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Review Article

Bone Marrow Edema Syndrome and Treatment by Utilization of Extracorporeal Shock Wave Therapy: Is it worth it?

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Abstract

Introduction: Bone Marrow Edema Syndrome (BMES) is a self-limited condition that can affect young or middle-aged women or men. It is manifested by sudden onset of pain localized in the affected region. Extracorporeal shock wave therapy (ESWT) has been utilized in several orthopaedic conditions including avascular necrosis and due to the subsequent promising outcomes; it was attempted on patients suffering from BMES as a non-operative option of treatment. The aim of our mini review paper was to describe BMES and discuss the current studies that were conducted regarding the utilization of ESWT as a non-invasive method of treatment in patients with BMES.

Material and Methods: A review of the literature was conducted using Pubmed, Scopus and Google scholar with the terms "extracorporeal shock wave" OR "extracorporeal shockwave" AND "bone marrow edema syndrome" OR "transient osteoporosis" to gather all current knowledge regarding BMES and ESWT. In total, 6 studies concerning BMES and treatment with ESWT were identified between November 2014 and April 2020 and were further analyzed in the discussion section.

Results: A total of 177 patients who were treated with ESWT in the context of BMES either in the hip joint (74 patients) or in the knee joint (103 patients) were identified in the literature. All of the 177 patients who suffered from BMES had been successfully treated with ESWT. Specifically, in 3 studies which had compared the use of ESWT with patients who received a variety of pharmacological agents including analgesics, bisphosphonates and alprostadil (control group), the results showed higher functional improvement, higher recovery rates, as well as higher reduction of Bone Marrow Edema (BME) on MRI in favor of ESWT group.In 1 study, comparing the use of ESWT with core decompression, ESWT had better results regarding the aforementioned parameters. In another 2 observational studies, ESWT had been successfully utilized and achieved statistically significant improvement in functional and pain scores, as well as reduction of BME on MRI.

Conclusion: ESWT has been used in off-label in patients with BMES with promising results, as it seems to achieve rapid pain relief and functional improvement, hence it may be a potential regimen for the rapid recovery of BMES. Due to the small number of studies, no evidenced based recommendations can be given.

ABBREVIATIONS

BME: Bone Marrow Edema; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; BMES: Bone Marrow Edema Syndrome; TO: Transient Osteoporosis; ESWT: Extracorporeal shock wave therapy; AVN: Avascular Necrosis; NSAIDs: Non-steroidal Anti-inflammatory Drugs; EFD: Energy flux density; HHS: Harris Hip Score

INTRODUCTION

The nomenclature of Bone Marrow Edema (BME) is a radiological term which refers to an area of increased signal intensity on Magnetic Resonance Imaging (MRI) on T2 sequences and decreased signal intensity on T1 sequences as a result of excessive water accumulation in the bone marrow caused by a variety of conditions [1, 2]. BME pattern can only be detected by MRI and in a few cases as an area of focal osteoporosis on plain radiographs or Computed Tomography (CT) [2]. Historically, Wilson was the first to describe the term of BME in patients who suffered from knee/hip pain and since then numerous studies have been published using this term [2,3]. BME can be observed in plenty of clinical conditions and is mainly divided into 3categories regarding the cause which consists of the ischemic

group (avascular necrosis, bone marrow edema syndrome), the mechanical group (bone contusion or bruise, stress injuries) and reactive group (osteoarthritis, tumor related conditions) [4].

Bone Marrow Edema Syndrome (BMES) is a benign entity characterized by transient BME pattern on MRI sequences which has been described under miscellaneous terms in the literature such as Transient Osteoporosis (TO), transient bone marrow edema syndrome, bone marrow edema-like lesions, regional migratory osteoporosis, reflex sympathetic dystrophy [5,6]. The treatment is mostly conservative and rarely operative including core decompression or subchondroplasty [6]. The aim of our mini review paper was to describe BMES and to further discuss the current studies that were conducted regarding the utilization of extracorporeal shock wave therapy (ESWT) as a non-invasive method of treatment in patients with BMES.

MATERIAL AND METHODS

A review of the literature was conducted using Pubmed, Scopus and Google scholar with the terms "extracorporeal shock wave" OR "extracorporeal shockwave" AND "bone marrow edema syndrome" OR "transient osteoporosis" to gather all current knowledge regarding BMES and ESWT. In total, 6 studies concerning BMES and treatment with ESWT were identified between November 2014 and April 2020 and were further analyzed in the discussion section.

