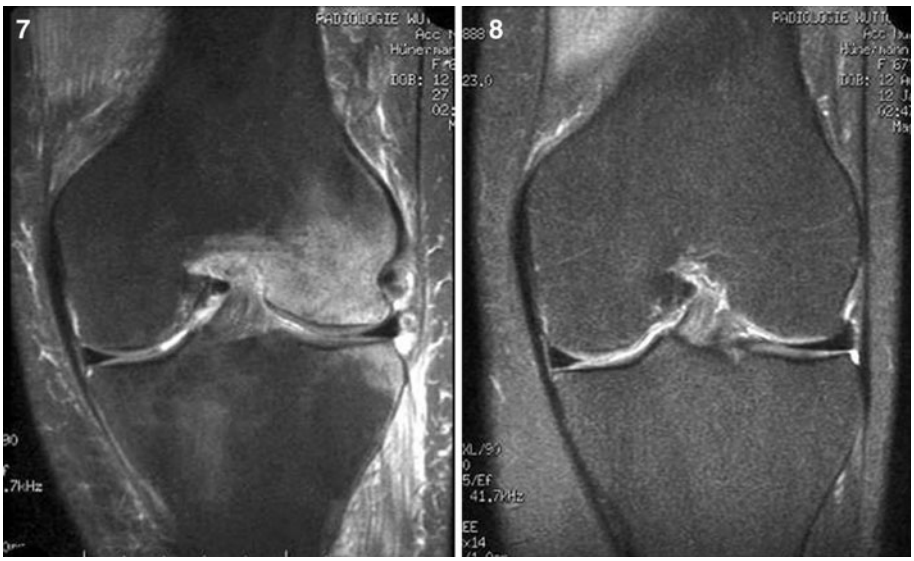
Side effects

In the bisphosphonate treatment group (group 1), we observed three mild acute-phase reactions with flue-like symptoms shortly after the infusion and one with musculoskeletal pain with a duration over 12 h (4 out of 30 patients; 13 %) as adverse events. All acute-phase-related symptoms were first dose dependent and were not observed at the second and third infusions.

These clinical symptoms in the Ibandronate infusion group could be managed adequately with use of NSAIDs in



Figs. 5 and 6 Massive idiopathic BME (stage 4) on a sagittal T2-weighted MR-image of the foot and ankle. Complete resolution of BME at the follow-up MRI after three Ibandronate infusions in a 21-year-old patient with stepwise return to activity



Figs. 7 and 8 BME of the lateral femoral condyle and the lateral tibia plateau (stage 4) at baseline. Complete resolution of BME on both sides of the joint with full return to activity in a 43-year-old woman

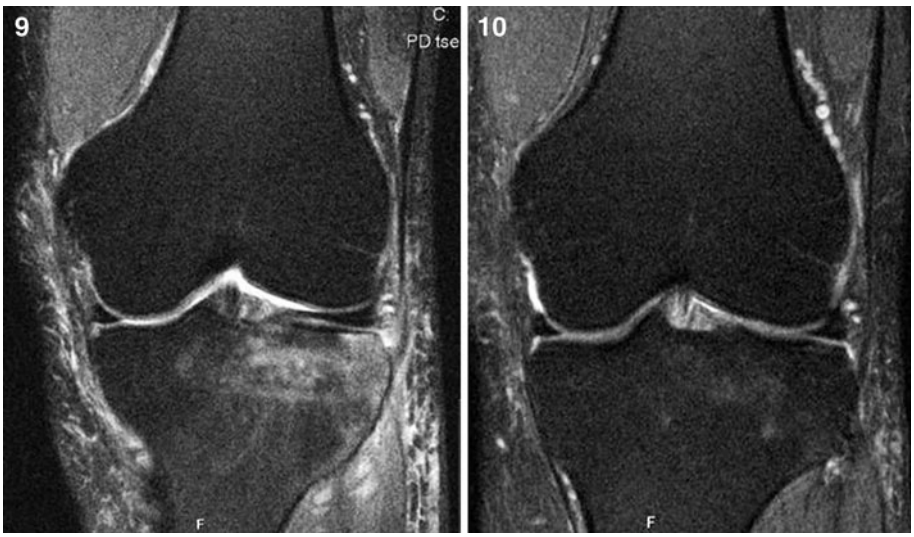
all cases. Over the whole study period, all patients in both groups could be treated with an outpatient visit. Over the study period, no case of osteonecrosis of the jaw or a kidney dysfunction was noted in the Ibandronate infusion group. We did not observe local side-effects or infections. In none of the cases, pain symptoms were aggravated by the infusion therapy. All patients in the infusion therapy group (group 1) completed the therapy regimen and none of the patients switched to an alternative treatment option.

In the control group (group 2), we did not observe any adverse events due to the analgesic treatment. No case of deep venous thrombosis was observed during the period of partial- or non-weight bearing.

After 12 months, four patients (22 %) in group 2 switched to bisphosphonate treatment with an intravenous infusion due to persistent pain on activity, two patients switched to iloprost treatment at another institution and one patient underwent arthroscopic knee surgery at another department.

