



Review Article

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Ultrasound based techniques for treatment of chronic Wounds: A comprehensive review of therapeutic efficacies and clinical considerations

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ABSTRACT

Ultrasound (US) waves have emerged as a promising alternative or adjunctive strategy for chronic wounds. However, the clinical efficacy of these techniques for different chronic wounds is still not fully understood and standard guidelines on the allowed doses and possible side-effects should be determined. This paper aimed to comprehensively review the therapeutic efficacies and clinical considerations of US based techniques for chronic wounds. The databases of PubMed (1985-2016), EMBASE (1985-2016), Web of Sciences (1985-2016), and Google Scholar (1980-2016) were searched using the set terms. The obtained results were screened for the title and abstract by two authors and the relevant papers were reviewed for further details. Despite of rigorous evidence on the therapeutic efficiency of US in chronic wounds, no definite dose-response existed on the clinical trials of US wave applications. However, there is a consensus on the spatial average temporal average dosage in the range of 0.5 W/cm² to 3 W/cm² with significant therapeutic outcomes and minimum adverse effects. The available data showed the therapeutic efficacy of US techniques for chronic wounds. However, further in vitro and clinical trials are needed to shed more light on the exact dose-response of US techniques for different wounds.

Key words: Ultrasound, Chronic Wound, Clinical Considerations, Dose, Therapeutic efficacy

INTRODUCTION

During the recent years, along with the advancements in new medications, different techniques have been developed for the treatment of wounds such as pressure relieving beds, cushions, and medicinal plants. They are generally used for prevention and treatment of pressure wounds. High worldwide prevalence of wounds, high costs of traditional methods and elimination of reimbursement for various wounds like burns, venous leg ulcers or infections have boosted the rapid raising of alternative wound healing methods. During the recent years several methods have been developed for chronic and acute wounds treatment including laser, direct current, electric and magnetic fields, light and electromagnetic fields (1-13).

Ultrasound (US) waves are among the most recent methods for treatment of wound with promising outcomes. US based techniques have major advantages over conventional and other alternative techniques. US waves can penetrate into the beyond of the wound bed and reach more deep-seated tissues compared with other methods. Furthermore, the US waves can be highly oriented and focused compared with other techniques.

Since the discoveries of potential therapeutic effects of US energy, various US technologies have been investigated for treatment of several disorders including skin wounds, malignant tumors, and bone fractures (14-31).

Advantages of US treatments have made them one of the most promising treatment options for the management of soft tissue injuries (32). Many experimental studies have shown various physiological efficacies of US on living tissues (33-36) and also vigorous evidence indicating the beneficial effects of these mechanical waves in the treatment of disorders involving soft tissues (37-39).

Some applications of high frequency US include treatment of tendon injuries and relief of the short-term pain (40-42). Furthermore, US waves have been demonstrated to accelerate healing of some acute bone fractures, venous and pressure ulcers, and surgical incisions (40, 43, 44). However, US treatment may cause burns or damage the endothelial under inappropriate parameters (45, 46). In line with the research progressions, different commercial modalities based on low frequency US were offered to the market. Use of high frequency US in clinical medicine is restricted due to the risk of tissue heating. As a result, considerable research attempts have exploited alternative US parameters. Low-frequency US waves are actually slow release technique associated with low tissue heating so that these techniques may become the standard technique treating slow-to-heal wounds, skin ulcers, and nonunion fractures. Surface acoustic wave (SAW) patch therapy is another US technique developed for wound treatment. It employs a different acoustic wave than traditional ultrasound, utilizing a scattered beam with a maximum penetration of 4 cm, while traditional ultrasound can penetrate 10 cm. Some studies have reported increased tissue oxygenation and saturation after the application of SAW patch therapy, which would prove beneficial for wounds or ulcerations being deprived of oxygen and healing factors (47, 48).

