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Review

Extracorporeal shockwave therapy for avascular necrosis of femoral head

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HIGHLIGHTS

- ESWT is an effective and non-invasive method in the treatment of ONFH.
- ESWT is more effective than core decompression and bone grafting for early ONFH.
- Cocktail therapy and ESWT show comparable results in ONFH.
- ESWT is equally effective for ONFH in SLE patients.

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ABSTRACT

The etiology of osteonecrosis of the femoral head (ONFH) is multifactorial. Treatment of ONFH is disease stage dependent. For early stages, femoral head preservation procedures are preferred including core decompression, muscle pedicle grafting and de-rotational osteotomy. Core decompression with bone grafting is considered the gold standard. However, the results are inconsistence and unpredictable. An effective non-invasive method of treatment is imperative. Recently, extracorporeal shockwave therapy (ESWT) has shown beneficial effects in ONFH. ESWT improves pain and function of the hip and regression of the ONFH lesion. ESWT is more effective than core decompression with or without bone grafting, cocktail therapy that combined HBO, ESWT and oral alendronate is shown effective for patients with early osteonecrosis. The purpose of the article is to review, update and summarize the clinical treatment of ONFH using shockwave therapy.

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1. Introduction

Osteonecrosis also named avascular necrosis (AVN), bone infarction, aseptic necrosis, and ischemic bone necrosis is a disease where there is cellular death (necrosis) of bone components due to interruption of the blood supply. Avascular necrosis of the femoral head (ONFH) is more common in the hip joint than in other locations (knee, talus etc.). The etiology of ONFH is multi-factorial. Treatment of osteonecrosis of the femoral head in hips remains controversial. Conservative treatments are preferable but are generally unsuccessful. Therefore, surgery is indicated in symptomatic hips with the type of surgery varying according to the stage of the disease [1,2]. Core decompression with or without bone grafting is considered the gold standard of femoral head preserving procedure. However, the results varied widely and most reports are unsatisfactory [3]. Therefore, there is a need for an effective and non-invasive method of treatment for ONFH.

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2. Shockwave treatment in ONFH

Various shockwave devices had been used for the treatment of AVN of the femora head including electrohydraulic, electromagnetic and others, and different setting of energy levels and the penetration are recommended, and the numbers of treatment sessions for different. Recently, several studies reported that extracorporeal shockwave therapy (ESWT) is effective in the treatment of ONFH [4–6]. Ludwig et al. reported comparable clinical results of ESWT in the treatment of patients with early stages (1–3) of ONFH [4]. The visual analog pain scores decreased from 8.5 before treatment to 1.2 at 1 year after treatment. Meanwhile, Harris hip score increased from 43.3 before treatment to 92 points after treatment. Complete resolution of the lesions was confirmed with MRI study in selected patients. In 2005, our study compared 23 patients with 29 hips treated with ESWT (28 kV, 6000 impulses) and 25 patients with 28 hips treated by core decompression with nonvascularized fibular bone grafting. Patients with stage-I, -II, or –III-α (Association Research Circulation Osseous; ACRO classification as in Table 1) ONFH were randomly assigned to either shockwave or core decompression and nonvascularized fibular grafting [5]. At average follow-up of twenty-five months, pain and Harris hip scores in the shockwave group were significantly improved as compared with the pretreatment scores ($p < 0.001$). ESWT group showed more effectiveness than core decompression and nonvascularized fibular grafting at short-term [5]. The long-term results showed significant improvements in pain and function at different time intervals favoring the ESWT group. There was a trend of decrease in the size of the lesion on X-ray and MRI in the ESWT group [5,7]. Another study included 17 patients with bilateral hip osteonecrosis that were treated with ESWT (28 kV, 6000 impulses) on one side and hip arthroplasty on the other hip. Both procedures resulted in favorable pain and functional scores. Of the 17 ESWT treated patients, the grade of bone marrow edema was observed (the grade of bone marrow edema definition was showed in Table 2) and 13 had grade $\geq$1 at baseline but only 5 at follow-up of 17 months [8]. Patients rated ESWT side better than THA in 13 cases (76.5%), ESWT side comparable to THA side in four cases (23.5%) and none rated THA better than ESWT. It showed that ESWT produced better functional outcome and higher patient satisfaction than THA. Patients with early stage of ONFH are at risk of progression of the avascular necrosis area or collapse of femoral head [6,8]. In 2012, Dr. Kusz et al. recruited nine patients with avascular necrosis of the femoral head from ARCO stage I to III for shockwave therapy [9]. In this study protocol, each of the four points of ONFH received 1500 impulses at an energy flux density of 0.4 mJ/mm^2 and each patient undergoes 5 therapy sessions. The results mentioned that most of patients were considerable improvement in the quality of life at 6 weeks follow-up but some patients reported intensified pain and worse hip function at 6 months. Next, a two year long-term follow-up of ESWT for early ONFH was reported [6]. Thirty-six patients with ONFH were treated with 2400 impulses at 0.50 mJ/mm^2, at 48–72 h intervals with four sessions. The results indicated that ARCO stages I and II were better to prevent progression of the area of avascular necrosis and manage pain after ESWT. Recently, another study reported long-term outcomes of ESWT and core decompression for early ONFH with 8–9 year follow-up [10]. Overall clinical outcomes showed good or excellent in 76% (22 of 29) fair and poor in 24% (7 of 29) for ESWT group, and 21% (6/28) good or excellent and 79% fair or poor in the surgical group respectively. These results demonstrated that ESWT is more effective than core decompression and bone grafting for early ONFH in long-term follow-up.

