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Shock Wave Therapy in Wound Healing

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Abstract

Background

Recently, shock wave therapy (SWT) has been investigated as an adjuvant therapy in the treatment of acute and chronic wounds. There are several devices with focused and unfocused shock waves that have been administered to a heterogenous group of wounds. Encouraging preclinical and clinical studies suggest that SWT may promote wound healing with little or no adverse events prompting investigations into the mechanism of action as well as additional clinical trials.

Methods

The peer-reviewed literature within the last 10 years was studied using an evidence-based approach.

Results

Preclinical studies demonstrate that SWT affects cellular function and leads to the expression of several genes and elaboration of growth factors known to promote wound healing. Limited clinical trials are encouraging for the use of SWT in the treatment of acute and chronic wounds. Serious complications including wound infections, bleeding, hematomas, seromas or petechiae have not been reported in the largest of these studies.

Conclusions

SWT is an intriguing physical modality that may play an important role as an adjuvant therapy in wound healing. To date, there is no consensus on which wounds are most likely to benefit from SWT and what the optimal power, degree of focus, and frequency or number of cycles should be. Well-designed pre-clinical and clinical studies are necessary to better understand SWT in wound healing.

Introduction

Extracorporeal shock wave therapy has revolutionized the treatment of urolithiasis

allowing fragmentation of stones at a distance, avoiding invasive surgery in most cases. Variants of this technology have been used to treat fractures[1,2,3,4], osteonecrosis of the femoral head[5], plantar fasciitis [6,7] and critical myocardial and limb ischemia[8]. Most recently shock wave therapy (SWT) has been used in the treatment of acute and chronic wounds, burns and skin flaps.

Shock waves are biphasic high-energy acoustic waves that can be generated by electrohydraulics. A high voltage spark is discharged under water, causing vaporization and the release of acoustic waves with high peak pressures that rapidly decline over 10 μs[9,10]. As the shock wave propagates over distance, energy is absorbed by the tissue. The degree of focus can be modulated by parabolic reflectors, resulting in a variable concentration energy at a desired location (Figure 1). Shock waves are defined by their waveform, the number of impulses, the frequency of impulses and energy flux density (mJ/mm^2).

The mechanisms of biological changes that result from shock waves are not entirely clear. One hypothesis is that shock waves act as transient micromechanical forces that induce perturbations at the cell structural level, thereby altering biologic activity. Mechanotransduction results from geometrical changes in the cellular cytoskeleton, which is analogous to design concepts of tensegrity articulated by architect Buckminster Fuller and sculptor Kenneth Snelson[11] and applied to biological systems by Ingber. Briefly, external deformations can be transduced to an already “prestressed” or internally balanced cytoskeleton through tensile linkages or cell surface receptors that would initiate a cascade of intracellular events leading to changes in cell activity[12]. Such an explanation for SWT would parallel our existing understanding of soft-tissue expanders in reconstructive surgery, distraction osteogenesis, and most recently, wound healing

with the vacuum-assisted closure(VAC) device, in which micromechanical forces promotes wound healing through increased cell division, angiogenesis and release of growth factors in the wound bed[13].

Pre-clinical experience using SWT in suggests a potentially important role in promoting healing in diabetic wounds, flap necrosis and burns. There have been clinical studies with low levels of evidence based on the criteria of the Center for Evidence Based Medicine[14]. Among these studies, only a few have been prospective, randomized, controlled studies that fail to meet several key CONSORT criteria[15]. The limited clinical evidence and lack of rigorous study design have made it difficult for clinicians and regulators to fully support SWT in wound healing at this time. Several questions, including optimal SWT parameters, timing of treatments and types of wounds most suited for SWT remain unanswered and warrant further clinical studies.

Methods

Literature search

We searched Medline, the Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register. The search strategy we used included MESH terms "WOUNDS AND INJURIES/THERAPY", "WOUNDS AND INJURIES/PATHOLOGY", "SOFT TISSUE INJURIES/PATHOLOGY", "SOFT TISSUE INJURIES/THERAPY", "UTRASONIC THERAPY/METHODS" and "HIGH-ENERGY SHOCK WAVES/THERAPEUTIC USE" along with text words. No other limits were applied to any of the searches. Additionally, reference lists of full-text papers obtained through these searches were searched.

