High-frequency and Noncontact Low-frequency Ultrasound Therapy for Venous Leg Ulcer Treatment: A Randomized, Controlled Study

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Abstract
Ultrasound therapy can be utilized to manage chronic wounds, including venous leg ulcers (VLUs). A randomized, controlled clinical study was conducted to compare the effectiveness of standard treatment and standard treatment plus either high-frequency ultrasound (HFU) or noncontact low-frequency ultrasound (NCLFU) on VLU outcomes. Ninety (90) outpatients (47 men, 43 women, average age 38.3 [SD 11.5] years) were randomized into the standard care (n = 30), HFU (n = 30), or NCLFU group (n = 30). Standard care included multilayered compression bandaging (40 mm Hg of pressure at the ankle graduated to 17 mm Hg to 20 mm Hg below the knee), nonadherent dressing, and regular debridement. Standard care dressing changes and ultrasound therapy were provided three times per week for 3 months or until healed. HFU delivers high-intensity (0.5–1 W/cm²), high-frequency (1–3 MHz) ultrasound for 5 to 10 minutes; and NCLFU delivers low-intensity (0.1–0.8 W/cm²), low-frequency (40 kHz) ultrasound for 4–10 minutes. After 3 months, patients continued to be followed until healed. Wound size, wound pain, and lower leg edema were assessed at baseline and after 2 and 4 months. Data were analyzed using Student’s t-test, ANOVA, chi-square, or Fisher’s exact test. \( P < 0.05 \) was considered significant. Initial wound measurements were 9.60 cm² (SD 5.54), 9.86 cm² (SD 3.95), and 10.01 cm² (SD 4.58) for the standard treatment, HFU, and NCLFU groups, respectively; after 4 months, measurements were 4.28 cm² (SD 2.80), 3.23 cm² (SD 2.16), and 2.72 cm² (SD 2.16), a statically significant difference \( (P = 0.04) \). All wounds were healed after an average of 8.50 (SD 2.17), 6.86 (SD 2.04), and 6.65 (SD 1.59) months in the standard treatment, HFU, and NCLFU groups, respectively \( (P = 0.001) \). Differences in the amount of edema and pain rating scores were also significant at the 4-month follow-up visit \( (P < 0.05) \). Outcomes of both methods of ultrasound therapy were better than standard care alone, and some differences between the two ultrasound therapy groups were observed, but they were not statistically significant.

Keywords: controlled clinical study, ultrasonic therapy, venous leg ulcers, pain, edema


Potential Conflicts of Interest: none disclosed

Venous leg ulcers (VLUs) are a frequent and persistent challenge in clinical wound care. According to Moffatt and Dorman, in 2003 the estimated global prevalence of VLU was 0.1% to 1.1%. The literature indicates that the recurrence rate of this disorder is 70%, the majority reoccur within 3 months of healing, and that VLUs occur most frequently in women and the elderly. Although the mechanisms that initiate and maintain VLUs remain uncertain, venous hypertension is associated with venous occlusion and insufficient veins or dysfunctional valves. A growing number of therapeutic approaches is available, but controversy about timing and duration of therapy persists. Also, because patients may be treated in multiple centers or settings, provision of care may be inadequate, costly, and inefficient due to problems with collection of detailed medical records, communication between therapeutic centers, and assessment of ultimate care outcomes and wound healing rates.

Therapeutic approaches. A systematic review of 48 randomized controlled trials (4,321 participants in total) showed high-compression bandaging is an effective treatment that reduces edema, reverses venous hypertension, and improves calf muscle pump function. Several treatment options can be employed as adjuvant to compression, including...
systemic therapy with pentoxifylline or aspirin, moisture-retentive dressings, autologous grafts, tissue-engineered skin, growth factor therapy, and/or vein surgery. Additionally, some clinical trial study of electrical stimulation, pulsed electromagnetic induction, negative pressure wound therapy, and high-frequency, pulsed-current ultrasound showed these noninvasive treatment options may facilitate chronic wound healing and can be used to stimulate normal physiological responses to injury to aid repair.

Ultrasound. In recent years, in a randomized control clinical trial, ultrasound therapy was utilized in the management of chronic wounds. Although high-frequency ultrasound (HFU) (1–3 MHz) has been used in clinical practice in most studies and has been shown to promote healing in some injuries, according to results of randomized, controlled, clinical trials, heat from this electrical devise can cause hot spots, burns, or endothelial injury; as such, use is limited in medical practice.

