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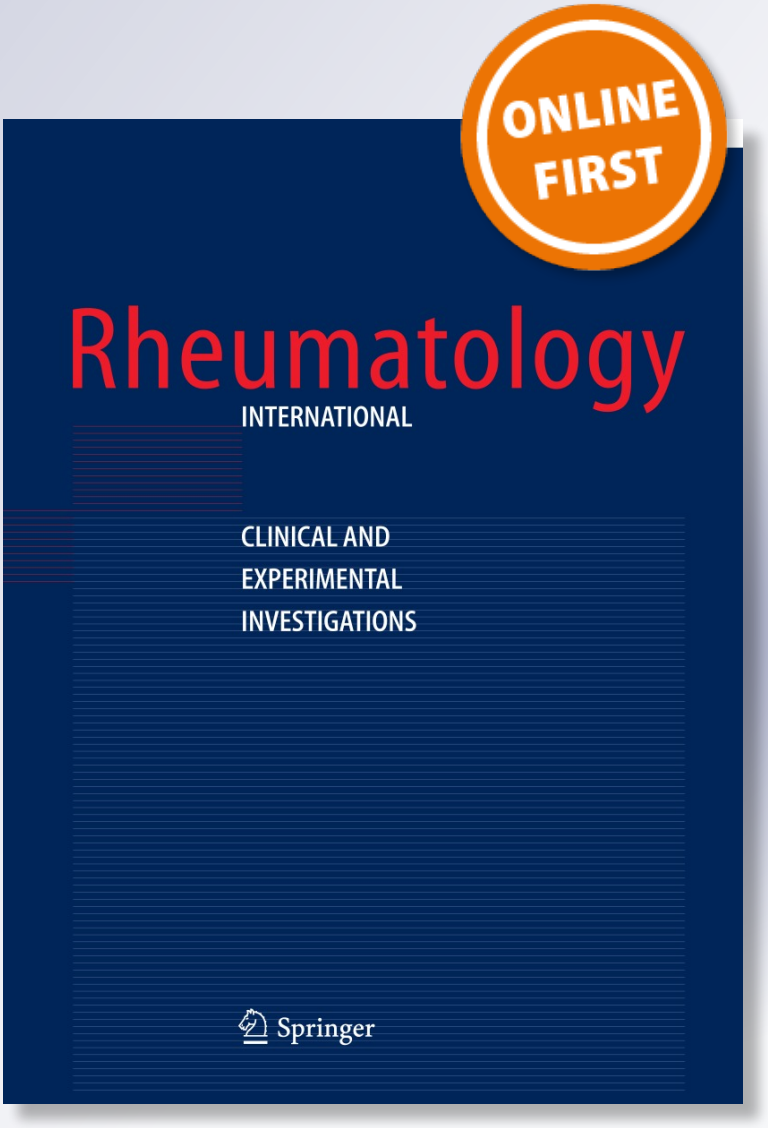

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ORIGINAL ARTICLE

Effectiveness of extracorporeal shock wave therapy in bone marrow edema syndrome of the hip

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Abstract There is no gold standard for treatment of bone marrow edema syndrome of the hip (BMESH). Usually, treatment is conservative, owing to the favorable and self-limiting prognosis. In musculoskeletal disorders, the effectiveness of extracorporeal shock wave therapy (ESWT) has been widely recognized and recent research supports its use in the treatment of the first stages of avascular osteonecrosis of the proximal femur and in other conditions where bone marrow edema is present. On this basis, we performed a prospective study to evaluate the effectiveness of ESWT in normalizing the symptoms and imaging features of BMESH. Twenty consecutive symptomatic patients underwent two treatments of high-energy ESWT and were followed-up at 2, 3 and 6 months, with a final clinical follow-up at mean 15.52 ± 1.91 months. Patients underwent magnetic resonance imaging of the hip and were evaluated according to the Harris hip score. The mean improvement in HHS over the course of the study was of 58.5 ± 14.9 points ($p < 0.0001$), and the mean edema area reduced from 981.9 ± 453.2 mm^2 pre-treatment to 107.8 ± 248.1 mm^2 at 6 months. ESWT seems to be a powerful, non-pharmacological tool that produces rapid pain relief and functional improvement and aids the normalization of the vascular and metabolic impairments which characterize BMESH.

