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Review

Biological mechanism of shockwave in bone

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HIGHLIGHTS

- ESWT is a novel method in musculoskeletal disorders and other disease.
- The biologied effects of ESWT may be through mechanotransduction.
- Applications of ESWT are increasing.
- ESWT promotes tissue regeneration, wound healing, angiogenesis, bone remodeling, and anti-inflammation.

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ABSTRACT

Shockwave is a rapid, short duration acoustic wave that carries energy and can propagate through tissue medium. This kind of physical force can be a mechanical stimulus that induces biological effects in living tissue. Extracorporeal shockwave therapy (ESWT) acts as a mechanical stimulus which promotes biological healing processes through a mechanotransduction. The biological effects of ESWT are reported such as tissue regeneration, wound healing, angiogenesis, bone remodeling, and anti-inflammation. Until now, however, little is known about the basic mechanism of action of this type of therapy. This article describes the molecular mechanism on the current status of ESWT with pre-clinical and clinical applications for treating disorders in bone.

Contents

1. Introduction

Extracorporeal shockwave therapy (ESWT) has been used for musculoskeletal disorders over 30 years. Several studies had

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investigated the effects of shockwave therapy on fracture healing and articular cartilage in animal and human experiments [1–4]. The positive effect of shockwave in promoting bone healing was demonstrated in both acute fracture and chronic non-union in animal experiments [2,5,6]. Despite of clinical success, the working mechanism of ESWT in bone healing has not been fully established. The mechanism of ESWT is suggested through mechano-transduction to induce the reaction of the bone lacunae-canalicular network to tensile, shear and compression forces [7,8]. It was speculated that shockwave produced micro-fracture that in turn causes hematoma formation and subsequent callus formation and eventual fracture healing [9,10]. However, there were insufficient data to scientifically substantiate the theory. In fact, other studies demonstrated that ESWT significantly promotes bone healing after fracture and tendon to bone healing in bone tunnel [10,11].

The use of ESWT has recently expanded from skeletal disorders to non-skeletal diseases such as acute and chronic wound healing, diabetic foot ulcers, ischemic myocardiac disease and erectile sexual dysfunction [12–16]. The clinical results showed some differences among different series, but the great majority of the reported series showed positive effects of ESWT in different skeletal and non-skeletal disorders up to 2014. Despite of clinical success of ESWT in different diseases, the working mechanism of ESWT has not been fully established.

2. ESWT treatment on tendon to bone

To explore the biological mechanism of ESWT in biological tissues, many studies attempted to elucidate the mechanism of ESWT from the basic science study and translate into clinical application [10,13,17,18]. In an experiment in rabbits, Wang CJ and his colleagues reported that application of ESWT caused the ingrowth of neovascularization associated with up-regulation of angiogenic and osteogenic growth factors including endothelial nitric oxide synthase (eNOS), vessel endothelial growth factor (VEGF), proliferating cell nuclear antigen (PCNA), and bone morphogenic protein-2 (BMP-2) at the tendon–bone junction of the Achilles tendon in rabbits [3,10]. The increase in neo-vessels began to rise in one week after ESWT application, and reached the plateau in four weeks and then, persisted through twelve weeks. The up-regulation of eNOS, VEGF and BMP-2 showed significant increases in one week, and reached the peak values at 12 weeks, then slowly returned to baseline data at the end of 12 weeks. The change of PCNA starts to rise at 1 week after ESWT application, and the highest value was observed at 12 weeks. The results indicate that ESWT causes the ingrowth of neovascularization beginning in one week after treatment and such effect persisted beyong 12 weeks after treatment. This is also supported by the persistent elevation of PCNA at 12 weeks after treatment although the maximal changes on the effects of eNOS, VEGF and BMP-2 returned to baseline value at 12 weeks after treatment. This is the first time that the biological responses had been conclusively shown in the literature. Subsequently, several studies reported similar results with various target tissues in biological tissues including non-union of the long bone fractures [11,19].

