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Low-Frequency Ultrasound Debridement in Chronic Wound Healing: A Systematic Review of Current Evidence

Le débridement par ultrasons à basse fréquence pour la cicatrisation des plaies chroniques : une analyse systématique des données probantes à jour

Ying-Ju Ruby Chang, MSc[1], Julie Perry, PhD[1], and Karen Cross, MD, PhD[1]

Abstract

Chronic wounds are painful and debilitating to patients, pose a clinical challenge to physicians, and impose financial burden on the health-care system. New treatment options are therefore highly sought after. Ultrasound debridement is a promising technology that functions to disperse bacterial biofilms and stimulate wound healing. In this review, we focus on low-frequency ultrasound (20-60 kHz) and summarize the findings of 25 recent studies examining ultrasound efficacy. Ultrasound debridement appears to be most effective when used 3 times a week and has the potential to decrease exudate and slough, decrease patient pain, disperse biofilms, and increase healing in wounds of various etiology. Although current studies are generally of smaller size, the results are promising and we recommend the testing of low-frequency ultrasound therapy in clinical practice on a larger scale.

Résumé

Les plaies chroniques sont douloureuses et invalidantes pour les patients, posent un défi clinique aux médecins et imposent un fardeau financier au système de santé. Les nouvelles possibilités thérapeutiques sont donc très recherchées. Le débridement par ultrasons est une technologie prometteuse qui provoque la dispersion des biofilms bactériens et stimule la guérison des plaies. Dans la présente analyse, les auteurs se concentrent sur les ultrasons à faible fréquence (de 20 à 60 kHz) et résument les résultats de 25 études récentes sur leur efficacité. Le débridement par ultrason semble particulièrement efficace lorsqu'il est utilisé trois fois par semaine. Il peut réduire les exsudats et les escarres, atténuer la douleur du patient, disperser les biofilms et accroître la guérison des plaies de diverses étiologies. Même si les études actuelles sont généralement de petite dimension, les résultats sont prometteurs. Nous recommandons de mettre à l'essai la thérapie par ultrasons à basse fréquence à plus vaste échelle en milieu clinique.

Keywords

debridement, low-frequency ultrasound, bacterial biofilm, chronic wound

Introduction

The management of chronic wounds has been guided by the tissue debridement, inflammation control, moisture balance, and epithelialization of wound edges (TIME) framework. Debridement is thought to be most critical in promoting healing, through the removal of unhealthy tissue and bacterial biofilms.[1] Biofilms are structured communities of bacteria found in more than half of all chronic wounds. Biofilms are problematic because they are highly resistant to antimicrobial agents and phagocytosis. As a result, biofilms trigger chronic inflammatory processes, inducing prolonged elevated levels of protease and reactive oxygen species. This inefficient inflammatory process not only hinders healing of damaged

[1] Department of Surgery, St Michael's Hospital, Toronto, Ontario, Canada

Corresponding Author:
Karen Cross, Department of Surgery, St Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada.
Email: crosska@smh.ca

tissue but also increases exudate, which perpetuates the vicious cycle.