Keywords Bone marrow edema syndrome · Extracorporeal shock wave therapy · Hip · Femoral head · Conservative treatment · Magnetic resonance imaging

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Introduction

The term bone marrow edema (BME) describes a wide range of focal bone lesions of different origin and is most likely a vascular reaction to external or internal disorders [1]. Although the correlations with other diseases such as aseptic osteonecrosis, algodistrophy, trabecular microfractures and osteoporosis of pregnancy are still debated, bone marrow edema syndrome (BMES) is now an accepted clinical entity. It is typified by an "inflammatory pattern" in MRI (low signal intensity in T1-W and high signal intensity in T2-W sequences). Typical BME histological features are not marked by intra or extracellular fluid effusion, but rather depending on the etiology, by fibrosis and inflammatory infiltrate which often reflects the occurrence of pain in the affected bone segment [2, 3]. BMES usually affects the epiphyses of weight-bearing joints—hip, knee, foot and ankle—although it may manifest itself as a "migratory" BME with multiple episodes in different locations [4, 5].

The hip is the most common site of BMES. Bone marrow edema syndrome of the hip (BMESH) is a non-traumatic, disabling, painful condition, which was first described in females during the third trimester of pregnancy [6], although it is found more commonly in middle-aged

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men. It is also referred to as "transient osteoporosis," "transitory demineralization" and "migratory osteolysis"—names which emphasize the transient nature of the radiologically apparent bone loss [7]. BMESH is normally spontaneously self-limiting within 4–24 months [4]; however, there is a risk of fracture due to the weakened bone architecture [8]. Progression to avascular osteonecrosis (AVN) is a rare occurrence, although it has been described in the literature [4, 9–11].

There is no gold standard for the treatment of BMESH; treatment is traditionally conservative and includes reduced weight-bearing, physical therapy, analgesics and vasoactive prostacyclin analog drugs like iloprost (IP), although some authors have even resorted to treating the condition surgically, performing a bone core decompression [4, 12, 13]. However, there is consensus regarding the importance of an early treatment to relieve pain and to avoid weakening the bone trabeculae which could potentially lead to a collapse of the subchondral bone.

Extracorporeal shock wave therapy (ESWT) has proved to be effective in treating musculoskeletal disorders due to its angiogenic, analgesic and anti-inflammatory effects [14–18]. Clinical trials also highlight their effectiveness in treating the early stages of AVN, reducing the bone edema and pain [19–21]. Moreover, recent experimental studies have shown the beneficial effect of shock waves (SW) on the metabolic processes which regulate bone homeostasis, with induction of bone formation in healthy bone and reduction in bone loss in osteoporosis [22, 23]. On this basis, we hypothesized that SW could be effective in the treatment of BMESH, accelerating the resolution of the bone edema and thus relieving the pain. The aim of this prospective study was to evaluate the effectiveness of ESWT in relieving pain and normalizing the MRI appearance of BMESH.

Materials and methods

From January to June 2012, twenty consecutive patients (12 male, 8 female), aged from 34 to 55 (mean 43.23 years), underwent high-energy shock wave treatment for symptomatic BMESH. All cases were classified according to the Association Research Circulation Osseous (ARCO) staging system [24]. The inclusion criterion for the study was a classification of ARCO stage I on MR images: BME and joint effusion without necrosis. Exclusion criteria were BME with any finding of avascular necrosis (demarcation) or advanced osteoarthritis (Ahlback's grade 3 or 4 [25]). Patients who had received any previous treatment were also excluded, along with those who had contraindications for ESWT. The average time period between the onset of symptoms and the beginning of treatment was 4.2 weeks (range 4–7 weeks). Informed consent was obtained from each patient, and the study was approved by the scientific review board of our institution.

All patients were evaluated by a single examiner according to the Harris hip score (HHS), which includes pain, ability to walk unaided, autonomy in daily activities and range of motion. HHS was assessed before treatment (t0), at 2 months (t1), 3 months (t2) and 6 months (t3) post-treatment). Prior to the writing of this report (mean 15.52 ± 1.91 months), a final clinical visit was performed, and HHS was again assessed. All the patients also underwent a hip MRI examination pre-treatment and at the second and sixth month post-treatment. An experienced radiologist calculated the edema area on the resulting films using the Sectra PACS software (Linköping, Sweden).

