Clinical Application of Extracorporeal Shock Wave Therapy in Musculoskeletal Disorders: A Review

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Abstract

Extracorporeal Shock Wave Therapy (ESWT) for the treatment of musculoskeletal diseases is a field that is developing rapidly and attracting increasing attention. In the last 10 years, ESWT has become the treatment of choice for many orthopaedic disorders such as plantar fasciitis, lateral epicondylitis of the elbow, calcific tendinopathy of the shoulder and nonunion of long bone fractures.

Evidence from basic research accredits the therapeutic outcome to biological effects. Most research into shock waves is focussed on understanding the mechanisms which result in a mechanosensitive feedback between the acoustic impulse and the stimulated cells, involving specific transduction pathways and gene expression. These concepts legitimize the potential role of ESWT in regenerative therapy and in treating other, new pathological conditions in which both incisive metabolic stimulation and angiogenesis are required, such as skin ulcers and "difficult" wounds, osteonecrosis or myocardial ischemia. Other research looks at further, more advanced clinical applications for ESWT, such as treating pathologies like muscle spasticity from neurological lesions, parodontopathies and cellulitis.

Keywords: Extracorporeal Shock Wave Therapy; Musculoskeletal diseases

Introduction

This article aims to give a short overview of ESWT, and its mechanisms of action, and to review the current and future clinical applications of ESWT in musculoskeletal disorders.

Physics and Biology of Shockwaves

Mechanisms of action

In physical terms, shock waves are rapid, short and distinct single fluctuations of acoustic energy from a positive to a negative phase. In the target tissue the induced energy converges into "the focal area or focal volume", whose size will depend on the nature of the therapeutic physical stimulus, the angle at which it is applied, and the induced pressure values. The intensity of positive pressure and the consequent energy discharged close to the target, because the direct effect of the shock wave. This event is influenced by the tissues which the wave front passes through, which can trigger phenomena of absorption, reflection, refraction and transmission of induced energy [1]. Tensile forces produced by the negative phase lead to the transition of the water molecules into cavitations bubbles which, as they expand, are immediately compressed. This leads to an increase in the temperature of the gas contained in the bubble until it implodes generating spherical shockwaves and vapour micro jets called "jet streams" [2].

The relationship between the induced energy and the therapeutic efficacy of shock waves is due to the features of the acoustic signal rather the intensity of the pressure. It has been described that high energy levels can cause irreversible alterations to the cell structure [3], whilst in sensitive cells, low energy levels induce modifications to the cell membrane and functional changes in the cytoplasm organelles which ultimately stimulate the nucleus. Consequently, the production of proteins, nitric oxide (NO) and specific growth factors contribute to the activation of the biological processes [4,5].

Mechanical effect and biological response: The mechanotransduction of the impulse

The mechanisms that enable tissues to recognise and convert intensity, frequency, amplitude and duration of the acoustic signal in a biological reaction are still unknown. Nevertheless, specific features of reactive cells, well-known for mechano sensibility [6], activate links of identification and transmission of the exogenous stimuli in "unidirectional units of biological information". They stimulate extracellular matrix (ECM), binding proteins and the nucleus via the cytoskeleton [7]. Physiological examples of mechanotransduction are endothelial cell homeostasis induced and maintained by shear stress [8], or the reaction of the bone lacunae-canaliculare network to tensile, shear and compression forces [9]. Similarly, experimental in vitro studies demonstrate that in stimulated cells, shock waves modify transmembrane fluxes which regulate redox reactions and, consequently, the extracellular-signal regulated kinase (ERK) signal transduction pathway which, in turn, regulates the gene expression in the nucleus [10,11]. Likewise, actual experimental findings underline the reversible structural changes in collagen conformation and orientation which are induced by shock waves in tendon samples [12].

