Evidence Table


Study Type: Randomized controlled trial.
Study Aim: To determine the safety and efficacy of a noncontact kilohertz-range ultrasound therapy (MIST therapy) for the treatment of recalcitrant diabetic foot ulcers.

Outcomes

Primary: Wound closure, defined as complete re-epithelization without drainage, during study period.

Design

- **Number of subjects**: N=133 randomized, N=55 included in the analysis (N=27 in the ultrasound group, and n=28 in the sham treatment group).
- **Description of study population**: The trial included 133 patients from 23 sites in the United States and Canada, however characteristics were provided for only the 55 patients included in the analysis. Ultrasound group: Mean age 56 years, 48% men, 63% White, 30% Black, 67% never smoked, mean size of index ulcer at baseline 1.7 cm², and mean duration of the ulcer 35 days (range 5-104). Sham treatment Group: Mean age 54 years, 68% men, 71% White, 21% Black, 68% never smoked, mean size of index ulcer at baseline 4.4 cm², and mean duration of the ulcer 67 days (range 4-521).
- **Inclusion criteria**: Patients ≥18 years of age, with type 1 or type 2 diabetes and a Wagner grade 1 or 2 diabetic foot ulcers located on the plantar surface and with >30 days duration and without tendons, ligaments, or bone exposure, recorded glycosylated hemoglobin ≤12 within 30 days of the study start date. Wound sizes were required to be >1cm² and <16 cm², and patients had to be ambulatory ≥75% of the time with weight bearing on the index foot.
- **Exclusion criteria**: Secondary ulcers, higher-grade ulcers with exposed tendons, ligaments, or bone, gangrene, received radiation or chemotherapy within 6 months before the trial, signs and symptoms of wound infection at the time of enrollment, taking antibiotics for or growth factors within the past 7 days, pregnancy, anemia, renal failure, malnutrition, malignancy, and several other exclusion criteria.
- **Intervention**: Baseline sharp wound debridement followed by quantitative culture biopsies was completed for all subjects who then received saline-moistened gauze for a 7-day washout period. Those with <30% reduction in wound area were randomized to receive 4-minute treatments 3 times weekly with active ultrasonic therapy using the MIST therapy system (Celleration Inc., Eden Prairie, MN.) or a sham device. Additional wound debridement was completed during treatment if deemed necessary by the clinician at each weekly assessment. Patients in the two treatment groups received the wound standard care. Topical wound care consisted of a contact layer that applies directly to the wound and secured with hypoallergenic tape, saline-moistened gauze, a layer of dry gauze, and an optional layer of petroleum impregnated gauze. Complete dressing changes were done 3 times weekly at the clinic and the secondary dressing was changed twice per day by the patient or a family member. All subjects used a fixed ankle-foot walker, and received the appropriate diabetes management.
• **Source of outcome data:** Weekly evaluation of the wound including wound photography, and a limited physical exam. The skin and wounds were assessed for exudates, quantity and quality of granulation tissue, eschar fibrin, and slough.

• **Length of follow-up:** Maximum of 12 weeks, healed wounds were followed up for 12 more weeks.

**Validity**

• **Blinding?** Outcome assessment was blinded. However, the clinicians who delivered the therapy were not.

• **Appropriate randomization procedures?** Yes.

• **Appropriate comparison intervention?** Yes.

• **Treatment/control groups comparable at baseline?** No there were several baseline differences between the two groups, mainly in the statistically significant larger size of and duration of the index ulcers in the sham therapy group.

• **Other than intervention, was care/follow-up similar in each group?** Additional wound debridement was performed according to the clinician’s discretion at the weekly assessment.

• **Adequate compliance with intervention?** Not provided.

• **Sufficient statistical power?** No discussed.

• **Intention to treat analysis?** Yes.

• **Completeness of follow-up:** Only 41% of the randomized patients were followed up for the study duration and included in the analysis.

• **Industry funding?** Yes.

**Conclusions regarding validity of methods:**

The trial had several limitations including but not limited to very high drop out rate, only 59% of the randomized patients were included in the final analysis. In addition, there were several baseline differences between the two study groups, with the index ulcers in the sham therapy being significantly larger (mean 4.4 cm² vs. 1.7 cm²) and of longer duration (mean 67 vs. 35 days) than those in the ultrasound group. The patients and investigators who assessed the wounds were blinded; however the clinicians who performed the procedures were not. Additional debridement was performed during treatment if deemed necessary by the clinician at each weekly assessment.

**Results**

*Proportion of wounds healed at 12 weeks, and healing times*

<table>
<thead>
<tr>
<th></th>
<th>Ultrasound group</th>
<th>Sham therapy group</th>
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</thead>
<tbody>
<tr>
<td><strong>Completer analysis</strong></td>
<td>n=27</td>
<td>n=28</td>
<td></td>
</tr>
<tr>
<td>Wound closed* No. (%)</td>
<td>11 (40.7 %)</td>
<td>4 (14.3%)</td>
<td>0.036*</td>
</tr>
<tr>
<td>Time to healing, weeks, mean (SD)</td>
<td>9.2 (0.58)</td>
<td>11 (0)</td>
<td>&lt;0.014</td>
</tr>
<tr>
<td><strong>ITT analysis</strong></td>
<td>n=70</td>
<td>n=63</td>
<td></td>
</tr>
<tr>
<td>Wounds closed, No. (%)</td>
<td>18 (26.0%)</td>
<td>14 (22.0%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NNT 4 among those who completed the study “efficacy population”

Only one of the closed wounds in the ultrasound re-opened in an additional 12 weeks of follow-up (none reopened in the control group)
There were no significant differences between the 2 groups in amount or frequency of debridement.

**Adverse events* (ITT analysis)**

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<th></th>
<th>Ultrasound group n=70</th>
<th>Sham therapy group n=63</th>
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</thead>
<tbody>
<tr>
<td>Mild</td>
<td>57 (51%)</td>
<td>38 (46%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>46 (41%)</td>
<td>32 (39%)</td>
</tr>
<tr>
<td>Severe</td>
<td>8 (7%)</td>
<td>12 (15%)</td>
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* Included cellulitis, development of additional wounds on the index foot, pain, drainage, and erythema. There was no significant difference between the two groups.

**Authors’ Conclusions**

The authors concluded that the results of the trial show that ultrasound therapy, when appropriately used, is a useful adjunct to the standard of care for the treatment of diabetic foot ulcers, and that it increased the ulcer healing time when compared to sham therapy.

**Reviewer’s Conclusions**

The trial was randomized and controlled, but had several methodological flaws which limit generalization of its results. The study had a very low completion rate due to dropouts or violations of the protocol, and there were significant baseline differences in the ulcer size and duration between patients in the two treatment groups. The results show significant difference in the wound closure favoring the ultrasound group when the analysis included only those who completed the trial, but no significant difference was observed when the analysis was based on intention to treat analysis.

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