The prevalence of chronic wounds (arterial, venous, pressure, Diabetic foot ulcer, iatrogenic) is estimated to be anywhere between 3% and 26% of the Canadian population (Canadian Institute for Health Information, 2013). The prevalence of wounds in patients with diabetes is even higher and is estimated to be 11% to 34%. With the projected increase in the number of Canadians living with diabetes (from 2.7 million Canadians currently to 4 million people with this chronic condition by 2018), these numbers can be expected to rise again. Not only is the burden of disease increasing but also the costs to the health-care system for the treatment of diabetic foot ulcers alone is more than Can$150 million annually (www.cawc.net/index.php/public/facts-stats-and-tools/statistics). As a consequence, new and cost-effective therapeutic strategies are highly sought after, and it is imperative as plastic surgeons that we are at the forefront of trialing new technologies to aid in the care of these patients. Ultrasound is defined as sound waves with frequencies over 20 000 Hz (cycles per second).[2] Low-frequency ultrasound spans the range between 20 and 60 kHz and has longer wavelengths and greater amplitude for a given input energy, which results in greater movement of molecules within tissues.[2] Low-frequency ultrasound debridement has been investigated as an adjunctive therapy for chronic wounds, to remove devitalized tissue through microstreaming and cavitational effects.[3] More specifically, ultrasound selectively emulsifies dead and dying tissues with microsized gas bubbles, stimulating the membranes of surrounding healthy cells, and rendering bacteria more susceptible to antibiotic treatment.[2,4] As a result, this modality is thought to both debride the wound and promote healing by upregulating cellular activity, promoting growth factor (and protein) synthesis, promoting fibrinolysis, and disrupting the biofilm.[5-8] In animal studies performed *in vitro* and *in vivo*, ultrasound has been shown to promote histamine release, angiogenesis, and mast cell degranulation; increase intracellular calcium, collagen deposition, and wound tensile strength; and reduce wound size.[9] Human studies have found some benefit to ultrasound therapy, but conclusions regarding the clinical utility of this modality are difficult because of small sample size, difficulties in comparing different ultrasound parameters and treatment protocols, heterogeneity of ulcer type, location and size, and secondary health problems in the treated population. Despite the number of confounding variables, there is a body of preclinical evidence that supports the utility of ultrasound debridement as an adjunct therapy. Here, we report the findings of a systematic review of current clinical evidence on the use of low-frequency (20-60 kHz) ultrasound in chronic wounds.

Methods

Searches were performed in Ovid MEDLINE, Ovid EMBASE, the Cochrane Central Register of Controlled Trials, Agency for Healthcare Research & Quality, and Google Scholar. The following keywords were searched in each of the databases—ultrasound, debridement, wound healing, and biofilm. The reference section of each article was searched for relevant publications. Only English publications from 2000 to present were included in this review. The initial literature search was appraised based on title and abstract, and 2 reviewers (R.C. and K.C.) finalized the list of articles included in the analysis. Studies were excluded if they were an expert opinion of little insight on biofilm and wound healing or a systematic review without meta-analysis (Figure 1).

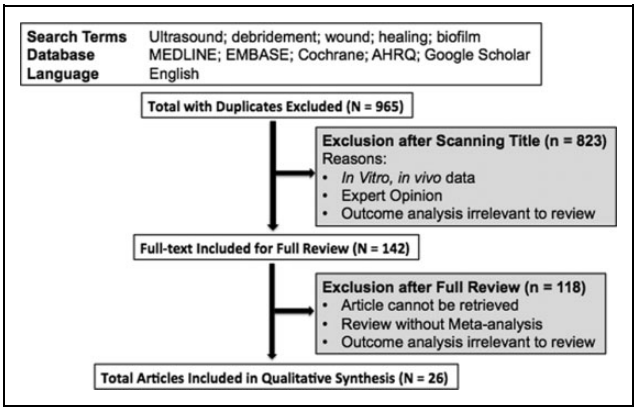

Figure 1. Summary of the workflow for study selection/exclusion.

Using the criteria established by the Oxford Centre for Evidence-Based Medicine (OCEBM Levels of Evidence Working Group, 2011, http://www.cebm.net/ocebm-levels-of-evidence/), level of evidence was scored for all included articles (Table 1). Pooling of results was not possible due to heterogeneity in study design, intervention, and outcome measure. Thus, no meta-analysis was conducted and all studies selected for this review were summarized individually.

Results

Of the 965 relevant articles found, 25 records met the selection criteria. Four studies outlining the results of case studies with level 5 evidence were discarded.

Ultrasound Frequency

The most widely used low-frequency ultrasound system is the MIST Therapy System, a noncontact ultrasound debridement tool that transmits low-intensity and low-frequency acoustic energy through a constant flow of saline mist (www.mistthera py.com). We also reviewed studies using Sonica 180 or Quostic ultrasound devices, which are equipped with a transducer that is applied directly to the wound surface (www.soering.com/products/ultrasonic_surgery/; www.arobella.com/products/qoustic-description.htm), and several studies utilized original ultrasound modalities that are not commercially available. All ultrasound modalities discussed use frequencies between 20 and 60 kHz.

Samuels et al reported complete healing of ulcers using 15 minutes of 20 kHz ultrasound, which was found to be superior

Table 1. Summary of the Evidence Supporting Low-Frequency Ultrasound Debridement as an Adjunctive Therapy.