US waves have emerged as promising alternative or adjunctive strategies for chronic wounds. However, the clinical efficacy of these techniques for different chronic wounds is still not fully understood. In addition the clinical guidelines on the allowed doses and possible side-effects of these techniques should be determined. Therefore, this paper aimed to comprehensively review the therapeutic efficacies and clinical considerations of US based techniques for chronic wounds.

MATERIALS AND METHODS

The databases of PubMed (1985-2016), EMBASE (1985-2016), Web of Sciences (1985-2016), and Google Scholar (1980-2016) were searched using the set terms. The search terms included "ultrasound wave", "chronic wound", "clinical considerations", "dose response", "treatment", and "therapeutic efficacy". The obtained records were reviewed for the title and abstract by two authors and they came to consensus whether the studies are related to the review. Animal and human studies in both in vivo and in vitro designs that evaluate the therapeutic effects of ultrasound waves in chronic wounds were included for further review. Because of the immense body of literature in this field, this study was aimed to provide a comprehensive and descriptive overview of the recent advances in applications of US waves for treatment of chronic wounds therapeutic efficacies and clinical considerations of US based techniques for chronic wounds

RESULTS

3.1. Physical Characteristics of Therapeutic US

The US waves delivered to the body and soft tissues are transformed by diffusion and vibration of molecules with a progressive loss of the intensity of the energy during passage through the tissue. The intensity of US waves undergoes attenuation because of absorption, scattering or dispersion, reflection, and rarefaction of the wave (49). The main parameter for assessing the therapeutic efficacy of US techniques is the power expressed in Watts. The amount of energy attained by a particular site is dependent on the US characteristics (frequency, intensity, amplitude, focus, and beam uniformity) and the type and physical characteristics of tissues through which the US beam travels.

The frequency range of therapeutic US is 0.75–3MHz and most machines are set at the frequency of 1 or 3 MHz. Low frequency US waves have more penetration depth, but are less focused. One- MHz US is adsorbed primarily by tissues located in depth of 3–5 cm (50) that makes it ideal choice for deeper injuries and in patients with greater subcutaneous fat. The frequency of 3 MHz is applied for more superficial lesions at depths of 1–2 cm (50, 51).

Tissues can be determined by their acoustic impedance, the product of their density and the speed at which US will transfer through it. Tissues with high-water content such as fat, have low absorption of US and thus high penetration of US waves, while tissues which are rich in protein like skeletal muscle have high US adsorption (52). The larger acoustic impedance difference between two tissues, the less portion of the US wave will transmit through the interface (53). When reflected US meets further transmitted waves, a standing wave may be generated, which has potential side effects on tissue (51). Such adverse effects can be minimized by ensuring that the machine renders a uniform wave, using pulsed waves, and moving the transducer during the treatment process (52).

The greater diameter of the radiating area of the transducer face, the more focused US beam is generated. Energy is unevenly distributed within the US beam and the greatest non-uniformity occurs near the transducer surface. The beam intensity variation is determined by the beam non-uniformity ratio (BNR), the ratio of the maximal intensity of the transducer to the mean intensity across its surface (54).

3.2. Clinical Considerations: US and Different Wounds

3.2.1. Wound Healing- Angiogenesis

In vitro studies on the tunneling or debilitation wounds and surface model demonstrated that US can eliminate multi-drug resistant bacterial organisms. Organisms like Vancomycin-resistant Enterococcus and resistant *Pseudomonas aeruginosa* in vivo were cultured and cured with different US outputs and exposure times (55). In vitro findings demonstrated that US treatment can enhance in vitro cell proliferation, collagen/ NCP production, formation of bone, and angiogenesis (56). Other similar studies have assessed the various US machines on wound treatment and proved the angiogenesis effects of US (57).

3.2.2 Chronic Wounds

Management of chronic wounds related pain is a long standing clinical challenge in patient care and there is no definitive solution for treatment of chronic wounds related pain (58). Different studies revealed that low frequency US is a useful device for chronic wounds management, not only for curing but also for pain relieving, pigmentation and odor decrease (59). However, findings of similar studies on chronic wounds are controversial. A systematic review of the efficacy of different US modalities on wound care management deduced inadequate evidence for clinical efficacy of therapeutic US in chronic wounds (46).

