



Opinion Piece: The Role of Extracorporeal Shockwave Treatment in Osteonecrosis of the Femoral Head and Patents Selection

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Opinion

Extracorporeal Shock Wave Treatment (ESWT) was first used to treat urinary calculus in 1980. Shockwave is a kind of high-energy mechanical wave, which can be converted into biological and therapeutic effects in living tissue. As a noninvasive alternative ESWT has been used for many kinds of musculoskeletal disorders [1], including acute fracture, chronic fracture non-union, calcifying tendinitis, and so on. Compared with the traditional treatments, ESWT has the advantages of non-invasiveness, adjustable stimulus intensity, less side effects, etc. Therefore, the choice of ESWT in the treatment of osteonecrosis of the femoral head appears very attractive.

Osteonecrosis of the Femoral Head (ONFH), especially non-traumatic ONFH, mainly involving young and middle-aged patients, is a chronic progressive disability disease [2]. Many conservative methods and surgical choices have been proposed for preserving the femoral head with reliable results, however, the optimal treatment modalities of ONFH is still controversial [3]. Several studies have investigated the effects of shockwave therapy on ONFH with different positive effects. Despite of clinical success of ESWT in ONFH, the exact working mechanism and reasonable selected patients have not been fully clarified, which have significant effects on the efficacy of treatment.

Although the majority of studies conformed the osteogenic effect of high energy shock waves, the interaction between shock waves and tissues has not been completely and detailed understood. Haupt et al. [4] postulated the action of shock waves on tissues as 4 sequential phases: physical phase (direct effects of the shockwaves), physical-chemical phase, chemical phase and biological phase. The hypothesis of micro-fractures [5] ascribed the positive results to direct shock waves and indirect cavitation effects. This mechanical theory was subsequently changed by the theory of cellular mechano transduction [6], which highlights the process by which cells turn mechanical signals into biochemical reactions.

The biological mechanism of ESWT in the treatment of ONFH is associated with repair and regeneration [7-9]. Wang et al. [10] verified the biomechanical effect of ESWT through the rabbit fracture model. ESWT promoted bone formation associated with higher neovascularization, and increased angiogenic and osteogenic growth markers, including Vascular Endothelial Growth Factor (VEGF), endothelial Nitric Oxide Synthase (eNOS), Proliferation Cell Nuclear Antigen (PCNA) and BMP-2. In the treatment of rabbit model of ONFH with ESWT, Ma H Z et al. [11,12] emphasized the up-regulation of VEGF and BMP-2, promote in growth of neovascularization, improve blood supply, and facilitate bone repair. Chen Y J et al. [13] found that the up-regulation of growth factors promote recruitment and differentiation of Mesenchyme Stem Cells (MSCs).

The above results were further confirmed in clinical trials. The study of femoral head removed during hip replacement revealed that ESWT promotes angiogenesis and bone formation [14], and that moderate intensity contributes to MSCs proliferation and osteoblast differentiation [15]. Based on the underlying mechanism that leads to ONFH, ESWT can promote cell activities, MSCs proliferation and differentiation, and significantly increase growth factors related to angiogenesis and osteogenesis, thereby promoting the growth of new blood vessels and the formation of new bone, and promoting the repair of necrosis [16]. However, high-quality evidence is still urgently needed to elucidate its theoretical mechanism.

Previous studies have showed the value of earlier detection, diagnosis and appropriate interventions for successful preserving of the femoral head. This principle should also apply to ESWT in ONFH. Ludwig J et al. [17] first described the use of ESWT in ONFH, and confirmed it

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as a potentially viable alternative for treating ONFH with pain relief. The encouraging result was correlated with the Association Research Circulation Osseous (ARCO) stage of diagnosis before treatment, and patient age as another possible factor. Vulpiani MC et al. [18] also declared that patients with ARCO stage I and II achieved better results than stage III, and the lesions in stage I and II had no further progression. Gao et al. [19] presented the largest patient population involving 528 hips of 335 patients, who were divided by ARCO stage system and grouped by whether involvement of the lateral pillar. The result of treatment mainly due to pain alleviation and reduction of bone marrow edema, were achieved in both groups. The results of those researches made a strong impression that the success rate of ESWT in ONFH was stage dependent, though there were no uniform and standard research designs. It appears that the application of ESWT contributes to the regeneration of ONFH and the prevention of disease progression. ESWT can be considered as an interventional option only for pain alleviation with advanced ONFH, which need further research.

ESWT was showed to be an effective and safe treatment modality in early ONFH with noninvasive and less complications. However, compared with other preserving methods of femoral head, the superiority of ESWT needs further study. Wang et al. [20] randomly assigned 48 patients with ONFH to the ESWT group and the surgery group, and the surgical methods were core decompression and non-vascularized fibula grafting, with an average follow-up of 25 months. The improvements of hip function were 79% and 29%, respectively, compared with pre-treatment. Moreover, the imaging results showed that the ESWT group was superior to the surgery group. When the follow-up extended to an average of 8 to 9 years [21], the improvements of hip function were 76% and 21% respectively, while the rate of total hip replacement were 24% and 64%, respectively. The short-term comparable effectiveness with or without alendronate also demonstrated the positive role of ESWT in early ONFH [22].

The advantages of ESWT are particularly obvious in special populations, such as patients with leukemia after allogeneic hematopoietic stem cell transplantation [23] and Systemic Lupus Erythematosus (SLE) [24], higher risk of infection and recurrence; it is beneficial to the improvement of hip function without increasing of side effects. Ludwig et al. [25] study of patients with an average age of 54.9 years (+/-12.3) showed that the results in the treatment group were significantly superior to that in the control group. ESWT may also be effective in treating ONFH in elderly patients but is prohibited for adolescents with epiphysis no closed and must be applied cautiously to the unstable arrhythmias.

As an effective biomechanical stimulation, ESWT can effectively improve the pain threshold of patients, promote the osteogenesis and angiogenesis of necrotic femoral head, thus changing the pathological and physiological state of femoral head and preserving and improving joint function. So far, the successful effect of ESWT on ONFH is mostly clinical observation or retrospective study. ESWT can be used as an important alternative for non-surgical treatment of ONFH [26], reducing pain and bone edema, and improving joint function. However, whether ESWT can delay the progression of the disease or even avoid collapse requires a prospective, randomized, controlled, large-sample clinical study to further verify its efficacy.

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