Noncontact, low-frequency ultrasound (NCLFU) therapy is among the newer modalities. It operates at a markedly lower frequency (40 kHz) and was approved for use in the wound care setting by the US Food and Drug Administration (FDA) in 2005 as a Class II device and received marketing clearance (K050129). Low-frequency ultrasound has been shown in vitro to mainly provide mechanical debridement; in noncomparative clinical outcomes trial, low-frequency ultrasound was found to have the potential to improve wound healing via the production, vibration, and movement of micron-sized bubbles in the coupling medium and tissue, which prepares the wound bed for healing by reducing biofilm burden, enhancing angiogenesis, assisting in debridement of necrotic and devitalized tissues, and stimulating cellular activity. According to an in vitro study, NCLFU therapy in the initial inflammatory stage also may promote tissue repair, with few adverse effects noted.

With current increases in longevity, including among persons with various wound types, VLUs are expected to place a great burden on healthcare systems. Controlling the previously described conditions and reining in costs of care will require the identification of accurate and appropriate strategies.

The purpose of this study was to evaluate the effectiveness of HFU and NCLFU therapy compared to standard care in patients with VLUs.

Methods

Patients. From April 2011 to April 2012, patients diagnosed with VLUs were assessed in the vascular and radiology clinics of Ali ebn-Abitaleb Hospital (Zahedan, Iran). Patients were enrolled if they had a wound duration >4 weeks and no clinical improvement after using the clinic’s standard care for healing during a 2-week period. Patients were excluded based on the following criteria: pregnancy, allergy to ultrasound contact gel, the presence of known ultrasound contraindications (ankle or knee prosthesis or metal in the lower leg; suspected or confirmed local cancer or metastatic disease and neuropathy; or clinical evidence of infection including suspicious thrombophlebitis, active cellulitis), and a history of antibiotic therapy at the time of enrollment. Persons with rheumatoid arthritis, diabetes, or peripheral arterial disease as indicated by an ankle brachial pressure index (ABPI) <0.8 confirmed by Doppler ultrasound and signs of arterial disease such as ulcers with a “punched out” appearance base of wound poorly perfused, pale, dry, and cold legs/feet (in a warm environment), shiny, taut skin dependent rubor, pale or blue feet, and gangrenous toes also were excluded.

Ethical approval. The study was approved by the ethics committee of the university before its initiation, and the protocols used conformed to the ethical guidelines of the 1975 Helsinki Declaration. All enrolled patients provided written informed consent.

Study protocol. Patients who were eligible to participate were randomized to the standard treatment group, HFU group, or NCLFU group following a centralized randomization schedule using sealed opaque envelopes containing computer-generated random numbers. Patients then received a code for anonymity available to the two investigators responsible for collecting data.

Investigators documented patient demographic information; medical, surgical, and leg ulcer history; and a detailed wound description. A wound assessment only was completed after 1 month, and all variables were assessed at the start of the study and after 2 and 4 months of treatment. Continuous ulcer pain was assessed using a numerical rating scale in which the patient was instructed to choose a number from 0 for no pain to 20 for unbearable pain. To assess leg edema, the investigator pressed a fingertip against a bony prominence for 5 seconds and then removed it. A residual indentation indicated pitting edema, which was graded on a scale of 1 (mild) to 4 (severe). Wound surface was measured by
tracing the margins of the open wound and measuring the two maximum perpendicular axes (length x width). Local findings and side effects were recorded after each treatment and in monthly visits.

After 4 months until complete wound healing was achieved (ie, 100% re-epithelialization and size of ulcer = 0 cm²), patients were instructed to visit the vascular clinic monthly to record healing.

All groups received standard wound care three times per week for 3 months or until healing. In groups where participants received standard wound care plus ultrasound, HFU therapy or NCLFU therapy was administered to wounds three times per week for 3 months or until healing was achieved as noted by the physician and expert nurse.

**Standard wound care.** Standard treatment for VLUs included compression bandaging, nonadherent dressing, and debridement. Patients with open ulcerations were treated three times per week for 3 months or until healed with nonadherent dressing and multilayered compression bandaging (Smith and Nephew, Hull, UK) aiming for achieving 40 mm Hg of pressure at the ankle, graduated to 17 mm Hg to 20 mm Hg at the upper calf. Also, sharp debridement was performed twice weekly by a trained nurse and physician using surgical instruments, including scalpel, scissors, and curette if necessary (according to a decision as to whether necrotic tissue should be left in situ).