The therapeutic protocol consisted of two sessions of shock wave therapy, 48 h apart, using a shock wave electromagnetic source [Modulith SLK Storz Medical,Switzerland] fitted with a double ecographic and radiographic pointing device. Each treatment consisted of 4,000 shots at high-energy level, with mean energy flux density (EFD) value of 0.5 mJ/mm^2 (range 0.4–0.6 mJ/mm^2). Partial weight-bearing (two crutches) was prescribed for 30 days after treatment.

Statistical analysis

The mean and standard deviations (SD) were calculated for the HHS values at each of the five time points (t0 through to t3 and final follow-up). The mean change and SD in HHS were calculated between each set of results, and the statistical significance calculated using the Student's *t* test.

Results

The treatment was well tolerated, and none of the patients experienced side effects. All patients showed a dramatic improvement in HHS at t1 (2 months post-treatment), and almost all patients continued to improve over the follow-up period (Table 1). The mean improvement in HHS over the course of the study was of 58.5 ± 14.9 points (range 31.2–81.5, $p < 0.0001$). The mean improvements were strongly statistically significant between t0 and t1 and between t1 andt2 ($p < 0.0001$) and less significant between t2 and t3 ($p < 0.01$). The mean improvement was not significant between 6 months (t3) and final follow-up.

The MRI findings demonstrated the progressive regression of the BME (Figs. 1, 2). Pre-treatment, the mean edema area of the cohort was 981.9 ± 453.2 mm^2. The largest improvement was seen at t1, when the mean edema area had more than halved, to 469.5 ± 306.8 mm^2. At the final MRI examination at t3, the mean edema area had reduced

Table 1 Harris hip scores: pre-treatment (t0), 2 months (t1), 3 months (t2), 6 months (t3), and at final follow-up

Patient no.	HHS at t0	HHS at t1	HHS at t2	HHS at t3	HHS at final follow-up*
1	69	93	99	100	100
2	45	92	96	92	94
3	46	97	98	100	100
4	32	86	97	100	100
5	11	77	85	96	92
6	65	86	100	100	100
7	20	69	91	96	92
8	30	85	86	94	93
9	24	73	85	86	100
10	65	95	90	95	90
11	38	76	92	96	98
12	24	62	90	86	90
13	31	82	89	86	88
14	48	83	92	96	100
15	25	77	89	96	93
16	42	95	96	100	100
17	15	60	91	95	92
18	29	72	92	95	92
18	39	82	88	100	100
20	43	82	88	95	97
Mean ± std. dev	39.08 ± 19.66	81.28 ± 10.8	91.76 ± 4.49	95.06 ± 4.53	95.55 ± 4.29

* Final follow-up performed at mean 15.52 ± 1.9 months. HHS rounded to nearest whole number

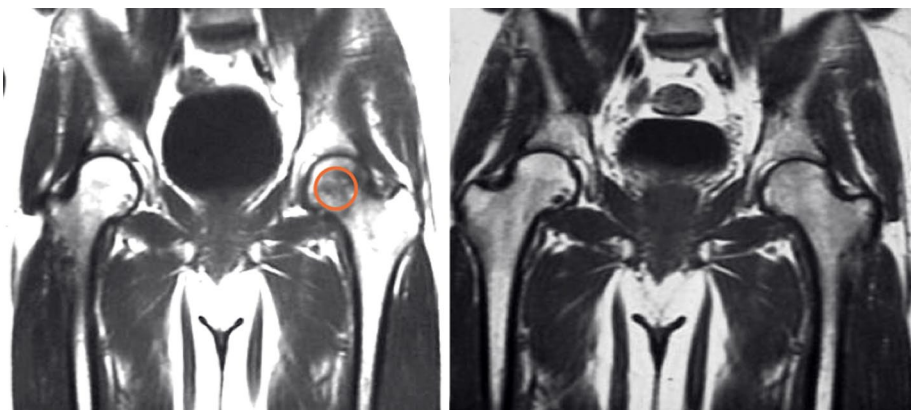

Fig. 1 Pre- and 6 months post-treatment T1-weighted images showing the normalization of a large bone marrow edema of the left femoral head, in a 47-year-old male patient. The *circle* marks the edema

