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REGULAR ARTICLE

Extracorporeal shock wave therapy could be a potential adjuvant treatment for orthopaedic implant-associated infections

Xiao-feng Chen [a], Xiao-lin Li [b,*]

[a] Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
[b] Department of Orthopedic Surgery, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai 200233, China

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Abstract Over the past half-century, biomaterials have been used in orthopaedic surgery world widely, but orthopaedic implant-associated infections (OIAIs) are still a puzzle for orthopaedic surgeons, which may result in prolonged hospitalisation, poor functional status and high costs. The presence of implants increases the risk of microbial infection; moreover, the formation of bacterial biofilm leads to a higher resistance to antibiotics and local immune response. In such cases, conventional systemic delivery of drugs seems to be fairly inefficient and out-dated. Owing to this, debridement and/or removing the implant always become the only solution. Hence, it needs a simple, minimally invasive and effective therapy to eradicate the problem. There are abundant evidences showing that extracorporeal shock wave therapy (ESWT) has favourable effects on stimulating callus formation, inducing angiogenesis, promoting osteogenesis and relieving pain. Studies also indicated that ESWs have a significant bactericidal effect on bacterial strains of bone- and implant-associated infections. Therefore, a hypothesis proposed herein is that ESWT may well be an effective adjuvant treatment for OIAI by controlling infection, inducing bone regeneration and promoting re-osseointegration.

* Corresponding author. Address: Department of Orthopedic Surgery, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, 600 Yishan Road, Xuhui District, Shanghai 200233, China. Tel.: +86 21 24058051; fax: +86 21 64701361.
E-mail address: lixiaolin@sjtu.edu.cn (X.-l. Li).

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Introduction

Background

In recent decades, with the advancements in the manufacture of synthetic biomaterials and in surgical techniques, orthopaedic implants have been used widely in orthopaedic operations. Up till 2010, there have been more than 4.4 million people implanted with at least one internal fixation device and more than 1.3 million people having at least an artificial joint.[1] Despite the excellent effects of implant therapy, orthopaedic implant-associated infections (OIAIs) are still conundrums for orthopaedic surgeons with an average rate about 2–5%,[2] which may lead to prolonged hospitalisation, poor functional status and high costs. The results of current treatments for OIAI are unsatisfactory; hence, removal of the implant becomes a global issue and the 'key' to the solution.

General information regarding OIAIs

OIAIs are defined as inflammatory processes associated with foreign bodies such as fixation devices and prostheses affecting bones and soft tissues,[3] which may lead to prolonged treatment cycles, more adverse reactions, high risk of complications such as chronic osteomyelitis and septicaemia, poor functional status and even disability.[2,4] According to Association of the Study of Internal Fixation (AO/ASIF),[2] about 50% of all nosocomial infection cases were associated with implants in the US, and the average cost of treatment reached 15,000–30,000 dollars. Actually, OIAIs are the result of bacterial biofilm formation at the implantation site.[5] Pathogenic microorganisms, particularly *Staphylococcus aureus* and *Staphylococcus epidermidis*, which are the prime culprits of OIAI, have been found to be on the surfaces of approximately 90% of all implants.[6] Thus the implantation itself is always accompanied with the risk of bacterial infection, especially for the fixation of open fractures and joint-revision surgeries, which are of more tissue damage and circulation destruction.[7] On the other hand, it was found that the presence of implants could decrease the minimal infecting dose of *S. aureus* 100,000-fold.[8] Moreover, the susceptibility of biofilm cells to antibiotics is 10- to 1,000-fold less than that of the same bacterium grown in free-floating culture[9] and the impaired blood circulation might deprive antibacterial agents and the local immune response of the access to the infected tissues.[10] Under this circumstance, conventional systemic antibiotic therapy is looked upon as useless inevitably since it may cause systemic toxicity; as a result, it is obvious that the only feasible solution to the problem is debridement and removal of the implant.[11] In spite of this, the recurrent infection rate yet remains at a high level.[12] What is more, non-surgical strategies, such as ultrasonic waves, eddies, enzyme treatments and electrical stimulation, are regarded to be not efficient in eliminating the infections, whilst the effects of functional nanostructured coatings are still need to be evaluated as well.[13] Therefore, seeking for an easy and effective method focussed on eradicating OIAI is a task of top priority.