Patients with healed ulcers were prescribed class 2 elastic stockings (Medi, Hereford, UK) and advised to wear these during the day. All patients were given standard written and verbal advice to elevate the affected leg and to exercise.

**HFU therapy.** HFU therapy was applied with a SoLo Therasonic 355 machine (EMS Physio, Wantage, UK). This device delivers high-intensity (0.5–1 W/cm²), high-frequency (1–3 MHz) ultrasound. The ultrasound transducer head was sterilized with alcohol wipes. Ultrasound was applied for 5–10 minutes to the skin surrounding the reference ulcer using a water-based contact gel recommended by the manufacturer. The transducer head was moved in a slow, controlled manner around the edges of the ulcer in overlapping circles to cover the skin evenly. Ulcers <5 cm² in area received ultrasound for 5 minutes; ulcers ≥10 cm² in area received 10 minutes of ultrasound. For ulcers between 5 cm² and 10 cm², treatment time in minutes equaled the ulcer area in cm² (ulcer of 6 cm² area = 6 minutes of treatment).

**NCLFU therapy.** NCLFU therapy was applied with a Celleration MIST Therapy™ System 5.1 (Celleration, Inc, Eden Prairie, MN). This device delivers low-intensity (0.1–0.8 W/cm²), low-frequency (40 kHz) ultrasound energy to the wound bed via atomized, sterile saline mist without directly contacting the body or the wound. The device consists of a unit with a transducer, generator, and disposable applicator that uses prepackaged sterile saline. The applicator contains a valve that controls the flow of saline to the transducer surface. The product’s recommended treatment algorithm is to apply in a manner similar to HFU and is based on longer treatment times for greater total ulcer area. For NCLFU, treatment time per session is dependent on the total ulcer area. In general, treatment time increases as total ulcer area increases. The manufacturer’s treatment algorithm for the NCLFU system covers ulcer areas from <10 cm² to 180 cm², with treatment times ranging from 3–20 minutes. The study protocol at the authors' facility is to treat wounds up to 4 cm² with 4 minutes of NCLFU therapy; ulcers ≥10 cm² in area received 10 minutes of ultrasound. For ulcers between 4 cm² and 10 cm², treatment time in minutes equaled the ulcer area in cm² (ulcer of 5 cm² area = 5 minutes of treatment).

**Data collection.** All data collected were extracted from the patient record and included demographic data; documentation of wound size, pain, and edema; and any side effects of treatment on a regular basis as completed by investigators using a wound data template. Also, after 4 months, investigators recorded progress every month until time of complete wound healing.

**Statistical analysis.** The statistical evaluation was performed by computer analysis using SPSS Software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL). Student’s t-test, ANOVA, chi-square, or Fisher’s exact test were used to test for statistical significance in differences between outcomes. Averages and standard deviations were computed for continuous data; \( P < 0.05 \) was considered significant.

**Results**

Of the 228 clinic patients eligible for screening, 32 had peripheral arterial disease, 18 were pregnant, 36 had metal in the lower leg, three had metastatic cancer, 19 had history of antibiotic therapy at the time of enrollment, 18 had diabetes, six had rheumatoid arthritis, and six did not consent to the study. Ultimately, 90 patients with VLUs (47 men and 43 women, age 38.3 [SD 11.5] years) provided informed consent and participated in the study. Demographic patient variables and clinical characteristics did not differ significantly among the three study groups, each with 30 patients (see Table 1).

Mean ulcer size at the first clinic visit was 9.60 cm² (SD 5.54) in the standard, 9.86 cm² (SD 3.95) in the HFU, and 10.01 cm² (SD 4.58) in the NCLFU group. After 4 months of treatment, the average ulcer sizes were 4.28 cm² (SD 2.80), 3.23 cm² (SD 2.39), and 2.72 cm² (SD 2.16) cm² in the standard, HFU, and NCLFU groups respectively (\( P = 0.04 \), see Table 2).

Edema at first clinic visit ranged from 1+ to 4+ in all groups: 10 patients in the standard treatment group, 12 patients in the HFU group, and nine patients in the NCLFU group had 1+ plus edema; seven patients in the standard treatment group, three patients in the HFU group, and eight patients in the NCLFU group had 4+. After 4 months, eight patients in the standard treatment group, 24 patients in the...
HFU group, and 22 patients in the NCLFU group had 1+ edema and five patients in the standard treatment group, one patient in the HFU group, and four patients in NCLFU group had 4+ edema. At the 4-month follow-up, the number of patients with decreased edema was significantly higher in the HFU and NCLFU group compared to the standard treatment group ($P = 0.00$; see Table 3).