According to the primary clinical evidence, patients with painful chronic lower-extremity wounds reported a wound pain reduction following US therapy. A low-frequency, non-contact US device for wound treatment, was approved for marketing by the United States Food and Drug Administration (58).

3.2.3. Purulent Wounds

Low frequency US techniques have been used in combination with standard wound care drugs or alone for treatment of purulent wounds. The findings of these studies showed the therapeutic effectiveness of US technique as an adjunctive or alternative treatment for purulent wound (60-62).

A case series study assessed the effectiveness of the combination of low frequency US together with gentamicin solution in 17 patients. This study revealed a reduction in the purulent septic complications from 35.7% to 5.9% (62).

A cross sectional experiment on 112 patients with diabetes mellitus and purulent surgical wound who were cured with low frequency US and laser radiation showed that US treatment had privileges in the first and second phases of wound curing procedure (60). Another study revealed that an US surgical device "SUGA -21f.02" applied in 76 patients and an intensification of diffusion of the medical preparation into the tissues was demonstrated among the deep layers of the wound channel (61). In a study which assessed the impact of US at two power densities of the range of $0.5\text{W}/\text{cm}^2$ and $1\text{W}/\text{cm}^2$ for treatment of crural ulceration found no significant difference in terms of granulation development rate and debridement of the wound.

3.2.4. Trophic Ulcers

Gostishchev et al. (1984) investigated the effects of low frequency US on the trophic ulcers. They assessed clinical, morphological and medium pH measurement and showed granulation tissue growth which allows fulfilling autodermatoplasty (63).

Other studies have tested the efficacy of low frequency US applied in combination with antibiotic. In this area, Radiske et al. (2000) demonstrated that continuous US and systemic gentamicin administration significantly decreased the viable bacteria concentration in the simulated implant putridity (64), whereas some scientists (Qian et al. 1997; Pitt et al. 1994) have reported that application of US in the bacterial cultures of *E. coli* and *P. aeruginosa* increased the efficacy of gentamicin (65, 66).

3.2.5. Pressure Ulcer

In a systematic review conducted by Flemming et al. (2004) showed no vigorous evidence on the therapeutic efficacy of US in the pressure sores. They attributed the inconsistency to the variations and limitations in the methodology and the small sample size of the reviewed studies (67).

Reit et al. (1995) conducted randomized controlled trials of US treatments in patients with pressure ulcers. They observed no significant differences between treatment groups (David et al. 1996, Riet et al. 1995) (68).

In a review of pressure ulcers therapy, Reddy et al. (2008) performed a randomized controlled clinical trial and found no significant proof for the US efficacy in the treatment of pressure ulcers. The review of randomized controlled clinical trials found no clear evidence for the effectiveness of US in healing of pressure ulcers (69). Akbari Sari et al. (2006) reviewed the effectiveness of US therapy on pressure ulcers. They showed no reliable proof of advantage of treatment by US in the healing of pressure ulcers. However, the feasibility of useful or harmful effect cannot be ruled out because of the small number of participants or other methodological limitations. Therefore, further studies are needed to reach a conclusive answer (67).

3.2.6. Extremity Lower Wounds

Extremity lower wounds are among the most common types of wound worldwide (70). US techniques have shown therapeutic efficacies for this type of wounds. Callum et al. (1987) applied weekly pulsed US therapy and compared this technique with standard wound care for chronic leg wounds. They used a 12-week treatment period and reported that the ratio of wound healed was 20% greater in the US group (71). In a randomized controlled trial conducted by Lundeborg et al. (1989) to investigate the efficacy of pulsed US in conjunction with a standard technique of curing chronic leg ulcers therapy on 44 patients (72). All patients received standard treatment (paste impregnated bandage and a self-adhesive elastic bandage) plus placebo US or pulsed US three times a week for 4 weeks. Then it was applied two times in a week for 4 weeks and once-weekly for the following 4 weeks. The rates of cured wound were tested after 4, 8 and 12 weeks (72). They showed no significant differences in the percentage of cured ulcers in the pulsed US treatment as compared with the placebo group (72).