Selection

We included SWT preclinical studies in animals, in-vitro studies and clinical studies

including prospective and retrospective trials that included wound healing, flap necrosis, and burns. Because of the scarcity of SWT clinical trials, we did not exclude non-randomized or poorly controlled trials. Outcomes of interest included: improved wound healing, flap necrosis, and reepithelization of burns.

Data abstraction

Review of randomized controlled trials was carried out based on the recommendations of the PRISMA statement[16].

Data analysis

The Centre for Evidence Based Medicine Levels of Evidence[14] were applied to the clinical studies reviewed. Additionally, the CONSORT checklist of information was applied to those that were randomized controlled studies[15].

Results

Wound Healing

Two preclinical studies have looked at SWT in diabetic wounds. Kuo et al[17] administered unfocused SWT (800 impulses at 0.09 mJ/mm^2) to STZ-induced diabetic rats with a dorsal skin defect. SWT significantly reduced wound size in diabetic rats with greater reductions seen with more treatment (Table I). There was increased blood perfusion, decreased pro-inflammatory activity, and increased VEGF, eNOS and PCNA expression[17].

A more recent study[18] in db+/db+ mice with a full thickness dorsal skin defect found that unfocused SWT (200 impulses at 0.1 mJ/mm^2) led to a prolonged and elevated expression of gene subsets. SWT had no effect on wound closure in diabetic or control mice. Multiple treatments with unfocused SWT further delayed wound healing after

initially increasing the size of the wound[18].

Schaden et al[19] found a 75% treatment response (as defined by 100% wound epithelization) in a Level 2b study of 208 patients with heterogeneous wounds treated with debridement and unfocused SWT (100 to 1000 impulses at 0.1 mJ/mm^2) with a mean of 3 treatments. One third of wounds were acute and nearly 40% of wounds had either partial or complete failure to heal after primary surgical closure, an important confounder unaccounted for in the analysis. Excluding venous stasis and arterial insufficiency ulcers, wound etiology did not affect treatment success, but statistical analyses to justify this conclusion were not performed. Analyses based on wound size and duration revealed small wounds (<10cm$^{2)}$ of short duration (<1 month old) were most likely to rapidly completely re-epithelialize.

Saggini et al [20] led a Level 3b study with 30 consecutive patients treated with focused SWT (100 impulses at 0.037 mJ/mm^2) every 2 weeks (range of 4-10 sessions) until complete healing was achieved. Unlike others, this study used focused SWT and a lower energy flux density. A 50% complete healing response (parameters not defined) with no adverse events was reported. This conclusion was obtained by grouping a heterogeneous patient population and their individual responses: posttraumatic ulcers (69% complete healing), venous ulcers (36% complete healing) and diabetic ulcers (25% complete healing). No subset analysis based on wound etiology was done. In the remaining ulcers without complete healing, increased wound bed blood supply was observed (data not provided). A significant decrease in pain based on the pain self-assessment numeric box scale in treated patients was also reported.

Wang et al[21] found complete healing (parameters not defined) in 31% of patients in a

Level 2b study with 72 patients with chronic diabetic foot ulcers treated with focused SWT (300 + 100 impulses/cm^2 at 0.11 mJ/cm^2) every 2 weeks for 6 weeks. Increased perfusion, cell concentration and activity were noted. Notably, the control arm received hyperbaric oxygen therapy (HBO) instead of standard therapy. The wounds studied were relatively large (SWT: 11.2 +/- 20 cm^2, HBO: 10.5 +/- 20 cm^2, mean size +/- SD). SWT was found to be superior to HBO. Rationale for treatment parameters and details of the clinical assessment are lacking. Because the study did not have long term follow up, the natural history of diabetic ulcers treated with SWT remains unknown.