RESULTS

A total of 177 patients who were treated with ESWT in the context of BMES either in the hip joint (74 patients) or in the knee joint (103 patients) were identified in the literature. All of the 177 patients who suffered from BMES had been successfully treated with ESWT. Specifically, in 3 studies which had compared the use of ESWT with patients who received a variety of pharmacological agents including analgesics, bisphosphonates and alprostadil (control group), the results showed higher functional improvement and higher recovery rates, as well as higher reduction of BME on MRI in favor of the ESWT group [7-9]. In 1 study, comparing the use of ESWT with core decompression, ESWT had better results regarding the aforementioned parameters [10]. In another 2 observational studies, ESWT had been successfully utilized and achieved statistically significant improvement in functional and pain scores, as well as reduction of BME on MRI [11,12].

DISCUSSION

Bone Marrow Edema Syndrome (BMES)

Curtiss and Kincaid were the first authors who published a study concerned about a transient syndrome characterized by demineralization of hip joint in pregnant women, calling it "transient osteoporosis"[13]. This syndrome is rare and mostly self-limited with a resolution time ranging from 4 to 24 months with an average of 6 months [14,15] It affects young/middle-aged individuals and rarely children with predominance in the male gender (ratio 3:1), typically 30 to 60 years old males or pregnant females aged between 20 and 40 or even non-pregnant cases [16] Patient's history reveals no traumatic causative factor, while sports activities or fall related BMES have been reported as well [14,17]. Classically, BMES presents to the lower extremities and rarely to the upper extremities, with the hip being the most common site (76%), knee, foot and ankle may be affected as well [18].

Patients present with symptomatology of limitation in joint motion and sudden onset of pain which is exacerbated on weight-bearing when lower limbs are involved. The pain severity can range from mild to debilitating pain leading to subsequent hospitalization. The majority of cases are misdiagnosed as idiopathic [5,18]. Traditionally, the pain is aggravated at its maximum in 2 months and resolves after 3-9 months from onset but with the possibility of recurrence in other or the same joint [5]. On clinical examination, findings include joint effusion; subcutaneous edema may be present, sensitivity on palpation and on percussion compared to contralateral joint and usually absence of neuromuscular wasting [18].

Pathologoanatomical specimens of bone marrow in patients with BMES show interstitial edema, necrosis, formation of fibrovascular tissue, trabecular abnormalities like increased bone formation without evidence of transient osteoporosis (TO) and increased osteoblast activity which is located in the exact region of BME as depicted on MRI. Bone scintigraphy is characterized by the increased uptake of trace in the areas of bone formation as shown in histological findings [19,20].

The diagnosis of BMES is established with the combination of clinical symptomatology, MRI findings compatible with BME which is observed 48 hours after the onset of symptoms (increased signal on T2, decreased signal on T1 sequences) and normal values on laboratory panel [21].

In the literature, several pathophysiological mechanisms have been suggested regarding the development of BMES but none of them have been proven [5,22]. Potential theories include alteration in the lipid profile, vascular factors abnormalities such as thromboembolism, thrombocyte aggregation, decreased antithrobin III, decreased fibrinolysis in pregnancy with increase in plasminogen activator inhibitor 1 or lipoprotein levels, venous obstruction, localized hyperemia, vasomotor response and synovial pathology [6,23]. Ischemic events in the small vessels proximal to nerve roots could be another hypothesis that was postulated by electromyographic findings. Obstruction in the blood flow results in nerve ischemia and to the manifestation of symptomatology and on the contrary restoration of flow and nerve regeneration is the subsequent event that leads to resolution of BMES [22,23]. The generation of pain may be attributed to the increase of intraosseous pressure from between 20 and 30 mmHg to 50 and 90 mmHg which results to subsequent sensory irritation [21].

BMES should be mainly differentiated from avascular necrosis (AVN) which is achieved by MRI. In early stages of BMES the radiological findings are almost similar although focal abnormalities, double line sign and subchondral signal alterations are pathognomonic of AVN [24].

The aim of the treatment of BMES is to reduce the clinical course (pain and disability) and resolve BME. Therapeutic protocols include partial weight-bearing, immobilization, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), while additional approaches include ESWT, iloprost, bisphosphonates. If all

the above fails, then core decompression may be a potential alternative [25].