The influences of EWST on bone and bacteria

ESWs are high-energy single sonic pulses generated underwater by high-voltage explosion and vapourisation, which propagate in a wavelike manner in water-like soft tissues with minimal tissue absorption and no thermal effect.[14] Shock waves are characterised by a high peak pressure (100 MPa) with an energy flux density in the range of 0.003–0.890 mJ mm^{-2}.[15] When the pressure waves meet an interface of different impedance in their flow, the energy will be released to generate shear forces and cavitation, which may then cause multi-biological effects. In recent years, ESWT has been becoming increasingly popular in orthopaedics, though this technique was originally developed for the treatment of nephrolithiasis in 1980.[16] Shock waves have been demonstrated to have great value in the treatment of bone and soft-tissue disorders, such as tennis elbow,[17] tendinitis calcarea of the shoulder,[18] delayed or nonunion of fractures,[19] femoral head necrosis,[20] osteoporosis[21] and chronic ulcers,[22] due to their favourable effects on stimulating callus formation, promoting osteogenesis, inducing neo-vascularisation, inhibiting inflammation and relieving pain.

It has already been evidenced that shock waves have a significant energy-dependent or impulse number-dependent bactericidal effect on both Gram-positive and Gram-negative strains *in vitro*, particularly bacterial strains of bone- and implant-associated infections such as *S. aureus* and *S. epidermidis*, with marked reduction of viable bacterial counts by up to 99%.[23–25] Besides, Horn et al. also found that high-energy shock waves could still inhibit bacterial growth even under growth-preventing conditions (cation-adjusted Muller Hinton broth, CAMHB),[26] which provided a favourable experimental basis for the application of ESWT *in vivo*.

The hypothesis

Considering the significant bactericidal effect and the favourable effects on stimulating callus formation, inducing angiogenesis and promoting osteogenesis of ESWT, a hypothesis can be posed that it may be an easy and effective adjuvant treatment for OIAI by means of controlling infection, inducing bone regeneration and promoting re-osseointegration, with or without conventional systemic delivery of drugs. Taking into account the achievements obtained and the obstacles faced by OIAI therapy, it is believed that ESWT is an up-dated and non-invasive approach that is worth using.

Evaluation of the hypothesis

The exact mechanisms and modes of action of ESWT

With respect to the molecular mechanisms, abundant studies have indicated that shock waves could stimulate the early expression of not only osteogenic factors (bone morphogenetic protein, BMP; alkaline phosphatase, ALP; osteocalcin, OC; osteopontin, OPN; transforming growth factor-β1, TGF-β1; and insulin-like growth factor, IGF)[27–31] which help promote growth and differentiation of bone-marrow stromal cells towards osteoprogenitor cells, thus then contributing to bone regeneration and re-osseointegration, but also angiogenic factors (fibroblast growth factor, FGF; endothelial nitric oxide synthase, eNOS; vascular endothelial growth factor, VEGF; and proliferating cell nuclear antigen, PCNA)[29,32] contributing to revascularisation. In addition, it was found that the mechanisms of anti-inflammatory action of shock waves might include enhancement of eNOS activity, increase in NO production, suppression of nuclear transcription factor-κB (NF-κB) activation and elevation of anti-inflammatory factors (soluble intercellular adhesion molecule (sICAM) and soluble vascular cell adhesion molecule sVCAM).[15,29]

In previous investigations, researchers found that shock waves had the potential to remove biofilm by three log steps[33] and could enhance the susceptibility of biofilm cells to antimicrobial agents *in vitro*.[34] Furthermore, proven effects of ESWT such as revascularisation and tissue regeneration might also be beneficial to improving the access of antibacterial agents and local immune response to the infected tissues,[10] and unaltered antibiotic efficacy after ESWT has been demonstrated *in vitro*.[26]

Although various studies have described the bactericidal effect of ESWs, the exact mode of action still remains as a mystery. So far, in contrast to eukaryotic cells, simply few studies with reputation known to the authors investigating the molecular or cellular mechanisms of shock waves have been made on bacteria. Horn et al.[35] explored that the bacterial cell walls would still remain intact after ESWT due to the stability of the murein layers composed of covalently bound macromolecules, and they also considered that the permeabilisation of bacterial cells might have only a minor impact, if any, on the bactericidal effect of ESWs. Therefore, compared with extracellular mechanisms, intracellular modes of action, such as formation of free radicals, modulation of gene activity and destruction of cell organelles or double-stranded DNA (dsDNA), some of which have already been reported in eukaryotic cells,[36] should be aspects of further investigations. Additionally, as mentioned above, ESWs could break up the biofilm layers and disperse individual bacteria into surrounding tissues, leading to increased susceptibility to antibacterial agents[34] and the access of antibiotics and inflammatory cells to avascular areas could be improved by neovascularisation and tissue regeneration.[10] However, it still remains unclear whether ESWT has direct favourable effects on the immune response.