Morretti et al[22] conducted a Level 2b study of 30 diabetic patients with neuropathic foot ulcers treated with debridement followed by unfocused SWT (100 pulses of 0.03 mJ/mm^2) for 3 sessions every 72 hours and wound care. The control arm was treated with debridement, pressure relief and treatment of infection. The wounds studied were small (SWT 300 +/- 130 mm^2, control 250 +/- 100 mm^2, mean size +/- SD). SWT parameters were based on the authors' clinical experience with SWT in orthopedics. In 20 weeks, the treatment arm had a healing rate of 53% versus 33% in the control. Though randomized, the random allocation sequence, its mechanism and implementation were not explained. The study excluded chronic diabetic ulcers greater than 5 cm to avoid selection bias.

Dumfarth et al[23] carried out a Level 2b study with 100 patients undergoing vein harvesting for coronary artery bypass graft (CABG) surgery, half of whom received unfocused SWT (25 impulses at 0.1 mJ/mm^2) at the wound closure site of the vein graft. Treated patients had lower ASEPSIS scores (serous discharge, erythema, purulent exudates, separation of the deep tissue, isolation of bacteria, and duration of inpatient stay) on postoperative days 3 and 7 with no reported complications from treatment,

suggesting better wound healing. Treated patients had a statistically significant lower use of antibiotics for leg wounds. However, the study was not powered for its primary outcome. The long term effects of SWT in these surgical wounds were not assessed.

Recently, Ottomann et al[24] conducted a Level 1b study with 28 patients with acute traumatic wounds and burns requiring skin grafting treated with unfocused SWT (100 impulses at 0.1 mJ/mm^2) to the skin graft donor site immediately after skin harvest. A significantly decreased time for reepithelization of skin graft donor sites in the SWT arm (13.9 +/- 2.0 days) versus control (16.7 +/- 2.0) was reported. The study was powered to detect a difference in time to epithelization with adequate randomization and blinding. However, the sample size was too small to study other outcomes including pain and the cosmesis of donor sites and did not have long-term follow up.

Flap Necrosis

Several preclinical studies examined the role of SWT in preventing necrosis of skin flaps in animal models, after the orthopedic and trauma literature suggested SWT could induce neovascularization and increase VEGF expression among other proangiogenic genes[25,26] (Table 2). Meirer et al[27] applied SWT (2500 impulses at 0.15 mJ/mm^2) to the random portion of an epigastric skin flap model immediately after surgery. There was significantly less necrotic surface area in SWT treated rats (2.2 +/- 1.9%) at one-week follow-up versus control (17.4 +/- 4.4%)[27]. In a later study, SWT was hypothesized to decrease flap necrosis through reciprocal increase in VEGF expression in adjacent skin but the detected difference in expression failed to reach statistical significance at a p-value of 0.05[28].

The same group compared SWT to gene therapy with VEGF and found SWT treated

rats to have significantly smaller necrotic zones of the flap[29], in a study where surgical procedures were performed by three different plastic surgeons and analyses were not blinded. SWT was found to be superior to gene therapy with transforming growth factor-b in a study of SWT (750 impulses at 0.15 mJ/mm^2) administered immediately after raising an epigastric skin flap in rats[30]. However, there was no significant difference in flap vascularization assessed by CD31 staining between SWT and gene therapy rats. Rationale for SWT parameters was also lacking.

Yan et al[31] administered SWT (750 impulses at 0.09 mJ/mm^2) to the mid and distal portions of a cranially based random pattern flap model in rats and found increased blood perfusion and expression of nitric oxide and VEGF. SWT parameters were based on pilot studies, though it is unclear whether focused or unfocused SWT was used. There was increased vasodilation of pre-existing vessels in the early post-operative period with neovascularization apparent on post-operative days 3 and 10[31]. This study suggested that SWT administered immediately postoperatively starts a series of discrete events that could explain when certain changes in the flap are seen.

Two studies have looked at the immunologic changes induced by focused SWT in flap necrosis models. Kuo et al[32] applied focused SWT (500 impulses at 0.15 mJ/mm^2) to five areas of a rat dorsal random flap model. Increased VEGF and PCNA expression, reduced leukocyte infiltration and decreased TNF-alpha expression in flap tissue ischemic zones were found, suggesting that SWT may dampen the inflammatory response in ischemic tissue[32]. Kuo et al[33] repeated the same experiment and found decreased leukocyte infiltration and tissue apoptosis, increased recruitment of skin fibroblasts, down-regulation of oxygen radical burst, and increased eNOS expression[33].