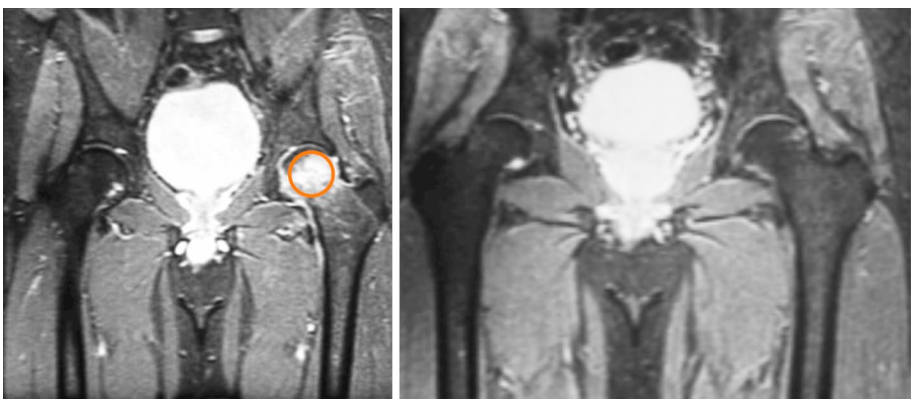

Fig. 2 Pre- and 6 months post-treatment T2-weighted images of the same patient

to 107.8 ± 248.1 mm^2. These reductions were highly statistically significant at both time points ($p > 0.0001$).

Discussion

There is still debate regarding the pathogenesis and implications of BME, and this is reflected in the lack of a gold standard in the treatment of this condition. The rationale for using ESWT to treat BME originates from the analysis of the recent discoveries about the mechanism of action of SW on musculoskeletal tissues, and the clinical results reported in other conditions that have similar features to BMESH. SW have already been used in the treatment of osteonecrosis of the femoral head and have been shown to reduce the extension of the necrotic area and avoid further bone collapse. Therefore, it is possible that SW may significantly delay the need for a total hip replacement. Furthermore, SW induce a significant reduction in the extent of the BME and of the associated pain [19–21, 26, 27]. The main mechanism by which SW act on tissues, even if still not completely understood, is probably a neoangiogenic effect, mediated by several specific factors which include nitroxide (NO). This is a vasoactive molecule produced by endothelial resident cells via endothelial NO-synthase (eNOS), and it is widely expressed in both marrow stromal cells and in cells of bone lineage [17, 28]. The link between NO activity and bone homeostasis is probably due also to the abundance of endothelial cells of the bone marrow stroma. In bone healing, the stimulus on new vessel ingrowth improves blood supply and initiates tissue regeneration [15]. NO acts also as a powerful inhibitor of bone resorption and causes rapid detachment and contraction of osteoclasts, while inducing a simultaneous activation of the osteoblasts [29, 30]. It also regulates the receptor activator of nuclear factor kappa-B ligand versus osteoprotegerin ratio (RANKL/OPG) promoting the differentiation of monoblastic precursors into the osteoclastic lineage. Experimental studies confirm the role of NO derived organic nitrates, including nitroglycerin, in limiting the bone loss associated with estrogen deficiency [31]. SW also stimulate osteoblasts and periosteal cells and induce the osteogenic differentiation of mesenchymal stem cells [32, 33]. Furthermore, SW significantly increase the production of osteocalcin, C-terminal procollagen type I (bone matrix deposition marker) and of several growth factors [22]. A noticeable increase in vascular endothelial growth factor (VEGF), transforming growth factor (TGF-Beta1), bone morphogenetic protein (BMP-2), von Willebrand factor (vWF) and alkaline phosphatase (ALP) was found in peripheral blood of patients treated with SW for non-unions and AVN of the femoral head [16, 34].

In addition to these stimulating biochemical effects, recent research emphasizes the direct role of SW on bone modeling and remodeling. In a preliminary in vitro study, Tamma et al. [22] showed that the acoustic pulse increases the proliferation and the differentiation of osteoblasts and that it reduces the production of pro-osteoclastogenic factors. Furthermore, experimental studies showed that bone microarchitecture can be affected by SW. Unfocused ESWT was effective in inducing bone formation in healthy bone, whereas in osteoporotic bone it reduced bone loss, indicating that ESWT might be useful for the treatment of osteopenia and osteoporosis [23]. In addition, previous clinical experience in AVN of the femoral head and of the lunate verified a strong correlation between ESWT and the regression of marrow edema and of pain [19, 35]. On the basis of this scientific evidence, we decided to use ESWT for addressing the vascular and metabolic disorders that characterize BMESH, "resetting" the mechanisms that govern the bone homeostasis.