		Wound Etiology						Ultrasound Modality				Healing					Antimicrobial				Pain	Level of Evidence					Duration	
Study	Sample Size	Burn Wounds	Surgical/ Trauma Wounds	Diabetic Ulcer	Pressure Ulcer	Arterial/ Venous Insufficiency	Other[a]	Sonica 180	MIST Therapy System	Quostic	Other	Complete Wound Closure	Decrease in Wound Size	Increase in Tissue Granulation	Increase in Rate of Healing	Decrease in Cytokine Level[b]	Improved Tissue Characteristic	Decrease in Exudate Amount	Decrease in Infection	Decrease in Bacterial Colony	Decrease in Pain	1	2	3	4	5	Treatment	Follow-Up
Bell and Cavorsi[13]	76		•		•	•			•				✓	✓				✓							•		4.3 wk	–
Breuing et al[2]	17		•		•	•	•	•					✓												•		3-8 mo	–
Caswell and McNulty[30]	2						•		•					✓												•	7 mo	–
Cole et al[14]	41		•		•				•				✓	✓			✓	✓	✓		✓				•		2-18 mo	–
Driver et al[21]	8[#]		•	•	•	•			•				✓		✓							•					–	–
Ennis et al[32]	133			•					•				✓	×	✓			✓	×	×			•				12 wk	3 mo
Ennis et al[18]	29			•		•			•			✓	✓		✓										•		20 wk	–
Escandon et al[23]	10					•			•				✓			✓				×	✓				•			
Fleming et al[33]	1						•		•			✓									✓					•	10 wk	–
Gehling and Samies[22]	15					•	•		•												✓				•		2-4 wk	–
Herberger et al[26]	62					•		•						✓			✓				✓	•					2-12 d	–
Li et al[12]	38	•									•		✓		✓					✓	✓			•			2 wk	–
Kavros and Schenck[31]	51			•		•			•			✓	✓												•		3-8 wk	–
Kavros et al[17]	70					•			•				✓									•					12 wk	–
Kavros et al[16]	210			•	•	•			•			✓			✓										•		90 d	3 mo
Maher et al[20]	2					•				•			×					✓							•		2-3 wk	–
Norris and Henchy[29]	4						•		•				✓	✓				✓								•	7-11 wk	–
Samuels et al[10]	20					•					•	✓			✓										•		?[d]	–
Selkowitz et al[9]	1				•						•				×										•		4 wk	–
Stanisic et al[7]	3				•	•		•													✓					•	1 d	–
Tan et al[19]	19					•	•	•					✓												•		12 wk	–
Thomas et al[27]	6				•				•						✓										•		4 wk	–
Voigt et al[3]	8[c]	•		•	•	•		•	•		•				✓							•					–	–
Wollina et al[11]	12					•					•						✓								•		?	–
Yao et al[15]	12			•					•				✓			✓									•		5 wk	–

Abbreviation: RCTs, randomized controlled trials.

[a]Sickle cell anemia (Breuing et al[2]; Gehling and Samies[22]; and Tan et al[19]), unspecified (Norris and Henchy[29]), Hay-Wells syndrome (Caswell and McNulty[30]), limited cutaneous systemic sclerosis (Fleming et al[33]), rheumatoid ulcer (Tan et al[19]).

[b]Interleukin/proteinase/growth factor.

[c]RCTs.

[d]Missing information/not specified.

to longer treatment (45 minutes of 20 kHz of ultrasound) or treatment at higher frequency (15 minutes of 100 kHz ultrasound).[10] Work by Wollina et al[11] also found superior healing with treatment frequency at the lower end of the spectrum (34 kHz was superior to 53.5 and 75 kHz and significantly increased oxygen saturation and superficial hemoglobin concentration in 12 patients). Treatment of residual burn wounds every other day with 25 kHz low-frequency ultrasound over a period of 2 weeks resulted in 100% wound healing and increased healing rate.[12] All wounds included were of an average of 3 months old. Based on these studies, low-frequency ultrasound appears to work best when applied at the lower end of the frequency spectrum.

How Often Should Debridement Occur?