One study compared preoperative SWT to no treatment in an epigastric skin flap model and noted a significant reduction in necrotic flap area[34]. However, a head-to-head comparison of preoperative versus postoperative SWT to determine optimal timing of SWT has not been done. Kamelger et al[35] assessed a dose-dependent effect of SWT in a murine epigastric skin flap model by varying impulses (200, 500, 1500, 2500, 5000 and 0) at 0.11 mJ/mm^2. Optimum enhancement of skin flap survival was at 500 with no significant increase at 1500 and 2500 impulses and increased necrosis observed at 5000 impulses. Changes in expression of growth factors or neovascularization with different impulses were not assessed.

No clinical studies of SWT for the prevention of flap necrosis have been conducted.

Burns

The application of SWT was examined in a murine model with full thickness cutaneous burns[36] (Table 3). Gene expression studies showed more than fivefold increased in chemokine and proinflammatory cytokine genes 4 hours postburn that were not seen in SWT-treated wounds. Davis et al[36] found that administration of unfocused SWT (200 impulses at 0.1 mJ/mm^2) one hour postburn led to a significant reduction in neutrophil infiltration at the wound margin and central wound bed at 4 and 24 hours postburn. No significant difference in macroscopic wound closure contraction, degree of subeschar keratinocyte migration, rate of wound reepithelization and granulation development were found. The study was neither randomized nor powered for its primary outcomes.

Meirer et al[37] described a Level 4 case report of a patient with deep partial thickness burns of the forearm who refused skin grafting for cosmetic reasons and instead received SWT (1500 impulses at 0.11 mJ/mm^2) on days 3 and 7 post-burn. The patient

had near complete reepithelization on day 15 and a well-healed wound without scarring at 6 months follow-up. Recently, Arno et al[38] conducted a Level 4 case-series study of 15 patients with <5% TBSA deep partial/full thickness skin burns who received unfocused SWT (500 impulses at mJ/mm^2) on days 3 and 5 post-burn. Patients underwent debridement and STSG in the absence of burn reepithelization 2.5 weeks or more after SWT therapy. 80% of the patients healed before 3 weeks; 15% of patients required surgical debridement and STSG and 5% developed hypertrophic scarring. Increase in perfusion based on laser Doppler imaging (LDI) images was also observed.

Discussion

The advent of SWT provides a potential new therapeutic modality for acute and chronic wounds which likely acts through mechanotransduction and immunomodulatory mechanisms. SWT promotes expression of macromolecules in wound healing, including VEGF, eNOS and PCNA. Because of the large experience using this technology to treat urolithiasis and other conditions in humans, it appears to be a safe technology. The clinical efficacy of this technology in specific wound types as well as the precise mechanisms of action is now beginning to be understood.

SWT may be perceived by cell surface receptors through extracellular matrix and fluid effects. Mechanoreceptors including integrins, ion channels, connexins and/or the lipid component of the plasma membrane activation could all possibly be affected by SWT. Akt-mediated mechanotransduction in fibroblasts has been show to play a role in hypertrophic scar formation in response to mechanical forces, suggesting that Akt and other upstream components like Focal Adhesion Kinase (FAK) would be important candidates to study in the future for SWT[39]. Future studies may further elucidate the mechanotranduction effects of SWT. Shock waves may also stimulate sensory nerve

fibers including nociceptors that produce the somatic sensation of mechanical force, which may explain why some patients treated with SWT report decreased pain.

Clinical studies of SWT in wound healing suggest that wound etiology, size, and chronicity may impact response to SWT. However, the actual administration of SWT in current clinical studies varies in type (unfocused versus focused), total number of impulses, energy flux density, and frequency. While the physics of SWT and preclinical studies suggest that unfocused SWT is superior for the treatment of superficial soft tissue defects, there has been no direct comparison of unfocused and focused SWT in clinical trials to date. Therefore, whether there is a clinically relevant difference in unfocused versus focused SWT remains unknown. Many authors who studied SWT in other clinical settings used the same devices in their studies of wound healing. To our knowledge, there have been no preclinical or clinical studies that have published data to suggest that there are experimental limitations that did not permit use of either type of SWT. Similarly, we do not have a complete understanding of the optimal SWT settings.