Table 2
The conditions of bone marrow edema.

Grade	Findings
Grade 0	No bone marrow edema
Grade 1	Peri-necrotic bone marrow edema
Grade 2	Bone marrow edema extended into femoral head
Grade 3	Bone marrow edema extended into neck of femur
Grade 4	Bone marrow edema extended into inter-trochanteric region

3. ESWT and cocktail therapy for ONFH

During the SARS outbreak in 2003, four healthcare workers from one hospital contracted the disease and were treated with corticosteroids that resulted in the development of ONFH [11,12]. All patients were treated with cocktail therapy that consists of ESWT, hyperbaric oxygen therapy (HBO) (2.5 ATA in 15 min) and oral alendronate (70 mg of oral alendronate sodium) [12]. Each hip was treated with 6000 impulses of ESWT at 0.474 mJ/mm^2 energy flux density in a single session. Each patient received HBO treatment for 100 sessions and oral alendronate 70 mg per week for one year. At 4 year follow-up of patients with cocktail therapy, significant improvements in pain score and Harris hip score were observed in all cases ($p < 0.001$). All patients returned to work as healthcare providers and no one required surgical intervention including hip replacement. In a later study of sixty three patients (98 hips) that were randomly divided into two groups for cocktail therapy and ESWT (0.474 mJ/mm^2 energy flux density, 6000 impulses) alone [13]. Group A consisted of 28 patients (50 hips) who received cocktail therapy, and group B consisted of 35 patients (48 hips) who received only ESWT. After a minimum follow-up of 2 years, the overall results showed 74% improved, 16% unchanged and 10%

Table 1
Association Research Circulation Osseous (ARCO) classification of femoral head osteonecrosis.

Stage	Findings	Location description	Quantification
0	Normal	None	None
1	Radiography and computed tomography are normal. Magnetic resonance imaging (MRI) and biopsy are positive.	Medial Central Lateral	Areas of involvement: A, B, or C (<15%, 15–30%, and >30%, respectively)
2	Radiography is positive. Sclerosis, osteolysis and focal osteoporosis are found	Medial Central Lateral	Areas of involvement: A, B or C (<15%, 15–30% and >30%, respectively)
3	Crescent sign and early flattening of articular surface	Medial Central Lateral	Areas of involvement: A, B or C (<15%, 15–30% and >30%, respectively) Amount of surface depression and collapse: A, B or C (<2 mm, 2–4 mm and >4 mm, respectively)
4	Femoral head with joint space is narrowing. Osteoarthritis with acetabular changes	None	None

worsened in group A; and 79.2% improved, 10.4% unchanged and 10.4% worsened in group B (P = 0.717). These results indicated that cocktail therapy is effective for early hip necrosis with comparable results to ESWT alone in short-term follow-up. Therefore, the synergistic effects of ESWT, HBO and alendronate treatments were not observed [13,14].