Studies by Bell and Cavorsi[13] and Cole et al[14] on chronic wounds of heterogeneous nature support treatment frequency of $\geq$2 times per week with level 4 evidence. MIST Therapy 3 times a week resulted in a statistically significant reduction in wound area, when compared to standard care or treatment once a week.[15] MIST therapy 3 times weekly also resulted in a greater proportion of patients achieving complete healing at a faster rate.[16-18] The treatment frequency (3 times per week) was maintained in all 3 studies for 12 weeks and resulted in greater healing and shorter healing time. Less frequent treatments appear to have variable outcomes, even if they are maintained for long periods: Tan et al examined chronic ulcers of venous, rheumatoid, and sickle cell origin. In conjunction with compression bandage, debridement was performed once every 2 to 3 weeks, over a minimum of 12-week duration. The authors found that if healing did not occur within 5 treatments, subsequent treatment did not yield additional benefit.[19]

Effect of Ultrasound on Wound Healing

Exudate and slough. The effect of ultrasound treatment on wound exudate and fibrin slough was noted by several authors. Treatment using the Quostic system resulted in improvement in wound condition (including a significant decrease in slough on wound surfaces) over a 2- to 3-week period.[20] The MIST therapy in conjunction with standardized care was also reported to decrease exudate and fibrin slough.[13,18] Cole et al[14] also noted significant decrease in erythematous and edematous skin, undermining, tunneling, and odor and a decrease in clinical evidence of infection.

Wound closure. Ultrasound debridement with MIST therapy affects wound size and rate of closure. In a nonrandomized, baseline-controlled clinical case series, patients showed significant reduction in wound size and a greater rate of closure with ultrasound therapy.[17] Two large meta-analyses also suggest ultrasound has a positive impact on wound size.[3,21] Pooled results presented by Driver et al[21] suggest an average of 85.2% wound area reduction over an average of 7 weeks, 79.7% wound volume reduction over 12 weeks, and an average time to heal of 9.2 weeks. In a large study done by Ennis et al, a 69% of wounds were healed using ultrasound as a stand-alone device or in combination with moist wound care, with significant reduction in wound volume and shorter healing time.[18]

Pain. Contrary to sharp and mechanical debridement techniques, ultrasound therapy is generally considered to be painless.[14] Furthermore, treatment with MIST Therapy was found to reduce patients' pain in a study of 15 ulcers of vascular ischemia, sickle cell anemia, and venous stasis origin.[22] Driver et al[21] also found an average reduction of 79% in subjective pain score in patients receiving ultrasound therapy. Patients also reported a decrease of almost 3 points on the subjective pain score following ultrasound treatment in a study by Cole et al.[14]

Mechanism of action. Few studies go beyond clinical measures of wound healing to explore the underlying mechanisms induced by ultrasound therapy. In 1 study, 10 patients with venous leg ulcers were treated with MIST Therapy 3 times a week over a 4-week period.[23] All patients had significant reduction in wound size and reduced pain, but the authors also report decreased tumor necrosis factor α; interleukins 1, 6, 8, and 11; and vascular endothelial growth factor compared to baseline values. A significant correlation between reduced wound size and decreased inflammatory cytokine expression was found. Samuels et al also report increased wound healing with ultrasound therapy correlated with a finding of increased cellular proliferation *in vitro*.[10] These authors also observed a trend of reduction in cytokines, matrix metalloproteinase, growth factor, and macrophage with treatment.

Effect on biofilm. Biofilms in chronic wounds are major barriers to healing, but techniques to assess microbial burden and species diversity *in vivo* in a clinical setting are currently underdeveloped. Ultrasound is thought to disperse biofilms *in vitro*,[24] but techniques to monitor these effects *in vivo* are limited. In 1 study that did assess total viable counts derived from tissue biopsy, there was no significant reduction in bacterial count over the treatment period.[23] However, it is widely recognized that culture-based techniques significantly underestimate the bioburden in a clinical sample.[25] This is especially true for wound swabs that have a limited role in wound care. We hypothesize that ultrasound may be having an effect on species of bacteria not readily cultured under laboratory conditions. Moreover, dispersal of the biofilm (without affecting bacterial viability) is a recognized therapeutic strategy. Once the biofilm is dispersed, bacteria become more sensitive to antibiotics and vulnerable to immune clearance.