Additional basic science studies along with RCTs and registry studies powered to detect clinically relevant outcomes will be necessary to increase our understanding of this technology. Specifically, better characterization of the effects of SWT in homogenous groups of wounds would lead to identification of subsets of patients that are ideal candidates for SWT. In order to achieve this, thoughtful investigations to determine the type and specific parameters of SWT suited for different wounds must be determined first.

Currently, the FDA has approved devices that administer SWT for the treatment of plantar fasciitis and lateral epicondylitis but has not approved its use to treat acute and

chronic wounds. SWT shows promise in improving our ability to enhance wound healing through mechanotransduction or immunomodulatory mechanisms. We look forward to future innovation in this field to understand more fully the mechanisms of action as well as optimal treatment of specific wound types.

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Figure Legends

Figure 1. Schematic diagram of SWT for wounds. A shock wave is produced by a sparkplug in a conductive device and can be focused with a parabolic reflector and conductive gel. The waveform shows peak pressures of 100 MPa after around 10 μsec, followed by a brief period of subatmospheric pressure. The wave is attenuated as it traverses the tissue

Table 1. Pre-clinical (*) and clinical studies using SWT in wounds

Wound Healing

Author	Year Published	Number of Subjects	Size of Injury	Number of Pulses	Density of Energy (mJ/mm2)	Focused or Unfocused
Kuo et al. [17]	2009	30 ESW, 20 control*	6 x 5cm	800	0.09	unfocused
Zins et al. [18]	2010	15 ESW, 15 control*	Circular 19 mm diameter (280 mm2)	200	0.1	unfocused
Schaden et al. [19]	2007	208	differing per patient	100	0.1	unfocused
Saggini et al. [20]	2008	30 ESW, 10 control	differing per patient	100	0.037	focused
Wang et al. [21]	2009	40 ESW, 42 HBO	11.2 +/- 20 cm^2	500	0.11	focused
Moretti et al. [22]	2009	15 ESW, 15 Control	300 +/- 130 mm^2	100	0.03	unfocused
Dumfarth et al. [23]	2008	50 ESW, 50 control	differing per patient	25	0.1	unfocused
Ottoman et al. [24]	2010	28	differing per patient	100	0.1	unfocused

*Pre-clinical

Table 2. Pre-clinical (*) and clinical studies using SWT in flaps.

Flap Necrosis

Author	Year Published	Number of subjects	Size of Injury	Number or Pulses	Density of Energy (mJ/mm2)	Focused or Unfocused
Meirer et al. 27	2005	10 ESW, 10 control	8 x 8cm	2500	0.15	Focused
Meirer et al. [28	2007	20 ESW, 20 control	8 x 8cm	500	0.11	Focused
Meirer et al. 29	2007	10 ESW, 10 control	8 x 8cm	500	0.11	Focused
Huemer et al. 30	2005	10 ESW, 10 control, 10 TGF-β	8 x 8cm	750	0.15	Focused
Yan et al. 31	2008	42 study,	3 x 10cm	750	0.09	Focused

		42 control				
Kuo et al. 32	2007	36	10 x 3cm	500	0.15	focused
Kuo et al. 33	2009	36	10 x 3cm	500	0.15	focused
Reichenberger et al. 34	2009	10 ESW, 10 control	6 x 10cm	500	0.11	Focused
Kamelger et al. [35	2010	36	8 x 8cm	200, 500, 1500, 2500, 5000 and 0	0.11	Focused

Table 3. Pre-clinical (*) and clinical studies using SWT in burns.

Burns

Author	Year Published	Number of Subjects	Size of Injury	Number of Pulses	Density of Energy (mJ/mm2)	Focused or Unfocused
Davis et al. 36	2009	20 ESW, 20 control*	15% TBSA (10 week old mice)	200	0.1	unfocused
Meirer et al. 37	2005	1	unknown, R forearm deep partial thickness burn	1500	0.11	focused
Arno et al. 38	2010	15	<5% TBSA deep partial/full thickness skin burns	500	0.15	Unfocused

*Pre-clinical

Figure 1