We observed a quick positive response to the therapy. The most marked clinical improvement occurred at 2 months post-treatment, where the mean HHS values were significantly higher than those recorded pre-treatment ($p < 0.001$). At this point, all patients had already regained a significant level of autonomy in their daily lives with a marked reduction in pain, which corresponded with the progressive normalization of MRI features. From 3 to 6 months post-treatment, the improvement in scores was more gradual, but still statistically significant with a gain of 10.6 points ($p < 0.001$) at t2 and of 3.35 points ($p < 0.01$) at t3. Although the area of edema on MRI had not disappeared in all cases, the functional results were all good or excellent. In ACL ruptures of the knee, it has been shown that the edema or bone bruise is not always linked to pain [36, 37], and it has been described that MRI abnormalities may take up to 16 months before resolution [37].

Our results compare favorably with the most effective forms of treatment that have been developed recently. These include vasoactive drugs, biphosfonates, bone core decompression and the anabolic agent teraparatide. In a study investigating the efficacy of infusions of iloprost for treating BMESH, Aigner et al. [13] reported an improvement in HHS from 64.7 points to 97 points 3 months after treatment, while Disch et al. [38] observed an increase from 56.5 points pre-treatment to 78.2 at 4 weeks and 80.5 points at 12 weeks. Jager et al. [39] showed an improvement in HHS from 52 to 79 points at mean 33 months. With regard to MR imaging, iloprost treatment produced the conversion to ARCO 0 in 33 of 42 patients at 6 months [39]. In Meizer et al.'s [40] series, in the MR images of 7 of the 27 patients, there was either no improvement or indeed deterioration.

The literature regarding the use of bisphosphonates mostly relates to their role in the treatment of AVN. Reports that demonstrate their success in treating the clinical and MRI features of BMESH concern either single case studies or report diverse anatomic sites. Nevertheless, some larger cohorts have been reported. Varenna et al. [41] reported 15 patients treated with intravenous pamidronate; clinical symptoms resolved in 2 months and the MRI features of BME normalized after 3 months. In another study, the BME was resolved on MRI at 6 months in the 8 cases studied [42]. Teriparatide, a treatment for osteoporosis, has also been shown to resolve BMESH 1 month after treatment [43].

With regard to core decompression, Aigner et al. [13] reported an improvement in HHS of 53.7 points pre-treatment to 95.1 at 3 months. Hofmann et al. [44] reported that at 33 months post-decompression, mean HHS in ten cases had improved from 48 to 98, and on MRI at 3 months postoperative, there was resolution of the BME in all eight of the patients examined. Another study reported that on MRI at 6 months, the BMESH features of 20 out of 20 hips had normalized, with a mean HHS of 93.7 [12]. Elsewhere, core decompression was shown to normalize MRI findings at 3 months, although only six patients were studied [45].

Although the results of the various current conservative treatments are similar to those observed in our study, it is important to note that ESWT is a simple, non-invasive treatment that does not require the assumption of pharmacological drugs, thus avoiding the reported potential side effects [38, 46]. Our treatment protocol required only two short treatments as opposed to the often time-consuming extended treatments proposed above.

We hypothesize that the early clinical response to high-energy dose treatment may be due to the direct, non-enzymatic production of NO as experimentally observed in vitro with high-energy values [17]. The close anatomical and functional links between vascular elements, marrow stromal and active bone cells may explain the positive effects of SW on bone metabolism. The production of NO induced by the acoustic stimulus would be the keystone of this result because of its dose-dependent, multiple action on both endothelial and bone cells. It seems to address both the vascular and metabolic impairment that distinguishes BME, acting as a sort of "reset mechanism."

We are aware that a weakness of this study is the lack of a control group. However, this was a retrospective study that reports our initial experience with the use of ESWT for treating BMESH, and in the absence of a gold standard treatment, we wished to test whether our rationale for its efficacy was valid. We believe that this experience might form the basis for future prospective controlled studies.

To our knowledge, this is the first study to describe the use of SW in BMESH. Our results show that ESWT is effective, bringing a swift clinical improvement, followed by a progressive normalization of the MRI appearance. Consequently, it seems possible that it might also prevent the, admittedly rare, development to AVN of the femoral head. Furthermore, ESWT is a non-invasive technique that is well tolerated and with no side effects. Nevertheless, further controlled studies, with different treatment protocols in terms of number of shots, energy level and frequency employed, and the number of treatments, are needed to establish the optimal regimen.

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