Is Ultrasound Debridement Better Than The Current Standard of Care?

Unlike most studies that compared ultrasound debridement to standard treatment, Herberger et al compared contact ultrasound (Sonica 180) to surgical debridement (Stiefel ring curette). Sixty-two patients with vascular ulcers were randomly allocated

to unblinded treatment 3 times over the course of 4 to 12 days. Overall, no differences between the modalities were observed. Both were deemed to be effective tools that significantly reduced fibrin, increased granulation, and improved quality of life.[26] A meta-analysis of randomized controlled trials (RCTs) identified 8 studies published from 1997 to 2011 that compared traditional sharp debridement to ultrasound.[3] At high frequency, ultrasound performed better than sharp debridement, with complete healing that was sustained up to a treatment period of 5 months in diabetic foot ulcers and venous stasis ulcers. In the same meta-analysis, low-intensity ultrasound treatment over a 3-month treatment period achieved greater healing when compared to sham treatment, also in diabetic foot ulcers and chronic venous ulcers.

However, the results of ultrasound therapy are not universally positive. Although 1 retrospective case study of 6 patients with stage II pressure ulcers found accelerated healing with MIST Therapy 4 times/wk,[27] a second study found no difference in healing rate between treatment and control.[9] In a single-arm, prospective study, 17 participants with varying wound etiology were treated with the Sonica 180 system with variable frequencies over a 3- to 8-month period.[2] The authors noted ulcers of pressure, arterial insufficiency, and surgical etiology responded better than venous stasis and diabetic origin. However, a direct comparison of such different wound types in a heterogeneous patient population is difficult at best.

Discussion

The current body of evidence supports the use of low-frequency ultrasound as adjunctive therapy at least 3 times a week in the treatment of chronic wounds. However, the majority (21 of 25 studies) of the evidence is limited by study design, representing mostly level 3 to level 5 evidence. There are several factors that make comparisons of these studies difficult. First, this review identified 8 distinct types of ultrasound debridement tool, raising uncertainties regarding the efficacies and mechanism of action of each tool. Currently, the majority (19 of 25) of studies have evaluated the MIST Therapy system. The use of this modality is further supported by the meta-analysis of Driver et al.[21] One of the major limitations of the study, however, was its inability to discern the efficacy of treatment on different types of wound etiology due to the lack of sufficient study numbers for the pooling of data. This limitation also rings true for all other ultrasound modalities due to the lack of well-designed clinical trials.

The likely reason behind the scarcity of clinical trials is an economic evaluation of an RCT of ultrasound therapy for venous leg ulcers.[28] This study, published in the *British Journal of Surgery*, was a multicentre trial designed to assess the cost-effectiveness of low-dose ultrasound therapy. The authors concluded that ultrasound therapy provided no benefits over standard care but was likely to be more costly, with a recommendation against adopting the modality in the British National Health System. However, this report should be evaluated with caution based on several limitations. First, the ultrasound system that was used in this study has not been evaluated separately by other studies. Second, the dosing of the ultrasound was reported to be at 1 MHz, which is considered a high-frequency treatment modality. Our review of the literature suggests that sound frequencies between 20 and 34 kHz yield best results. Finally, the application of such device was only evaluated on venous leg ulcers,[28] which require multimodal care such as compression and offloading as adjuncts to debridement to fully heal their wounds. Ultrasound debridement has a role to play in wound care, but elucidating its mechanism of action, effect on biofilms, and treatment parameters for debridement and postdebridement are part of the current research trajectory. Outcome measures are improving in wound care, and sound clinical research is improving our knowledge in the area of chronic wounds

Chronic wound healing continues to pose great resource and financial stress on health-care systems worldwide. With an aging population and increasing prevalence of chronic health conditions such as diabetes and cardiovascular diseases, treatment protocols addressing associated chronic wounds are urgently needed. Future studies should stratify patients according to comorbidities. Patients with chronic wounds tend to be geriatric patients with a multitude of conditions that needs to be considered to further understand the inherent challenges of their healing trajectory. Nutrition, smoking, and general health also need to be implemented as a part of the study design, as it is an integral part of multifaceted care needed by this population.

Declaration of Conflicting Interests

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