3. Treatment of osteonecrosis of the hip

Some studies examined the biological mechanism of ESWT in the treatment of osteonecrosis of the hip joint [20–22]. The patients with osteonecrosis of the femoral head were treated with ESWT [23]. In histopathological examination, ESWT treated hips showed significantly more viable bone and less necrotic bone, higher cell concentration and more cell activities including phagocytosis than those without ESWT before hip replacement. In molecular expression analysis, ESWT showed significant increases in vWF, VEGF, CD 31, Wnt3 and PCNA, and decreases in VCAM and Dickkopf-1 (DKK-1) than those without ESWT before surgery [23]. In another study, bone marrow stromal cells (BMSCs) were harvested from the bone marrow cavity of the proximal femur in six patients with osetonecrosis [22]. There were significant increases in cell proliferation, VEGF, alkaline phosphatase, BMP-2, runt-related transcription factor 2 (RUNX2) and osteoclast in mRNA expressions in the shockwave group. These results demonstracted that ESWT significantly enhances the angiogenic and osteogenic effects of the BMSCs mediated through the nitric oxide pathway in hips with osteonecrosis, and these findings gave some insights into the biological effects of ESWT in bone [22].

Recently, additional studies reported the use of shockwave in osteonecrosis of the hip in 35 patients with 47 hips with special attention to nitric oxide (NO_3) pathway. At 12 months, 83% showed improvement and 17% unimproved. At 1 month, ESWT-treated cases demonstrated significant elevations of angiogenic growth factors including NO_3, VEGF, vWF and FGF basic and a decrease in TGF-β1. There were also significant increases in osteogenic factors including BMP-2, osteocalcin, alkaline phosphatase and IGF and a decrease in DKK-1 at one month after treatment. These changes in peripheral blood tests only lasted for 1 month post-shockwave [21].

4. ESWT on osteoarthritis

The biological effects of ESWT in osteoarthritis (OA) of the knee has been studied, and the results showed that application of ESWT to the subchondral bone of the medial tibia condyle showed time dependent, site specific chondroprotective effects in the initiation of OA changes of the knee in rats [19,24,25]. There were significant increases of VEGF, BMP-2, and osteocalcin in the subchondral bone as compared to the control at week 2, 4, 8, and 12. The most beneficial effects of ESWT in the OA knee occurred at 4 weeks after shockwave application. Such effects seemed to continue until 12 week [19]. Recent research demonstrated osteoporosis (OP) increased the severity of cartilage damage in osteoarthritis of the knee. ESWT showed effectiveness in the reduction of osteoporotic osteoarthritis of the knee in rats. In immunohistochemical analysis, DKK-1 significantly increased, but VEGF, PCNA, and BMP-2 decreased in groups with osteoarthritis, osteoporosis, and osteoarthritis plus osteoporosis relative to the sham group, and ESWT significantly reversed the changes of osteoarthritis of the knee [26].

5. ESWT treatment on bone to cartilage

Many studies reported intensive osteochondrogenesis in segmental femoral defects after shockwave treatment, but no shockwave-induced crack or micro-damage was noted on bone [27–29]. Therefore, shockwave-augmented bone formation may be attributed to shockwave-sensitive osteogenesis, rather than damage to the bone architecture. However, some reports showed high-energy ESWT *in vivo* affected the structural integrity of articular cartilage [30]. Tenascin-C and Chi3L1 expressions showed signals indicating reorganization in matrix protein composition connected to cartilage injury at 10 weeks after high-energy ESWT [30]. This study speculated the possibility of long-term degenerative effects of ESWT on cartilage. Other studies demonstrated that TGF-β1, BMP-2 and VEGF regulated the mechanical stimulation of fracture healing [31,32]. Recent studies showed that shockwave promotion of fracture healing coincided with increased TGF-β1 and BMP-2 expressions and extracellular signal-regulated kinase (ERK) and P38 kinase in callus [27–29]. A growing number of studies demonstrated that the increases of systemic osteogenic factors reflecting a local stimulation of bone formation during fracture

healing [33–35]. Current studies reported the biological mechanism of ESWT in bone healing, and investigated that ESWT accelerates fracture healing with the improvement of neovascularization and enhancement of angiogenesis and osteogenesis growth factors including eNOS, VEGF, PCNA and BMP-2 [10]. Other studies showed that ESWT triggers the cascade of angiogenic and osteogenic transcription factors (Cbfal/Runx2, HIF-1α and VEGF) in osteoblast cells [36,37]. Meanwhile, evidence showed that shockwave energy induces nitric oxide (NO) elevation that promotes proliferation and differentiation of human osteoblasts [38].

6. Conclusion

ESWT is a non-invasive therapeutic modality with effectiveness, convenience, and safety. ESWT can replace surgery with no surgical risks in many orthopedic disorders including non-union of long bone fracture. The complication rates are low and negligible. However, the exact biological mechanism of shockwave therapy in bone healing is still unknown. Additional studies such as proteomics, transcriptome and next generation sequencing technologies are needed to elucidate the biological mechanism of ESWT in biological bone tissues.

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

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Conflict of interest

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