In a randomized controlled study, Eriksson et al. (1991) investigated the efficacy of US against the standard model of chronic leg ulcers healing. All patients received standard treatment plus placebo US with the intensity of 1.0 W/cm² at 1 MHz, for 10 min twice a week for 8 weeks. The percentage of cured wound area and the number of healed wounds were compared after 2, 4, 6, and 8 weeks. The authors observed no significant differences in the percentage of cured ulcers in the US treatment group as compared with the placebo group (73). Peschen et al. (1997) examined the effect of low-frequency (30 kHz) low-dose US on the chronic venous leg ulcers treatment in combination with conventional outpatients' therapy. Patients were randomly divided into conventional treatment with topical application of hydrocolloid dressings and compression therapy (conventional treatment plus US treatment). The US therapy included 10-min of foot-bathing with continuous US wave 100 mW/cm² thrice-weekly for three months. The ulcer area was measured by planimetry, using a millimeter grid before therapy and after 2, 4, 6, 8, 10, and 12 weeks of treatment. The group evaluated the radius of ulcer and the daily decrease of ulcer radius. After each therapy, adverse effects were recorded. After the period of treatment the mean decrease of ulcerated area in control group patients was 16.5% while this factor in the US group was 55.4%. The daily decrease of ulcer size in the US-treated group was 0.08 mm whereas this ratio in the placebo patients was 0.03 mm. Both US and placebo groups just recorded minor adverse effects. The authors concluded that the low-frequency and low-dose US technique is a beneficial therapeutic method in chronic venous leg ulcers (74).

Johannsen et al. (1998) carried out a meta-analysis study in order to explain the effect of chronic leg ulcer treatment by applying US. The result of their study demonstrated that when US was delivered in low doses around the ulcer edge, it has the best therapeutic effects (75). In a randomized, double-blinded, controlled, multi-center study, Ennis et al. (2005) performed a randomized double blinded, controlled, multi center experiment and they tested the efficacy of MIST US treatment for the recalcitrant diabetic foot wounds therapy. This study was conducted on 55 patients and they received standard care, which consisted of products that prepare a moist environment, without using diabetic shoes and socks, debridement, as well as wound assessment. The "treatment" was done using US wave of 40 kHz frequency achieved by a saline mist or a "sham device" that delivered a saline mist without applying US. This procedure has been applied for 3 months which significantly increased the ratio of wounds healing compared with the control group. In this experiment no difference was observed in the frequency and type of side effects between the two groups. This findings showed that the MIST US treatment accelerated the healing rate of diabetic foot ulcers (76).

Kavros et al investigated ischemic wounds with noncontact, low-frequency ultrasound, finding significant improvements in wound healing in patients with critical limb ischemia after use of the device combined with standard wound care.

Ennis et al. (2006) assessed the effectiveness of MIST US on the occurrence of wound closure for chronic non-healing lower extremity wounds of different etiologies. Their study showed the appropriate and optimal treatment duration was correlated with a maximal clinical response and identified potential synergistic therapies that could be

