Extracorporeal Shock Wave Therapy in Musculoskeletal Disorders: A Review

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Abstract

Regenerative therapy is one of the most challenging and intriguing branches of modern medicine. Basic research has demonstrated the effectiveness of extracorporeal shock-waves (ESWT) in stimulating biological activities that involve intra-cell and cell–matrix interactions. These interactions are at the basis of the current clinical applications, and open the horizons to new applications in tissue regeneration. It is also feasible that shock waves could be used to treat various orthopaedic pathologies, removing the need for surgery. However, suitable translational studies need to be performed before ESWT can become a valid alternative to surgery.

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Introduction

Extracorporeal shock wave therapy (ESWT) for the treatment of musculoskeletal diseases is a field that is developing rapidly and attracting increasing attention. Currently, ESWT is commonly used to treat many orthopaedic disorders such as plantar fasciitis, lateral epicondylitis of the elbow, calcific tendinopathies of the shoulder and non-union of long bone fractures.

Evidence from basic research accredits the therapeutic outcome to biological effects. Most research into shock waves (SW) has 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 legitimate 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 ischaemia. Other research looks at further, more advanced clinical applications for ESWT, such as treating pathologies like muscle spasticity from neurological lesions and parodontopathies.

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

Physics and Biology of SW

Mechanisms of Action

In physical terms, SW 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 physical therapeutic

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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 cause the direct effect of the SW. This event is influenced by the tissues through which the wave front passes, 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 water molecules into cavitation 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 SW and vapor microjets called 'jet streams' [2].

The relationship between the induced energy and the therapeutic efficacy of SW is due to the features of the acoustic signal rather the intensity of the pressure. It has been recognized that high energy levels can cause irreversible alterations to the cell structure [3], while 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 (GF) contributes 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 recognize and convert the intensity, frequency, amplitude and duration of an acoustic signal into a biological reaction are still unknown. Nevertheless, specific features of reactive cells, well known for their mechanosensibility [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 lacuno-canalicular network to tensile, shear and compression forces [9]. Similarly, experimental in vitro studies have demonstrated that, in stimulated cells, SW modify transmembrane fluxes which regulate redox reactions and, consequently, the extracellular signal-regulated kinase (ERK) signal transduction pathway which in turn regulates gene expression in the nucleus [10, 11]. Likewise, actual experimental findings underline the reversible structural changes in collagen conformation and orientation induced by SW in tendon samples [12].

Clinical Applications of SW in Bone and in Soft Tissues

Focused SW
Focused SW are generated by electrohydraulic, electromagnetic and piezoelectric devices. They concentrate the acoustic energy on a well-defined point of the target tissue, with varying focal volume, depth of penetration, level of energetic flux density (EDF) and total energy administered [1]. In electrohydraulic tools, a high-voltage discharge generates the primary SW that follows the vaporization of the water enclosed in the applicator. An elliptical reflector directs the wave into the focal area. In an electromagnetic apparatus, the SW 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 SW, 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, patient feedback is usually sufficient.

Defocused SW Therapy
Some electromagnetic and electrohydraulic generators convert the acoustic wave into planar or defocused (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, therapeutic use is limited to superficial lesions like cutaneous ulcers [13].

Radial SW Therapy
Pneumatic generators produce radial waves, or pressure waves, whose physical properties significantly differ from those of focused SW. The linear pressure, the low energy values, the relatively low velocity of propagation and, above all, the short duration of the rise time differentiate radial waves from focused SW [14]. In radial SW 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 SW

Disturbances in Bone Healing

Surgery is considered the treatment of choice for delayed unions and non-unions of fractures. The use of extracorporeal SW is still considered a secondary alternative, although several clinical studies have shown analogous results with respect to surgery [23, 25]. Experimental models of fractures demonstrate that SW promote bone repair through a typical biological response characterized by the production of GF and bone morphogenetic proteins (BMP). It is hypothesized that the osteoblast proliferation induced by SW affects the upregulation 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 TGF-β_1 [4, 15]. Furthermore, it is postulated that the effect of SW on the transduction signal in bone cells is realized by the activation of the cyclin E2/CDK2 complex [16] and ERK and p38 kinase activity [17]. Finally, SW have been reported to have a favourable effect on the colonization of bioscaffolds, a precursor of future applications in tissue engineering [18]. It has been observed that, after SW stimulation, osteoblast-like cells proliferate and increase the expression of ALP, osteocalcin, collagen type I, and bone proteins involved in de novo bone formation (such as BMP2, BMP4 and BMP7). A remarkable feature of the stimulated cells is their significant migration into scaffolds, whereas untreated cells remain on the surface.