Extracorporeal shock wave therapy (ESWT)

The definition of shock wave comprises of a sonic pulse that may transmit in a wavelike form which subsequently acts as generator of high stresses on interfaces and tensile forces that lead to cavitation [26] Cavitation is the creation and motion of bubbles inside a fluid substance produced by acoustic field [27]. Shockwave therapy is uni-phasic compared to ultrasound waves which are biphasic and also shockwave may reach a peak pressure of 500 bars compared to the maximum pressure of 0.5 bar that is achieved with ultrasound wave (1000 times higher in the shockwave pattern) [28]. 3 main principles are of great importance regarding the ESWT which are the pressure distribution, Energy Flux Density (EFD) and the total acoustic energy [28]. Special extracorporeal electrohydraulic or electromagnetic or piezoelectric pulse generators are responsible for the production of shock waves which along with the application of fluoroscopic or ultrasound guidance can be propagated through a water coupling and the body into the designated region [27].

For orthopaedic purposes, shockwaves are utilized to stimulate tissue regeneration through activation of different extracellular pathways compared to lithotripsy in which the application is primarily used to dismantle renal stones [28].The utilization of ESWT in the orthopaedic community is a developing field which has been applied to treat a variety of musculoskeletal disorders including lateral epicondylitis, calcific tendinopathies of the shoulder, plantar fasciitis, painful heel syndrome, non-unions and AVN of femoral head [26,29]. Regarding the mechanisms by which the ESWT promotes bone and musculoskeletal processes, several theories have been speculated but it mostly remains uncertain. Some mechanisms include stimulation of neovascularization of avascular or minimally vascular tissues and proliferation of tenocytes, activation of osteoprogenitor cells, increase of leucocyte infiltration, promotion of accumulation of topical growth factors and through cavitation inducement of micromechanical events on tissues which cause a variety of biochemical alterations at cellular level [26,30] Adverse events related to the treatment with ESWT are minor including local soft tissue swelling, transient pain, and skin redness/pain [30].

Application of ESWT on BMES

In the literature, whether BMES constitutes a separate disease or a subdivision of AVN remains unknown [4]. It has been reported that early stages of AVN have been successfully treated with the use of ESWT by reduction of BME and the pain associated with it [7,8,11]. Therefore, encouraged by the effects of ESWT in other orthopaedic conditions and in AVN, a handful of clinicians attempted the utilization of ESWT in patients suffering from BMES in the knee and hip joint (Tables 1 and 2) [7-12].

In a prospective study which was carried out by d' Agostino et al, 20 cases (43.23 mean age) underwent ESWT in the setting of BMES in the hip joint. All patients were assessed with Harris Hip Score (HHS) and MRI. ESWT comprised of 2 sessions of high energy therapy, 4000 shots per treatment with EFD of 0.5mJ//mm^2 followed by restriction of weight-bearing for 30 days. MRI showed gradual resolution of BME over the follow-up period and HHS was significantly improved as well. None of the patients experienced any side effects related to the ESWT [11].

In a retrospective comparative study conducted by Gao et al, comparison between the efficacy of ESWT and core decompression in patients who presented with clinical and radiological findings compatible with TO of hip was made. The patients divided into 2 groups of 20 patients (ESWT) and 26 patients (core decompression) with a mean age of 42.3. All patients had been treated conservatively with NSAIDs and alendronate along with restriction of weight-bearing before inclusion. As for the outcomes, all patients clinically and radiologically resolved in 12 weeks and 6 months respectively. VAS score and HHS were improved significantly more in the ESWT group compared with the core decompression group. Remission of symptoms and return to daily activities were significantly earlier in ESWT group. Lastly, hospital costs along with intraoperative radiation exposure were both lower in the ESWT group as well [9].

In another study by the aforementioned author, 40 consecutive patients suffering from BMES of the knee were prospectively analyzed in a randomized trial. The study included 2 groups consisting of 20 patients each (ESWT group and control group). Mean age of ESWT was 41.6 ± 9.7 while of control group was 45.1 ± 8.9. ESWT group was administered with a high energy therapy with EFD of 0.44mJ/mm2, 3000-4000 impulses and frequency of 2-3 Hz in 2 sessions, while on the contrary the control group was subjected to intravenous prostacyclin and bisphosphonate therapy. All patients in the ESWT group had significantly better improvement of VAS, WOMAC and SF-36 scores at 1, 3 and 6 months post-treatment compared with the control group. MRI depicted gradual regression in the BME pattern which was significantly higher in the ESWT group. At 6 months, 65% (ESWT) compared to 25% (control group) had complete resolution of BME, while at 1 year post-treatment almost all patients in both groups were MRI free of BME [10].