used in conjunction with this therapy. In addition, they investigated the effect of MIST US treatment on the micro circulatory flow patterns within the wound bed. Control data were obtained from a previously published, prospectively gathered database. This experiment lasted 8 months. A total of 29 lower extremity wounds which were observed in the 23 patients who met inclusion criteria were treated with MIST US treatment. Standard treatment period was prepared for 2 weeks for all wounds observed for the experiment. A breakage to obtain an area of reduction more than 15 % qualified the patient for registering the trial and the addition of MIST US therapy to the current cure regimen. The criteria for inclusion were the decrease of wound healing, area and volume, and laser Doppler-derived mean voltage. Totally, 69 % of the wound was healed by applying the desired therapeutic model. When MIST US was applied alone, the average time which was required for healing was 7 weeks, whereas the mean time to heal control groups was 10 weeks. The outcomes of this experiment demonstrated that using MIST US treatment alone or in combination with moist wound care could attain healing in 69% of chronic wounds. Non-contact US was evident within 4 weeks of therapy. The authors demonstrated that a well-designed clinical experiment based on health economics is required to evaluate this method (77).

Kavros and Schenck (2007) performed a non-randomized, baseline-controlled clinical case series study in order to describe the efficacy of non-contact low-frequency US treatment for chronic, rebellious lower-leg and foot ulcer. They first treated patients were initially treated with the Mayo Clinic standard method of care, and then they combined low-frequency US therapy with the former approach. They surveyed the medical records of 51 patients with one or more conditions cited below: diabetes mellitus, neuropathy, limb ischemia, chronic renal insufficiency, venous illness, and inflammatory connective tissue disease. All patients had leg and foot ulcer with 65% of patients having mellitus and 20 % of them having a history of amputation. 63 % of all the wounds had a multi-factorial etiology, and 65 % had correlated transcutaneous oximetry levels less than 30 mmHg. The mean time of wounds therapy during the baseline standard of care control period was almost 9.8 weeks while the non-contact US therapy of low frequency time was approximately 5.5 +/- 2.8 weeks. The results showed that utilizing non-contact low-frequency US could improve the curing and closure in recalcitrant leg and foot ulcer (48).

In a randomized controlled trial study, Kavros et al. (2007) applied the MIST-US to treat non-healing leg and foot ulcers associated with ischemia of chronic critical limb. The treatment protocol consisted daily five-minute treatment for three times a week continued for three months or until wounds achieved full recovery. The main outcome measure was the percentage of patients with greater than 50 % falling in size of wound from the index of measurement after 3 months of treatment. The correlation between transcutaneous oximetry pressure in response to low-frequency of the supine and dependent position was assessed as a factor in evaluating the ability to heal the ischemic foot and leg ulcer. A significantly higher percentage of patients cured with the standard of care plus MIST US therapy obtained greater than 50% wound healing at 3 months than those which were just treated with the standard care. Therefore, failing to reach the minimal wound healing requirement happened in 37% of subjects in the treatment group and 71% of patients in the control group. The predictive value of baseline transcutaneous oxygen pressure may profit the clinician when evaluating the ability to ischemic wounds healing. The authors demonstrated that when they applied MIST US addition to the standard wound care model, the velocity of cutaneous foot and leg ulcer healing in patients with chronic limb ischemia cured greatly. It should be considered that though the study discussed the significance of baseline transcutaneous oxygen pressure on therapeutic wound, patients with high (21 to 40 mmHg) and low (1 to 20 mmHg) transcutaneous oxygen pressure levels are not equally distributed equally between the groups (47).

The American Society of Plastic Surgeons evaluated the efficacy and feasibility of US treatment for leg and foot ulceration (78). Their assessments which were based on the clinical experiment guideline on chronic wounds of the leg and foot ulcer (2007) did not note the application of US as a choice of treatment (78).

Kavros et al (2008) performed a retrospective analysis, evaluating the clinical efficacy of non-contact, low-frequency MIST US in the chronic leg and foot ulcer therapy. They authors observed that a significantly larger percentage of wounds were healed by MIST US therapy plus standard wound care compared with the standard care alone. In addition, application of the MIST US therapy accelerated the rate of wound healing compared with the standard model. The authors concluded that when MIST US therapy was added to standard wound healing model, the rate of curing and closure of chronic wounds significantly improved. They concluded that the combine MIST US and standard wound care model accelerates the healing of chronic wounds in the leg and foot ulcer (79).