Interesting areas of research include the possible correlation between the acoustic stimulation and production of NO, which is one of the main mediators of the biological action of SW and is involved in bone metabolism [19]. Indeed, it has been postulated that mechanical exogenous impulses can induce an increase in the non-enzymatic production of NO as well as of PGE-2 and PGI-2 in osteocytes as a consequence of an expected activation of the lacuno-canalicular network [8]. Clinical investigations seem to confirm this possibility. In a study of patients treated with ESWT for long bone non-unions, Wang et al. [20] reported significant increases in the systemic concentrations of NO, TGF-β_1, VEGF and BMP-2 one month after treatment. Although their study presents some limitations due to the low number of patients and the lack of controls, it suggests a new approach for managing bone fractures.

As various studies show, the healing rate of bone non-unions seems to depend on the site, the type of fracture, previous treatments, the time between the trauma and SW treatment, adequate stabilization and immobilization of the lesion and the size of the fracture gap [21, 22]. Retrospective studies show that tibial non-unions heal in 6 months (80% of cases) after a single administration of SW (electrohydraulic generator, 4,000 shocks – 0.40 mJ/mm^2), especially when the fracture is closed and proximally located and the pseudoarthrosis is hypertrophic [23]. Nevertheless, the validation of clinical outcomes is a critical aspect of SW treatment for bone fractures. The low rate of non-unions limits the possibilities of performing controlled studies with an adequate number of homogeneous patients. For this reason, the only studies currently published are multicentric and retrospective. Furthermore, non-unions may have been treated originally with different methods of osteosynthesis, with or without the use of bone grafts. Finally, the ethical implications of using a control group (that remains untreated) must also be considered.

Despite the multiple and simultaneous variables that characterize the non-union of long bones, SW treatment is a non-invasive procedure that is appropriate for every type of non-union as long as the above-mentioned treatment criteria are respected. To evaluate the effectiveness of SW, predictive and probabilistic models of analysis have been used. Stojadinovic et al. [24] demonstrated the potential of the bayesian model which simultaneously analyses multiple clinical data and incorporates all outcomes and covariates into a single network. In an analysis of 349 consecutive patients treated over a 10-year period, the authors evaluated the probability of the presence or absence of persistent non-union at 6 months after the first SW treatment. They observed that the time from trauma to treatment with SW therapy and the anatomic site of the fracture had a significant effect on the outcome [24]. The highest probability of healing occurred when treatment began between 6 and 11 months after trauma. A retrospective, non-randomized cohort study showed a similar healing rate (around 73%) in SW therapy versus surgery [23], and a randomized, double-blind, multicentric clinical trial reported significantly better healing in the SW groups between 3 and 6 months, with equivalent results between 12 and 24 months [25].

Tendinopathies

The most frequent application of SW therapy is in the treatment of 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 [26]. Both tendon cells and the collagen structure are potential targets of ESWT, particularly in later degenerative phases. However, it is not clear wheth-

er SW activate tendon cells directly, or whether they regulate the pathogenetic alteration of the ECM homeostasis that occurs in tendinopathies.

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 SW [27]. A neovascular proliferation at the bone-tendon junction associated with the release of proangiogenic regulatory factors [NO synthase (NOS) and VEGF] and proliferating GF (PCNA) has also been demonstrated [28].

In vitro, the dose-dependent effect of SW at low energies results in a proliferative action and an increase in the gene expression of collagen types I and III and TGF-β_1, followed by the production of NO and collagen synthesis [29, 30]. NO is a highly reactive molecule and, in tendon healing, all 3 isoforms of the activating enzyme NOS are expressed by fibroblasts. NO enhances ECM synthesis and should be overexpressed in injured as well as in overused tendon models [31]. Nevertheless, NO itself may lead to an oxidant status, revealed by high levels of malondialdehyde, which is an end product of lipid peroxidation [32]. It has not been clarified whether SW regulate the levels of NO in tendons toward physiological values. The regulatory effect of SW has been observed in the expression of tenocytic markers such as scleraxis, tenomodulin, tenascin-C, and type I and III collagens, as well as in interleukin (IL)-6 and MMPS 1 and 13 in cultures of pathologic tenocytes [33, 34].

Though 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 [35]. This is mainly due to an objective difficulty in comparing data from non-homogeneous studies, which have adopted various types of SW generators, with differing energy parameters and treatment protocols [36, 37]. The data published regarding patellar tendinopathy are particularly controversial; although some studies describe the efficacy of ESWT [35–37], others report no significant difference between ESWT and placebo for inducing angiogenesis and clinical improvement [38].

New Perspectives 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 spasticity, skin ulcers, myocardial revascularization and vascular bone disease.

Spasticity

The mechanism of action of SW on spastic muscles is still unknown, but it seems that the sonic impulse of SW acts on muscle spasticity differently from normal vibratory stimulation. Previous studies on poststroke upper limb spasticity suggest that a single administration of low-energy SW results in a significant long-term reduction in muscle tone [39]. The hypothesis that SW act specifically on muscles derives from the observed lack of change in peripheral nerve conduction and spinal excitability, and an absence of signs of denervation in the muscles. On a functional level, a decrease in the Ashworth scale score has been observed, with a contemporary increase in the range of motion and, for the lower limbs, a significant increase in plantar surface area and peak pressure at the pedobarometric evaluation [40]. In vivo studies on healthy rats suggest that ESWT can affect the neuromuscular junctions, causing degeneration and a reduction in the number of acetylcholine receptors, which in turn induces a significant decrease in the maximum compound muscle action potential [41].