Discussion

Bone marrow edema is a rare but painful bone disorder. Correct diagnosis is often delayed and the existing therapeutic options are limited, with most of them being only



Figs. 9 and 10 MRI appearance of a BME of the proximal tibia (stage 2) in a 52-year-old man before the start of therapy. Nearly complete BME regression after three Ibandronate infusions

symptomatic. BMES responds poorly to conventional analgesic and non-pharmacologic treatment and a surgical approach to BMES in absence of an associated bone necrosis is considered not justified as first-line therapy [1, 3, 4, 7, 8, 14]. The natural course of this so called "self-limiting disease" can result in an impaired limb function and prolonged pain, with a duration of up to 12 months or more. Clinical evaluation and diagnostic imaging with use of MRI allows an early diagnosis and immediate therapy [5, 7, 11, 19–21].

The main goal of the study was to investigate if the natural course of the disease can be shortened with the Ibandronate infusion therapy compared to conventional treatment. Therefore, pain scores and regain of function and the BME-extent on standardized MRIs were assessed in this study.

Intravenous Ibandronate is a potent osteoclast inhibitor with proven efficacy and good tolerability in osteoporosis conditions and metastatic bone disease [15–18]. In these studies, also a fast-acting and strong effect on bone pain was observed. Until now, Ibandronate and other intravenous bisphosphonates have been successfully used to treat BMES only in studies with small patient numbers [19–21, 26, 27].

In this study, that is the largest series up to date in patients with this bone disorder, we tested the efficacy of intravenous Ibandronate for the treatment of BMES in 30 patients compared to a control group receiving pain medication and partial weight bearing in an MRI-controlled study.

We could show that intravenous Ibandronate infusion produced a rapid and effective bone pain relief already after 1 month and over the whole 12-month period, gaining a significantly better pain relief compared to the results of the control group. Already at the 3-month follow-up, patients in the Ibandronate infusion group achieved functional results comparable to those treated with pain medication and partial weight bearing alone at the final 12-month follow-up. In addition, specific functional scores, ability to work and activities of daily living were significantly improved by the Ibandronate infusion therapy compared to the analgesic treatment in the control group.

Pre- and post-treatment visual assessment of bone marrow edemas on defined MRI-planes showed a significant decrease in BME-size only in the Ibandronate treatment group (group 1), whereas the control group (group 2) showed only a minor reduction of BME-size. We did not observe newly formed areas of bone necrosis in or around the former BME region.

In this study, the intravenous application of Ibandronate, given at an outpatient visit, was generally well tolerated with a low rate of mild side-effects (13 %) and no serious complication.

In a comparable study using intravenous bisphosphonates for the treatment of BMES, Varenna et al. [20] achieved good clinical results with significant BME-regression on MRI after 3 months in 16 patients with LTO of the hip after three infusions of pamidronate. In an observational study, Ringe et al. [19] showed that intravenous Ibandronate was effective in the treatment of 12 patients with LTO of the femoral head in terms of pain relief, but in that study, no functional scores and no follow-up MRI were performed to evaluate BME regression after the infusion therapy.

In a study comparing intravenous iloprost with operative core decompression in BMES of the femoral head, Aigner et al. [8] found an equal effect for both treatment strategies after 3 months. Aigner et al. and Meizer et al. showed in two MRI-controlled studies [3, 4] that intravenous iloprost

is effective in the treatment of BMES at various joint regions with fast pain relief and significant functional improvement. Compared to studies with iloprost treatment for BMES [3, 4, 7, 8], intravenous Ibandronate therapy achieved similar results for pain reduction and functional improvement, but a more pronounced effect on BME-regression measured on MRI-scans [20]. On the other hand, the rate of side effects was far lower in BMES-patients treated with Ibandronate in the present study (15 %) and in a study by Ringe et al. (0 %) compared to intravenous iloprost treatment for BMES (overall 46 % rate of side effects) reported by Meizer et al. and Aigner et al. [3, 4, 7, 8, 19, 29].

The pathophysiologic mechanism that is responsible for the dramatic pain reduction in BMES patients, observed in all patients following Ibandronate infusion, is still unclear, as there is no proved effect of bisphosphonates on pain. It seems that bisphosphonate treatment of BMES with increased bone turnover reduces pain by eliminating the BME and shortens the natural course of the so called "self-limiting disease". The high regression rate of BME with no present bone osteonecrosis at the follow-up MRI in this study also underlines the hypothesis that BMES is a distinct clinical entity, rather than an early form of bone osteonecrosis [11, 12]. Furthermore, bisphosphonates were also shown to be effective in the treatment of avascular necrosis of the hip and necrosis-associated BME with substantial pain relief and prevention of collapse of the femoral head [27, 28].

The limitation of this study is that it was not conducted as a double-blind randomized, placebo-controlled trial. As there is no randomized controlled trial for the treatment of BMES until now, we could demonstrate a good efficacy of administering an intravenous bisphosphonate for the management of BMES compared to a control group with analgesic treatment and partial weight bearing in the control group. The results of this MRI-controlled pilot study can serve as the basis for a randomized clinical multicenter trial comparing intravenous bisphosphonate treatment with a control group and a higher number of patients.

In conclusion, intravenous Ibandronate was shown to be an effective treatment option for BMES of the knee and ankle. Pain scores and functional scores were significantly more improved by the bisphosphonate treatment compared to analgesic treatment in the control group. Follow-up MRI detected a significant reduction of BME size only in the bisphosphonate treatment group. With a low rate of side effects compared to other treatment options, intravenous application of Ibandronate in an outpatient setting represents an effective, safe, patient friendly and economic option for the treatment of BMES.

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