Debridement par ultrasons à basse fréquence dans la guérison chronique des plaies

Examen systématique des données probantes actuelles Les blessures chroniques sont douloureuses et débilitantes pour les patients, posent un défi clinique aux médecins et imposent un fardeau financier au système de santé. De nouvelles options de traitement sont donc très recherchées. Le débridement par ultrasons est une technologie prometteuse qui fonctionne pour disperser les biofilms bactériens et stimuler la guérison des plaies. Dans cette revue, nous nous concentrons sur l’échographie basse fréquence (20-60 kHz) et résumons les résultats de 25 études récentes portant sur l’efficacité de l’échographie. Le débridement par ultrasons semble être le plus efficace lorsqu’il est utilisé 3 fois par semaine et a le potentiel de diminuer l’esudat et le slough, de diminuer la douleur du patient, de disperser les biofilms et d’augmenter la guérison dans les plaies d’une étiologie différente. Bien que les études actuelles soient en général de moindre envergure, les résultats sont prometteurs et nous recommandons de tester l’échographie à basse fréquence en pratique clinique à plus grande échelle.

Low-frequency ultrasound debridement in chronic wound healing: A systematic review of current evidence

Ying-Ju Ruby Chang¹, Julie Perry¹, Karen Cross MD, PhD, FRCSCT

The prevalence of chronic wounds (arterial, venous, pressure, DFU, iatrogenic) is estimated to be anywhere between 3-26% of the Canadian population (CIHI, 2013). The prevalence of wounds in patients with diabetes is even higher, and is estimated to be 11-34%. 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 the costs to the healthcare system for the treatment of diabetic foot ulcers alone is more than $150 million CDN annually (www.cawc.net/index.php/public/facts-stats-and-tools/statistics). 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 tissue, but also increases exudate, which perpetuates the vicious cycle.

The prevalence of chronic wounds has been guided by the TIME framework (tissue debridement, inflammation control, moisture balance, and epithelialization of wound edges). 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, producing prolonged elevated levels of protease and reactive oxygen species. This inefficient inflammatory process not only hinders healing of damaged tissue, but also increases exudate, which perpetuates the vicious cycle.

The prevalence of chronic wounds is even higher, and is estimated to be 11-34%. 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 the costs to the healthcare system for the treatment of diabetic foot ulcers alone is more than $150 million CDN 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. It is imperative that 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 etiologies. While current studies are generally of smaller scale, the results are promising and we recommend the testing of low frequency ultrasound therapy in clinical practice on a larger scale.

Key Words: Debridement; Low-frequency ultrasound; Bacterial biofilm; Chronic wound

METHODS

Searches were performed in Ovid MEDLINE, Ovid EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Agency for Healthcare Research & Quality (AHRQ), and Google Scholar. The following keywords were searched in each of the databases: ultrasound, debridement, wound healing, and biofilm. The references section of each article was searched for intracellular calcium, collagen deposition and wound tensile strength, and reduce wound size [reviewed in (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 pre-clinical 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.

Figure 1) Summary of the work flow for study selection/exclusion

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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 two reviewers (RC and KC) 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).

Using the criteria established by the Oxford Centre for Evidence-based Medicine (OCEBM Levels of Evidence Working Group, 2011), 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 non-contact ultrasound debridement tool that transmits low intensity and low frequency acoustic energy through a constant flow of saline mist (www.misttherapy.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.arobella.com/products/qoustic-description.html), and several studies utilized original ultrasound modalities that are not commercially available. All ultrasound modalities discussed use frequencies between 2060 kHz.

Samuels et al reported complete healing of ulcers using 15 minutes of 20 kHz ultrasound, which was found to be superior to longer treatment (45 minutes of 20KHz of ultrasound) or treatment at higher frequency (15 minutes of 100 kHz ultrasound) (10). Work by (11) also found superior healing with 180 kHz ultrasound, which was found to be superior to longer treatment (45 minutes of 20-60 kHz).