Clinical applications of SHOCK WAVES in the bone and in soft tissues

Focused shock waves: Focused shock waves are generated by electro-hydraulic, electromagnetic and piezoelectric devices. They

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concentrate the acoustic energy in a well-defined point of the target tissue, with varying focal volume, depth of penetration, level of Energetic Flux Density (EFD) and total energy administered [1]. In electrohydraulic tools a high voltage discharge generates the primary shock wave that follows the vaporization of the water enclosed in the applicator. An elliptical reflector directs the wave into the focal area. In electromagnetic apparatus, the shock waves generated by the coil are converged by an acoustic lens. Lastly, the deformation of the crystals distributed along the spherical cap of the piezoelectric systems generates a series of waves which, added together, are concentrated in the target area [2].

The use of focused shock waves, especially when high energy levels are used, requires accurate identification of the area to be treated. This allows the most favourable therapeutic effect and avoids damage to the surrounding tissue. For this purpose radiographic or ultrasound guidance is necessary. In the treatment of soft tissues the patient feedback is usually sufficient.

De-focused shock wave therapy: Some electromagnetic and electro-hydraulic generators convert the acoustic wave into planar or into de-focused (soft-focused) waves, which retain the same physical characteristics but deliver the energy to a larger surface area. The depth of penetration will obviously be lower and therefore, the therapeutic use is limited to superficial lesions like cutaneous ulcers [13].

Radial shock wave therapy: Pneumatic generators produce radial waves, or pressure waves, whose physical properties significantly differ from focused shock waves. The linear pressure, low energy values, relatively low velocity of propagation and, above all, the short duration of the rise time, differentiate radial waves from focused shock waves [14]. In radial shock wave generators, the compressed air strikes a bullet contained in a cylinder. At the top of this cylinder is the applicator. The energy produced by the pressure wave is highest at the skin surface, diverging and weakening as it penetrates deeper.

Main therapeutic applications of extracorporeal shock waves

Disturbances in bone healing: Surgery is considered as the treatment of choice for delayed unions and nonunions of fractures. The use of extracorporeal shock waves is still considered a secondary alternative, although several clinical studies show analogous results with respect to surgery. Experimental models of fractures demonstrate that shock waves promote bone repair through a typical biological response characterised by the production of growth factors and bone morphogenetic proteins. It is hypothesised that the osteoblast proliferation induced by shock waves affects the up-regulation of genes involved in skeletal development and osteoblastic lineage differentiation [15], such as the differentiation of bone marrow mesenchymal cells into the osteoblast lineage via transforming growth factor beta 1 (TGF-β1) [4,16]. Furthermore, it is postulated that the effect of shock waves on transduction signal in bone cells is realized by the activation of the cyclin E2/CDK2 complex [17] and the extracellular signal-regulated kinase (ERK) and p38 kinase activity [18]. Finally, shock waves have been reported to have a favourable effect on the colonization of biological scaffolds [19].

Interesting areas of research include the possible correlation between the acoustic stimulation and the production of NO, which is one of the main mediators of biological action of shock waves, and is involved in bone metabolism [20]. Indeed, it has been postulated that mechanical exogenous impulses can induce an increase in non-enzymatic production of NO as well as of prostaglandin E-2 and prostacyclin (PGI-2) in osteocytes, as a consequence of an expected activation of the lacuno-canalicual network [8]. Clinical investigations seem to confirm this possibility. In a study of patients treated with ESWT for long bone nonunions, Wang et al. report significant increases in the systemic concentrations of NO, TGF-β1, Vascular Endothelial Growth Factor (VEGF) and bone morphogenetic protein 2 (BMP-2), one month after treatment [21].