Sansone et al had also published a retrospective comparative study in which 86 patients with symptomatic BMES of the knee joint were included. The study comprised of 2 groups with 55 patients receiving ESWT (mean age 59.8 ± 11.7) while 21 patients (mean age 61.1 ± 13.71) were treated conservatively (control group). ESWT protocol consisted of 3 sessions of 2000 shots of high energy and EFD ranging from 0.22 to 0.43mJ//mm^2 and 4 Hz frequency. Both groups showed statistically significant improvement in clinical and radiological parameters but the ESWT group showed better results. Specifically, BME area showed a reduction of 86% (ESWT) compared to 41% (control group), improvement in VAS score by 88% (ESWT) compared to 42% (control group), and WOMAC score by 65% (ESWT) compared to 22% (control group) [8].

In another retrospective comparative study conducted by Vitali et al, the effectiveness of ESWT in patients with BMES of the knee joint compared to control group was assessed. The study included a total of 56 patients who admitted to the hospital due to knee pain and difficulty on walking. Patients were divided into 2 groups with the first one comprising of 28 patients (mean age 61.64 ±10.93) that underwent ESWT and the other 28 cases (mean age 60.98 ±12.66) were subjected to conservative treatment with

Table 1: Demographics and treatment protocols.

Authors	Study design (LE)	Treatment protocols	Population	Mean age	Gender	Site
d'Agostino et al [25] (2014)	Therapeutic; Prospective Observational Study (II)	2 sessions (48 h apart), 4000 shots at high-energy, EFD mean of 0.5mJ/mm^2. PWB for 30 d post-treatment.	20 (ESWT)	43.23	12M 8F	Hip
Gao et al [28](2015)	Therapeutic; Retrospective Comparative Study (III)	*ESWT group:* EFD of 0.5mJ/mm^2, 3-4 levels, 2 series of 3 treatments, 2000-3000 impulses, alendronate tb 70 mg po weekly for 14 d and alprostadil 10 μg ivgqd for 14 d. PWB 4-6 w post-treatment. *Control group:* Core decompression PWB 4-6 w post-treatment.	20 (ESWT) 26 (Control)	42.3	24M 22F	Hip
Gao et al [29] (2015)	Therapeutic; Randomized Controlled Study (I)	*ESWT group:* 2 sessions, high-energy ESWT, levels 3-4, EFD of >0.44 mJ/mm^2, 3000-4000 impulses, Hz=2-3. *Control group:* Alendronate tb 70 mg poqw and alprostadil 10 μg ivgttqd.	20 (ESWT) 20 (Control)	43.35	20M 20F	Knee
Sansone et al [27] (2016)	Therapeutic; Retrospective Comparative Study (III)	*ESTW group:* 1 session every 3 w for 9 w, 2000 shots of high-energy, EFD ranging from 0.22-0.43 mJ/mm^2, Hz=4. *Control group:* PWB and analgesics for pain control.	55 (ESWT) 31 (Control)	60.26	32M 54F	Knee
Vitali et al [26](2017)	Therapeutic; Retrospective Comparative Study (III)	*ESWT group:* 1 cycle, 3 sessions once a w for 3 w, 4000 shots of high-energy, EFD of 0.55 mJ/mm^2. *Control group:* Analgesics and protected weight-bearing.	28 (ESWT) 28 (Control)	61.31	17M 39F	Knee
Zhang et al [30](2020)	Therapeutic; Retrospective Observational Study (III)	Each session, 4 to 5 treatment points were selected and each treatment point was impacted 500 shocks, 2500 to 4000 shots, EFD of 0.50 mJ/mm^2. One treatment course was 10 days for a total of 2 treatments. The treatment interval is 20 to 30 days, for a total of 8 w. Weight bearing restriction with the use of 2 crutches until partial or full weight bearing was tolerated	34 (ESWT)	39.4	23M 11F	Hip

LE: Level of Evidence; ESWT: Extracorporeal Shock Wave Therapy; EFD: Energy Flux Density; d: days; F: Female; M: male; PWB: Partial Weight Bearing

Table 2: Follow-up, outcomes and complications.