**TABLE 1**

**Summary of the evidence supporting low-frequency ultrasound debridement as an adjunctive therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Wound Etiology</th>
<th>Ultrasound Modality</th>
<th>Healing</th>
<th>Antimicrobial</th>
<th>Pain</th>
<th>Level of evidence</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell &amp; Cavorsi, 2008</td>
<td>76</td>
<td>Burn Wounds</td>
<td>MIST Therapy System</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>2w</td>
<td>4.3w</td>
</tr>
<tr>
<td>Breuing et al, 2005</td>
<td>17</td>
<td>Pressure Ulcer</td>
<td>MIST Therapy System</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>3-8m</td>
<td>7m</td>
</tr>
<tr>
<td>Caswell &amp; McNulty, 2008</td>
<td>2</td>
<td>Other</td>
<td>Sonica 180</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>1-2w</td>
<td>12w 3m</td>
</tr>
<tr>
<td>Cole et al, 2009</td>
<td>41</td>
<td>Diabetic Ulcer</td>
<td>Quostic</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>2-18m</td>
<td>20w</td>
</tr>
<tr>
<td>Driver et al, 2011</td>
<td>8*</td>
<td>Arterial Venous Insufficiency</td>
<td>Quostic</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>3-8m</td>
<td>3-8m</td>
</tr>
<tr>
<td>Ennis et al, 2005</td>
<td>133</td>
<td>Other</td>
<td>MIST Therapy System</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>12w</td>
<td>2w</td>
</tr>
<tr>
<td>Ennis et al, 2006</td>
<td>29</td>
<td>Arterial Venous Insufficiency</td>
<td>MIST Therapy System</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>2w</td>
<td>20w</td>
</tr>
<tr>
<td>Escandon et al, 2012</td>
<td>10</td>
<td>Other</td>
<td>MIST Therapy System</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>10w</td>
<td></td>
</tr>
<tr>
<td>Fleming et al, 2008</td>
<td>1</td>
<td>Burn Wounds</td>
<td>MIST Therapy System</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>2-4w</td>
<td>2-4w</td>
</tr>
<tr>
<td>Gehling &amp; Samilies, 2007</td>
<td>15</td>
<td>Pressure Ulcer</td>
<td>MIST Therapy System</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>2-12d</td>
<td>2-12d</td>
</tr>
<tr>
<td>Herberger et al, 2011</td>
<td>62</td>
<td>Other</td>
<td>MIST Therapy System</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>2w</td>
<td></td>
</tr>
<tr>
<td>Li et al, 2009</td>
<td>38</td>
<td>Burn Wounds</td>
<td>Sonica 180</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>2w</td>
<td></td>
</tr>
</tbody>
</table>

**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 >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 (13). MIST therapy 3 times weekly also resulted in a greater proportion of patients achieving complete healing at a faster rate in studies by Cavorsi et al and Ennis et al (16-18). The treatment frequency (3 times per week) was maintained in all three 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 (19) 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).

**Effects 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 with the Quostic system resulted in improvement in wound condition (including a significant decrease in slough on wound surfaces) over a 2-3 weeks period (20). MIST therapy in conjunction with standardized care was also reported to decrease exudate and fibrin slough by (13,18). Cole et al 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 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.
A Review of Low-Frequency Ultrasound Debridement

Kavros & Schenck, 2007  51  •  •  •  •  √  √  3-8w —
Kavros et al., 2007  70  •  •  •  •  •  •  12w —
Kavros et al., 2008  210  •  •  •  •  •  •  90d  3m
Maher et al., 2014  2  •  •  •  •  •  •  2-3w —
Norris & Henchy, 2010  4  •  •  •  •  •  •  7-11w —
Samuels et al., 2013  20  •  •  •  •  •  •  •  ? —
Selkowitz et al, 2002  1  •  •  •  •  •  •  4w —
Stansic et al, 2005  3  •  •  •  •  •  •  1d —
Tan et al, 2007  19  •  •  •  •  •  •  12w —
Thomas et al, 2008  6  •  •  •  •  •  •  4w —
Voigt et al, 2011  8*  •  •  •  •  •  •  •  •  — —
Wollina et al, 2011  12  •  •  •  •  •  •  •  •  — —
Yao et al, 2014  12  •  •  •  •  •  •  5w —

* Sickle Cell Anemia (2,19,22) unspecified (Norris & Henchy, 2010), Hay-Wells Syndrome (Caswell & McNulty, 2008), Limited Cutaneous Systemic Sclerosis (Fleming, 2008), rheumatoid ulcer (19). ** Interleukin/Proteinase/ Growth Factor, # RCTs, — None, ? Missing information/ not specified

A Review of Low-Frequency Ultrasound Debridement

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 (Cole et al., 2009). 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 one 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 TNF alpha, IL-1, 6, 8, 11, and VEGF 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 to 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 one 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 which 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 better than standard of care
Unlike most studies that compared ultrasound debridement to standard treatment, Herberger et al (26) compared contact ultrasound (Sonica 180) to surgical debridement (Stiefel ring curette). 62 patients with vascular ulcers were randomly allocated to unblinded treatment 3 times over the course of 4-12 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 identified eight 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 months 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. While one retrospective case study of 6 patients with stage II pressure ulcers found accelerated healing with MIST Therapy 4 times/week (27), a second study found no difference in healing rate between treatment and control (9). In a single-arm, prospective study 17 subjects with varying wound etiology were treated with the Sonica 180 system with variable frequencies over a 3 to 8-months 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 wounds 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 of the evidence (21 of 25 studies) is limited by study design, representing mostly level 3 to 5 level evidence. There are several factors that make comparisons of these studies difficult. Firstly, 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 of studies (19 of 25) have evaluated the MIST Therapy system. The use of this modality is further supported by the meta-analysis of (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 multicenter 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 costlier, 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. Firstly, the ultrasound system that was used in this study has not been evaluated separately by other studies. Secondly, 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 20-34 kHz yield best results. Lastly, 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 post debridement are part of the current research trajectory. Outcome measures are improving in wound care and sound clinical research are 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 like 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 needs to be implemented as a part of the study design, as it is an integral part of multifaceted care needed by this population.

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