At the first visit, the mean pain scores in the standard treatment, HFU, and NCLFU groups were 6.20 (SD 1.64), 6.00 (SD 1.59), and 6.16 (SD 1.51) respectively ($P = 0.58$). After 2 months, the mean pain score was not significantly different among all groups. The mean decrease in pain scores was significantly different after the 4-month visit among the three groups. At this visit, the mean pain scores in the standard treatment, HFU, and NCLFU groups were 5.10 (SD 1.88), 3.96 (SD 2.88), and 3.26 (SD 3.06) respectively ($P = 0.02$; see Table 4).

Patients were followed for an average of 7.5 (SD 1.80) months. Mean time to complete wound healing in the standard treatment, HFU, and NCLFU groups was 8.50 (SD 2.17), 6.86 (SD 2.04), and 6.65 (SD 1.59) months, respectively ($P = 0.001$; see Table 2) and was statistically significant. No side effects occurred during the study period (treatment and monthly assessment).

**Discussion**

Compression bandages are the mainstay and standard treatment for chronic venous ulcers. In this study, all wounds eventually healed with the use of compression bandages and standard, nonadherent dressings with or without ultrasound therapy. However, wounds in the standard treatment group took an average of 2 months longer to heal than those in the ultrasound groups. At the 4 month visit — 1 month after ultrasound treatment was stopped— decreases

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**Table 1. Baseline patient characteristics**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Standard treatment group (n=30)</th>
<th>High-frequency ultrasound group (n=30)</th>
<th>Noncontact, low-frequency ultrasound group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>15/15</td>
<td>16/14</td>
<td>16/14</td>
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<tr>
<td>Average (SD) age (years)</td>
<td>39 (SD 10.9)</td>
<td>38.2 (SD 9.9)</td>
<td>40.4 (SD 8.5)</td>
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<tr>
<td>Average (SD) body mass index (kg/m²)</td>
<td>60.2 (SD 9.8)</td>
<td>66.2 (SD 6.7)</td>
<td>64 (SD 5.8)</td>
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Comorbidities (n)

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<th>Standard treatment group (n=30)</th>
<th>High-frequency ultrasound group (n=30)</th>
<th>Noncontact, low-frequency ultrasound group (n=30)</th>
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<td>12</td>
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<td>Arthrosis</td>
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<tr>
<td>Contact dermatitis</td>
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<tr>
<td>Smoking</td>
<td>9</td>
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<td>10</td>
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<tr>
<td>History of DVT</td>
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<td>8</td>
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<td>History of venous surgery</td>
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<td>Average (SD) ABPI</td>
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<td>1.04 (SD 0.08)</td>
<td>1.10 (SD 0.12)</td>
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**Table 2. Ulcer size**

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<th>Time</th>
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<th>Number of patients</th>
<th>Mean (cm²)</th>
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<th>$P$ value</th>
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<td>Standard treatment</td>
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<td>3.28</td>
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<td>30</td>
<td>4.28</td>
<td>2.80</td>
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<tr>
<td></td>
<td>High-frequency ultrasound</td>
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<td>3.23</td>
<td>2.39</td>
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<td>2.72</td>
<td>2.16</td>
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One-way ANOVA; *P value was calculated between the three groups in each visit.
in ulcer size, edema, and wound pain were all statistically significantly greater in the ultrasound groups than in the control patient group.

These results are supported by other research. In a randomized, controlled, double-blinded study, Ennis et al. examined the effectiveness of NCLFU therapy for the healing of recalcitrant diabetic foot ulcers in 55 patients after 12 weeks of care. The authors concluded the proportion of wounds healed in the active ultrasound therapy device group was significantly higher than in the control group (40.7% versus 14.3%, \( P = 0.0366 \), Fisher’s exact test).

In a noncomparative study, Ennis et al. used NCLFU therapy for 8 months to treat 23 patients from a single tertiary-referral, hospital-based wound clinic. Control data were obtained from a previously published, prospectively collected database from the same clinic. Sixty-nine percent (69%) of wounds were healed during a median of 7 weeks when NCLFU was used as a stand-alone therapy.