As various studies show, the healing rate of bone nonunion seems to depend on the site, the type of fracture, previous treatments, the time between the trauma and shock wave treatment, adequate stabilization and immobilization of the lesion and the size of the fracture gap [22,23]. Retrospective studies show that tibial nonunions heal in six months (80% of cases) after a single treatment (electro hydraulic generator 4000 shocks-0.40 mJ/mm²), especially when the fracture is closed and proximally located, and the pseudoarthrosis is hypertrophic [24]. In addition, as reported in a detailed analysis from a Bayesian model, the time from trauma to treatment with ESWT and the anatomic site of the fracture nonunion significantly impacted healing outcomes [25]. Finally, comparative analysis shows a similar healing rate (around 70%), in ESWT versus surgery, with significantly better healing in the shock wave groups between the third and sixth month, and with equivalent results between 12 and 24 months [26].

Tendinopathies: The small cellular population of tendons (5% of the normal tissue volume) is made up of a mixed population of tenocytes and tendon stem progenitor cells [27]. Both tendon cells and the collagen structure is a potential target of ESWT, particularly in later degenerative phases.

Early in vivo experimental studies showed typical histomorphological patterns characterized by a reversible inflammatory reaction (which was mostly dose-dependent) in tendon cells treated with shock waves [28]. A neo-vascular proliferation at the bone-tendon junction associated to the release of pro-angiogenic regulatory factors (nitric oxide synthase, VEGF) and proliferating growth factors (proliferating cell nuclear antigen-PCNA) has also been demonstrated [29].

In vitro, the dose-dependent effect of shock waves at low energies results in a proliferative action and the increase of gene expression of collagen type 1 and III and TGF-β1, followed by the production of NO and collagen synthesis [30,31]. In cultures of pathologic tenocytes a reduction in the levels of matrix metalloproteinases 1 and 13 of IL-6 has been observed, followed by a regulating effect on the expression of traditional tenocyte markers [32,33].

Although supported by clinical data, the validity, effectiveness and reliability of ESWT in the treatment of tendinopathies do not always meet the criteria of evidence-based medicine [34]. This is due mainly to an objective difficulty in comparing data from non homogeneous studies which have adopted various types of shock wave generator, with differing energy parameters and treatment protocols [35,36]. The data published regarding patellar tendinopathy are particularly controversial; although some studies describe the efficacy of ESWT, others report no significant difference between ESWT and placebo for inducing angiogenesis and clinical improvement [37].

New Horizons in ESWT

The modern concept of tissue regeneration is strictly related to neoangiogenesis. This is a new interpretation of the therapeutic effect, and opens up new horizons for the use of ESWT, over and above its traditionally orthopaedic applications. Potential new applications...
include skin ulcers, myocardial re-vascularization, and vascular bone disease.

**Chronic skin ulcers**

The use of ESWT in chronic skin lesions stems from the observation of a “collateral” trophic effect during the treatment of bone non-union in the presence of an ulcer [38]. The subsequent development of the de-focused technology allowed the extension of the treatment to various chronic vascular lesions of different aetiology, with evidence of complete healing, or at least a reduction in size of the area of the lesion. Wound healing after ESWT is characterized by the production of granulation tissue with the arrival of leukocytes, which is closely correlated to an increase in vascular density and local blood flow. This effect has been shown with laser Doppler imaging in the case of ESWT for the treatment of burns [39,40].

The increase in capillary density of the treated tissues, after a single dose of de-focused shock waves, has been observed in various experimental studies. Human micro endothelial cells (HMEC-1) expanded on a three-dimensional matrix show an increase in capillary connections at 12 hours post-treatment, together with an early (3 hours) down-regulation of pro-apoptotic genes [41]. Stojadinovic et al. reported an increase in vascular flow at 4 and 7 days after treatment of ischemic skin and a significant up-regulation of pro-angiogenic genes after 6 hours [42]. This improvement of the viability of the ischemic tissue subjected to shock waves has been correlated to an increase in capillary density, supported by enlarged expression of von Willebrand factor and smooth muscle actin protein. In ischemic tissues, the vascular effects of shock waves seem to be independent of the time of their application, whether it is pre-ischemia, immediately after ischemia, or at 24 hours after [43]. Furthermore, the protective mechanism of shock waves has been postulated as a function of the pre-surgical prophylaxis. The experience of Dumfarth et al. shows an enhanced capacity for healing of the surgical wound in the donor site of the transplant vein used for the revascularization of the myocardium, as shown by the better trend of the ASEPSIS score [44]. They reported a statistically significant difference in the incidence of complications between patients treated with shock waves versus controls (4% versus 22%, p=0.015).

