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

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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.

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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. 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%, 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, which may lead to prolonged treatment of immunologically foreign bodies such as fixation devices and prostheses affecting bone and soft tissues,2 resulting in 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 On the other hand, it was found that the presence of implants could decrease the minimal infecting dose of Staphylococcus aureus 100,000-fold. 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 culture5 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 On the other hand, it was found that the presence of implants could decrease the minimal infecting dose of S. aureus 100,000-fold. 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 culture5 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 On the other hand, it was found that the presence of implants could decrease the minimal infecting dose of S. aureus 100,000-fold. 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 culture5 and the impaired blood circulation might deprive antibacterial agents and the local immune response of the access to the infected tissues.

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. 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.

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) which help promote growth and differentiation of bone-marrow stromal cells towards osteoprogenitor cells, thus then contributing to bone regeneration and promoting 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) 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.
In previous investigations, researchers found that shock waves had the potential to remove biofilm by three log steps and could enhance the susceptibility of biofilm cells to antimicrobial agents in vitro. 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, and unaltered antibiotic efficacy after ESWT has been demonstrated in vitro.

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. 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, 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 and the access of antibiotics and inflammatory cells to avascular areas could be improved by neo-vascularisation and tissue regeneration. 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 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. 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. 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. Furthermore, Gollwitzer et al. 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.

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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References