More recently, in a randomized placebo-controlled clinical trial, the effects of radial ESWT on spasticity consequent to cerebral palsy were analysed [42]. The positive results (a decrease in the Ashworth scale score and an increase in the range of motion) were statistically significant compared to the placebo group and were maintained for at least 2 months after treatment.

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 [43]. The subsequent development of defocused technology allowed the extension of the treatment to various chronic vascular lesions of different aetiologies, with evidence of complete healing or at least a reduction in the size of the area of the lesion. Wound healing after ESWT is characterized by the production of granulation tissue with the arrival of leucocytes, 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 [44, 45].

The increase in capillary density of the treated tissues after a single dose of defocused SW has been observed in various experimental studies. Human microendothelial

cells (HMEC-1) expanded on a three-dimensional matrix show an increase in capillary connections at 12 h after treatment, together with an early (3 h) downregulation of proapoptotic genes [46]. Stojadinovic et al. [47] reported an increase in vascular flow at 4 and 7 days after treatment of ischaemic skin and a significant upregulation of pro-angiogenic genes after 6 h. This improvement in the viability of the ischaemic tissue subjected to SW has been correlated to an increase in capillary density, supported by increased expression of von Willebrand factor and smooth muscle actin protein. In ischaemic tissues, the vascular effects of SW seem to be independent of the time of their application, whether it be before ischaemia, immediately after ischaemia, or 24 h after ischaemia [48]. Furthermore, the protective mechanism of SW has been postulated as a function of the presurgical prophylaxis. The experience of Dumfarth et al. [49] shows an enhanced capacity for healing of the surgical wound at the donor site of the transplant vein used for revascularization of the myocardium, as shown by the better trend of the ASEPSIS score. They reported a statistically significant difference in the incidence of complications between patients treated with SW and controls (4 vs. 22%, p = 0.015).

Other clinical applications of ESWT for the treatment of vascular skin lesions include chronic posttraumatic, venous and diabetic ulcers which have been unresponsive to other conservative treatments [50]. Chronic diabetic foot ulcers in particular require a multidisciplinary approach, as the results of surgical treatment are often unsatisfactory. Adjunctive therapies have been developed for treating ulcers, and various studies have reported the beneficial effect of hyperbaric oxygen therapy. However, Wang et al. [51] showed that ESWT is more effective than hyperbaric oxygen therapy in improving the blood flow perfusion rate and cell activity, with an associated decrease in apoptosis.

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 also been shown compared to 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 oedema patterns and associated pain [52, 53]. SW improve new vessel in-growth and blood supply. Furthermore, they induce a significant increase in the production of osteocalcin and transforming GF (TGF-β_1) and stimulate osteoblasts and periosteal cells and the osteo-

genic 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 (core binding factors or CBFs) [11, 54]. In addition to the regenerative effect, recent hypotheses emphasize the direct role of SW in bone modelling and remodelling. The experience of Tamma et al. [16] in murine osteoblasts highlights the effect on the RANKL/OPG ratio, and the authors theorize a potential inhibition of osteoclastogenesis. Otherwise, in vivo experiments show that SW treatment affects the dynamics of the bone architecture, with potential applications in conditions characterized by altered metabolism such as osteopenia and osteoporosis [55]. Finally, preliminary clinical experiences report the effectiveness of ESWT in the early stages of Kienböck disease [56].

Myocardial Ischaemia

ESWT is currently one of the new alternative treatments for cardiac ischaemia, due to the above-mentioned neoangiogenic effects of low-energy SW. Research into the specific effect of SW on cardiac primitive cells, isolated from normal and explanted pathologic postischaemic human hearts, reveals a positive influence on both the proliferation and the differentiation of cardiomyocytes, smooth muscle and endothelial cell precursors [57]. In animal models of chronic myocardial ischaemia, the application of SW has resulted in the recovery of left ventricular ejection fraction and an improvement in regional myocardial blood flow associated with an upregulation of VEGF expression [58, 59]. An increase in vascular density 6 and 14 weeks after SW treatment was described in a rodent model of ischaemic heart failure [59].

Building on the positive results of the in vitro research, clinical studies are starting to be published. A patient cohort treated with low-energy SW showed an improvement of their left ventricle ejection fraction [60]. Although more clinical studies are required to validate the efficacy of ESWT in cardiac ischaemic conditions in comparison to 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 SW could enhance alveolar bone regeneration in infected gingivalis tissue [61]. The use of unfocused SW gradually normalizes the volume of healthy bone at 1–2 weeks after a single treatment, and the anti-inflammatory effect continues for at least 6 weeks. It has also been observed that

certain species of oral bacteria react to treatment with SW; the response is dependent upon the energy level used and the species of the 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* [62]. 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.

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