Authors (years)	Follow-up	Clinical outcome data	Averse events
d'Agostino et al [25] (2014)	2 m, 3 m, 6 m, 15.52 ± 1.9 m (final).	Significant improvement in HHS at 2m, continued to improve over the rest of the follow-up. Significant improvement in MRI at 2m and 6m (p<0.0001).	none
Gao et al [28](2015)	1 m, 3 m, 6 m, 10 m (final).	Postoperative VAS was significantly improved greater in the ESWT group compared to core decompression group (p<0.5). HHS for unilateral lesions was improved more in the ESWT group compared to core decompression (p=0.5), for bilateral lesion (left, p=.042; right, p=.912). Earlier symptoms disappearance in the ESWT group for both unilateral lesions (*p*=.007) and bilateral lesions (*p*<.05).	*ESWT:* Transient soft tissue swelling, minor bruising *Control:* Local hematoma (3 cases), pure wound healing (1 case)
Gao et al [29](2015)	1 m, 3 m, 6 m, 1 y (final).	ESWT group greater-earlier improvement in VAS, WOMAC Osteoarthitis Index and SF-36 score post-treatment (p<0.05). MRI-higher reduction-complete resolution at 6 m in ESWT compared to Control group (95% vs 65%, p=0.018).	*ESWT:* Transient soft tissue swelling, minor bruising *Control:* Headache (3 cases) facial rash (2 cases)

Sansone et al [27] (2016)	3 m, 6 m, 18 m (final).	Both groups showed statistically significant improvement in all parameters ($p<0.05$). *ESTW:* VAS improved 88% compared to Control group 42% ($p<0.001$). WOMAC score improved 65% compared to control 22 % ($p<0.001$). MRI reduction of BME in 86% compared to control 41%.	none
Vitali et al [26](2017)	1 m, 4 m (final)	*ESWT:* KSS functional scores improved by 44% at 4 m compared to control group 18% ($p<0.00001$). VAS improved by 81.08% at 4 m compared to control 47.39%. MRI reduction in BME improved by 77% at 4 m compared to control 40% ($p<0.00001$).	*ESWT:* Pain upon administration
Zhang et al [30](2020)	1 m, 3m, 6 m, final >12 m	HHS was significantly improved, and the VAS was significantly reduced at S1–2 (1- and 3-months post-treatment) after therapeutic intervention ($P<.05$). In the VAS and HHS score during the peri-treatment time, mean improvement between S0 and S1,S2, S3, and between S1 and S2 had statistical significance ($P<.05$), and the HHS of S1 and S3 also had significant statistical significance ($P<.05$), while the mean VAS and HHS improvement between S2 and S3 had no significant statistical significance The MRI findings demonstrated thatthe diffuse BME in the femoral head and neck disappeared basically	*ESWT:* subcutaneous congestion points (n=5)

NSAIDs and restriction of weight-bearing. At final evaluation on 4 months post-treatment both groups had statistically significant improvement on VAS and KSS scores. ESWT group had better results regarding VAS, KSS functional score and MRI regression of BME (81% compared to 47%, 44% compared to 18% and 77% compared to 40% respectively). The authors concluded that ESWT is a potential and valid non-surgical method in the management of BMES [7].

Last but not least, a study by Zhang et al, included 34 patients suffering from BMES of the hip joint. All patients underwent ESWT with minimal side effects in 5 patients including transient subcutaneous congestion point. Both VAS and HHS were significantly improved on follow-up compared to pre-treatment time and BME in MRI disappeared [12].

CONCLUSION

ESWT is a non-invasive method that has been used in off-label in BMES with promising results, as it seems to achieve rapid pain relief and functional improvement, hence it may be a potential safe non-invasive regimen for the rapid recovery of BMES either in the knee or hip joint. In the currently published studies, ESWT had been successfully used to treat patients suffering from BMES and in studies compared with the control group showed statistically significant superiority regarding the clinical and radiological outcomes (faster recovery/remission of symptoms, faster resolution of BME on MRI, better and faster functional improvement). Compared with core decompression in one study it showed superiority in all the aforementioned parameters as well. Due to the small number of published studies, we report a lack of standardized guidelines with regard to the use of ESWT as an alternative method for the treatment of BMES and suggest further future studies, in order to acquire evidence based recommendations.

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