Cullum et al. (2010) conducted a Cochrane review on the efficacy of US on the rate of venous leg ulcer healing. They concluded that venous leg ulcers trial assessment with US is small, poor-quality and heterogeneous. There is no trustworthy proof that US improves venous ulcers healing. There is a number of weak evidence which showed enhanced curing with US; however, to reach a more conclusive answer, further confirmation in larger, high-quality RCTs is required (80).

Game et al. (2012) stated that the result of diabetic foot ulcers administration is poor, and there is continuing doubt concerning optimal methods to management. For this reason, in 2006 the International Working Group of the Diabetic Foot (IWGDF) group carried out a systematic review of the proof to inform protocols for current care and to highlight areas which must be considered for further research. This group updated the review by considering papers, published during December 2006 to June 2010, on the interventions to improve the chronic ulcers healing. Two research groups independently evaluated methodological quality of the selected studies using Scottish Intercollegiate Guidelines Network criteria. The selected studies were divided into ten categories: (1) sharp debridement and preparation of wound bed with hydrotherapy; (2) preparation of wound bed by using antiseptics, applications and dressing crops; (3) the chronic wound elimination; (4) HBOT; (5) compaction or negative pressure treatment; (6) designing products to correct aspects of biochemistry of wound and cell biology which associated with impaired wound curing; (7) cells application, containing stem cells and platelets; (8) bioengineered skin and skin bounds; (9) magnetic, electrical, electromagnetic, lasers, shockwaves and US; and (10) other systemic treatments which were not found in the mentioned categories. Major challenges which prevented pooled analysis of outcomes are heterogeneity of experiments. With the exception of HBOT and, feasibly, negative pressure wound therapy, there is little evidence to justify the usage of newer treatments. This conclusion is consistent with a recent Cochrane review and the systematic review by the NICE Guidelines Committee in the United Kingdom. Analysis of evidence showed considerable difficulties in this field particularly as controlled studies are few and the majority suffer poor methodological quality (81).

Gottrup and Apelqvist (2012) carried out a review of available evidence and new methods in the diabetic foot ulcer therapy (82). They evaluated the treatment efficacy of several types of wound healing methods including antimicrobial agents, dressings, topical negative pressure, hyperbaric oxygen treatment, electrical, electromagnetic, laser, shockwave, and US techniques, growth, and cell biology modulating factors, cell products and tissue engineering, bioengineered skin and skin grafts, and adjuvant therapies. Their review demonstrated that there is restricted proof on the level I evidence level to recommend these techniques as usual clinical methods. However, using some of these techniques including US technique can be used as an alternative of adjunctive treatment for some types of chronic wounds.

There is a lack of strong evidence, mostly because of insufficient sample size, short follow-up, non-random allocation to treatment arms, non-blinded outcomes evaluation, poor description of control, and simultaneous intervention. The heterogeneity of the population of ulcer and people, with multiple factors help both ulcer frequency US in the management of several kinds of chronic wounds like burns, digital ulcers, infected surgical beginning and failure to heal. Another main cause for the lack of evidence is the general utility of the measure of "complete healing". Therefore, it is necessary to enhance the quality and methodology of clinical trials (82).

Furthermore, there are some case studies as well as case-series studies on the applications of non-contact, low-wounds, and sacral pressure ulcers (83-89).

CONCLUSION

Besides accelerating the healing speed of open wounds, low frequency US can be an effective early treatment for suspected deep-tissue injuries. In vitro and in vivo studies have shown therapeutic efficacies of US techniques in different wounds. However, there is not an exact dose-response for clinical applications of US treatments in different wounds. Considering the promising therapeutic effects of US techniques on the treatment of different wounds, we can expect that US will be a new standard for early treatment of some kinds of wounds.

However, to reach such a standard treatment, further studies are required to shed light on the exact mechanism of action and also to provide exact dose-response of therapeutic US for different wounds.

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