4. Shockwave treatment on systemic lupus erythematosus (SLE) with ONFH

Patients with systemic lupus erythematosus (SLE) frequently receive chronic corticosteroids therapy which is often associated with ONFH [15,16]. In 2006, a 19-year-old woman with two-year history of SLE developed bilateral ONFH secondary to corticosteroids therapy was successfully treated with ESWT (0.474 mJ/mm^2 energy flux density, 6000 impulses) [17]. The19-year-old woman with 3-year follow-up showed that both hips had no pain on activities for daily living. Magnetic resonance image (MRI) showed substantial reduction of bone marrow edema, and no further collapse of the lesions. There are no changes in the staging of the disease on radiographs and MRIs. Another study was performed in 39 patients including 15 SLE patients (26 hips) and 24 non-SLE patients (29 hips) [18]. Total hip replacement was performed in 12% of SLE patients and 14% of non-SLE patients (P = 0.802). There was no statistically significant difference in pain scores (0.86 vs. 0.89; P = 0.467) and functional scores (89% vs. 91%; P = 0.194) between patients with SLE and patients without SLE. SLE with ONFH responded to ESWT with comparable results as compared to patients with non-SLE. It appears that ESWT alone is equally effective for SLE patients with ONFH.

5. The mechanism of shockwave therapy in ONFH

The exact mechanism of shockwave therapy in ONFH remains unknown. In 2008, the effects of shockwave in osteonecrosis of the femoral head were studied [7]. There were 14 femoral heads from 14 patients undergoing total hip arthroplasty for ONFH. Histopathological examination revealed more viable bone, cellular proliferation and cellular activities in patients treated with shockwave prior to hip surgery. In immunohistochemical analysis, patients received ESWT prior to hip replacement showed significant increases in vWF (P < 0.01), VEGF (P = 0.0012) and CD 31 (P = 0.0023), Wnt3 (P = 0.008) and PCNA (P = 0.0011), and decreases in VCAM (P = 0.0013) and DKK1 (P = 0.0007) than the control group. It appears that application of shockwave results in regeneration effects in hips with ONFH. In animal experiment, ESWT was shown to increase mRNA and protein of BMP-2 as well as up-regulation of VEGF expression in perinecrotic subchondral bone of the femoral head. VEGF expression suggests the ingrowth of neovascularization and improvement of blood supply to the femoral head [19,20]. Marrow stromal cells from hips with osteonecrosis are treated with ESWT *in vitro* [21]. Shockwave significantly up-regulated cell proliferation, VEGF, alkaline phosphatase, BMP2, RUNX2 and osteocalcin mRNA expressions and more mature mineralized nodules as compared with the control. The findings are in concert with the results of histopathological observation and immunohistochemical analysis, ESWT was suggested to promote angiogenesis and bone remodeling and regenerative effect through the induction of the NO pathway in ONFH [7,21]. It also showed that ESWT may be effective in the prevention of collapse of the femoral head with early ONFH.

6. Conclusion

ESWT is a new therapeutic technology and has the potential of replacing surgery in patients with ONFH without the surgical risks. In animal experiments, ESWT was shown to induce a cascade of biological responses and molecular changes ranging from neovascularization to tissue regeneration. Many fundamental issues such as the dosage, timing, frequency and the intensity of treatment of ESWT are to be clarified with larger scales of clinical trials before the efficacy and safety can be confirmed.

Ethical approval

None.

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Author contribution

Ching-Jen Wang, conception and design, writing, final proof of the manuscript.

Jai-Hong Cheng, conception and design, writing, final proof of the manuscript.

Chung-Cheng Huang, assessment of image studies, data analysis, correction, final proof of the manuscript.

Han-Kan Yip, conception and design, writing, final proof of the manuscript.

Sergio Russo, conception and design, writing, final proof of the manuscript.

Conflict of interest statement

None.

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