Other clinical applications of ESWT for the treatment of vascular skin lesions include chronic post-traumatic, venous and diabetic ulcers, which have been unresponsive to other conservative treatments [45].

**Bone vascular diseases**

ESWT has been shown to be effective in the early stages of femoral head osteonecrosis by reducing the extension of the necrotic area, avoiding further bone collapse. The effectiveness of the treatment has been shown also when it is compared with core decompression and bone grafting. The treatment may delay the requirement for total hip arthroplasty and, in addition, it can cause a significant decrease in bone marrow edema patterns and in associated pain [46,47]. Shock waves improve new vessel in-growth and blood supply. Furthermore, they induce a significant increase in the production of osteocalcin and transforming growth factors (TGF-β1), and stimulate osteoblasts and periosteal cells and the osteogenic differentiation of mesenchymal stem cells. These effects arise via the activation of free radicals and oxygen reactive species such as NO, and involve the activation of signal proteins (ERK) and transcriptional factors (CBFs - core binding factors) [11,16]. In addition to the regenerative effect, recent hypotheses emphasize the direct role of shock waves on bone modelling and remodelling. The experience of Tamma et al. in murine osteoblasts highlights the effect on the RANKL/OPG ratio, and the Authors theorize a potential inhibition of osteoclastogenesis [17]. Otherwise, in vivo experiments show that shock wave treatment affects the dynamics of the bone architecture, with potential applications in conditions characterized by altered metabolism such as osteopenia and osteoporosis [48]. Finally, preliminary clinical experiences report the effectiveness of ESWT in the early stages of Kienböck disease [49].

**Myocardial ischemia**

ESWT is currently one of the new alternative treatments for cardiac ischemia, due to the above-mentioned neo-angiogenic effects of low energy shock waves. Research into the specific effect of shock waves on cardiac primitive cells, isolated from normal and explanted pathologic post-ischemic human hearts, reveals a positive influence on both the proliferation and the differentiation of cardiomycocytes, smooth muscle and endothelial cell precursors [50]. In animal models of chronic myocardial ischemia, the application of shock waves has resulted in the recovery of left ventricular ejection fraction, and an improvement in regional myocardial blood flow associated with an up-regulation of VEGF expression [51,52]. An increase of vascular density at 6 and 14 weeks after shock wave treatment was described in a rodent model of ischemic heart failure [52].

Building on the positive results of the in vitro research, clinical studies are starting to be published. A patient cohort treated with low energy shock waves showed an improvement of their left ventricle ejection fraction [53]. Although more clinical studies are required to validate the efficacy of ESWT in cardiac ischemic conditions, in comparison with other more invasive treatments, it seems to be safe and without adverse effects.

**Dental conditions**

Bone resorption is typical in periodontal inflammation. Recent in vivo experience has demonstrated that shock waves could enhance alveolar bone regeneration in infected gingivalis tissue [54]. It has been observed that certain species of oral bacteria react to treatment with shock waves; the response is dependent on the energy level used and on the species of pathogen. Different energy levels can cause the disaggregation of Gram-positive and Gram-negative bacteria, and some pathogens that are associated with serious oral and systemic infections like streptococcus mutans and porphyromonas gingivalis [55]. When considered together, these data seem to suggest potential new therapeutic approaches for the treatment of dental disease.

**Conclusions**

In conclusion, ESWT is a modern, non-invasive therapeutic tool which is effective, safe and advantageous. ESWT may replace surgery in several orthopaedic pathologies with at least the same results, but without its drawbacks. The potential for translational research and development of ESWT technology is remarkable and probably still undisclosed.

**References**