The safety of ESWT

Although abundant studies describing the effects of ESWT on a multitude of orthopaedic disorders exist, no accurate data are available concerning evaluating the potential therapeutic role of ESWT in destroying bacteria in humans. In fact, infected target areas are still considered as a contraindication for ESWT because of the risk of bacterial spreading which might induce secondary abscess formation and bacteraemia after ESWT. However, the risk of treating an infected target area with ESWT has not yet been adequately studied in any controlled experiment, and only single cases of secondary infections have been documented after shockwave lithotripsy of infected kidney stones.[37,38] On the other hand, as for the controversy over the transient bacteraemia after ESWT of infected stones and the necessity of prophylactic antibiotics during extracorporeal shockwave lithotripsy, it was hypothesised that lesions in the mucous membrane caused by sharp stone fragments rather than ESWs themselves might contribute to the bacterial spreading.[39–41] Additionally, one study by Schaden applying high-energy ESWs on both septic and aseptic nonunions reported a healing rate of 77% for both types of nonunion without any ESWT-related side effects.[19] Furthermore, Gollwitzer et al.[10] observed positive effects of ESWT on bone infections in a rabbit model of osteomyelitis without bacterial spreading and worsening of infection. Therefore, local infections should no longer be considered to be a contraindication for ESWT of orthopaedic disorders.

Potential clinical significance

Orthopaedic implants are extremely useful for the restoration in patients with fracture, osteoarthritis or other orthopaedic disorders. In order to improve the success rate, the application of ESWT into the treatment using orthopaedic implants may reduce the incidence of OIAI with its bactericidal effect; the rehabilitation time may also be shortened because of the acceleration of bone regeneration.

When OIAI occurs, ESWT may act as an adjuvant therapy by controlling infection, inducing bone regeneration and promoting re-osseointegration with the aim of avoiding repeated surgeries such as debridement and enhance the longevity of the prostheses.

ESWT is non-invasive, characterised by simple operation, short duration of each treatment, precise focussing, minimal damage to surrounding tissues and rare incidence of complications which can be negligible.[42]

Testing the hypothesis

Respecting the application of ESWT in clinical cases, further investigations are necessary to confirm the hypothesis. Controlled animal experiments should be done firstly to verify the effectiveness of ESWT in controlling infection, promoting bone and soft-tissue regeneration and relieving pain so as to investigate the optimal energy flux density, impulse number and treatment frequency. At the same time, negative side effects could be observed *in vivo* and its incidence rate should be minimised. Additionally, the exact mechanisms of killing bacteria of ESWs, especially intracellular modes of action, should be clarified; meanwhile the influences of ESWs on immune response are also need to be investigated. When the concerns are clear, we believe that ESWT could become an important option in the prevention and treatment of OIAI and might be helpful to other bone and soft-tissue infectious diseases.

Conflicts of interest

We declare that there is no conflict of interest with regard to the content of this article.

Overview Box.

What do we already know about the subject?
ESWT has a significant bactericidal effect and other biological effects such as stimulating callus formation, inducing angiogenesis and promoting osteogenesis.

What does your proposed theory add to the current knowledge available, and what benefits does it have?
ESWT could prevent and treat OIAI by controlling infection, inducing bone regeneration and promoting re-osseointegration. It is a simple and non-invasive therapy that could avoid repeated surgeries such as debridement, shorten the rehabilitation time, promote early function training and reduce the costs.

Among numerous available studies, what special further study is proposed for testing the idea?
Controlled animal experiments should be done first to verify the effectiveness and safety of ESWT and to investigate the optimal energy flux density, impulse number and treatment frequency. The mechanisms of killing bacteria and the influences on the immune response of ESWT should also be clarified through multi-basic study.

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