In an open-label, nonrandomized, baseline-controlled clinical case series, Kavros et al. assessed NCLFU therapy in the treatment of nonhealing leg and foot ulcers associated with chronic critical limb ischemia. Participants included 35 patients who received NCLFU plus the standard of wound care for 12 weeks (treatment group) and 35 patients who received the standard of wound care alone (control group). A significantly higher percentage of patients receiving NCLFU treatment achieved >50% wound healing at 12 weeks than those treated with the standard of care alone (63% versus 29%; \( P < 0.001 \)). Another open-label, nonrandomized, baseline-controlled clinical case series study analysis (\( N = 51 \)) by

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### Table 3. Changes in edema

<table>
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<td>2+ (16.6)</td>
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<td>4+ (23.3)</td>
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<td></td>
<td>High-frequency ultrasound</td>
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<td>2+ (23.3)</td>
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<td>4+ (26.6)</td>
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One-way ANOVA; *\( P \) value was calculated between the three groups in each visit

### Table 4. Change in pain score

<table>
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<th>Time</th>
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<th>Mean (cm²)</th>
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<td>5.86</td>
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<td>2.88</td>
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<td>3.06</td>
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</tbody>
</table>

One-way ANOVA; *\( P \) value was calculated between the three groups in each visit

### Table 5. Time to complete wound healing (months)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard treatment</td>
<td>30</td>
<td>8.50</td>
<td>2.17</td>
</tr>
<tr>
<td>High-frequency ultrasound</td>
<td>30</td>
<td>6.86</td>
<td>2.04</td>
</tr>
<tr>
<td>Noncontact, low-frequency ultrasound</td>
<td>30</td>
<td>6.65</td>
<td>1.59</td>
</tr>
</tbody>
</table>

One-way ANOVA; *\( P \) value was calculated between the three groups in each visit = 0.00
Kavros et al\textsuperscript{36} indicated healing time reductions (9.8 ± 5.5
weeks versus 5.5 ± 2.8 weeks [P <0.0001]) and wound volume percent improvement (37.3% ± 18.6% versus 94.9% ± 9.8% [P <0.0001]) when NCLFU therapy was compared to the clinic’s standard care.

The current study reflects changes in patient pain after 4 months treatment. Wound pain decreased significantly in ultrasound-treated groups in comparison with standard treatment alone. In a retrospective study, Gehling and Samies\textsuperscript{37} assessed the pain scores of 15 consecutive patients (seven men, eight women, age range 28–88 years) with painful, nonhealing, lower-extremity wounds treated for 2 to 4 weeks with NCLFU therapy. Mean pain scores decreased from 8.07 ± 1.91 pretreatment to 1.67 ± 1.76 post-treatment (P = 0.0003).

Although the average age of patients in the current study was slightly lower than other studies in world, this could be due to the higher prevalence of the disease in Iran, especially considering a similar study conducted by Parsa et al\textsuperscript{38} involving patients of similar age range. More comprehensive studies with a greater number of patients need to be conducted in Iran and elsewhere.

No previous study compares NCLFU and HFU therapy in VLU treatment. The current data analysis does not show any significant differences between NCLFU and HFU therapy, although both techniques produce significantly different outcomes when compared with standard VLU treatment.

Although current results confirm the efficacy of ultrasound in VLU treatment, numerous studies published in recent years reported conflicting results regarding the effectiveness of ultrasound. A multicenter, pragmatic, parallel, two-armed, randomized controlled trial\textsuperscript{16} to compare the clinical effectiveness of low-dose ultrasound delivered in conjunction with standard care against standard care alone in the treatment of hard-to-heal venous ulcers found no statistically significant difference in the time to healing of the reference leg ulcer between the two groups (log-rank statistic 0.2544, P = 0.6140). A small, statistically nonsignificant difference was noted in the median time to complete ulcer healing of all ulcers in favor of standard care (median 328 days, 95% confidence interval [CI] 235 days, inestimable) when compared with ultrasound (median 365 days, 95% CI 224 days, inestimable). No statistically significant difference was found between groups in the proportion of patients with ulcers healed at 12 months (72 out of 168 in ultrasound versus 78 out of 169 standard care, Fisher’s exact test, P = 0.3854) nor in the change in ulcer area at 4 weeks. An industry-sponsored meta-analysis\textsuperscript{39} of seven studies (N = 429), evaluating NCLFU therapy for treating chronic wounds, found that a mean of 32.7% patients (95% CI: 23.3% to 42.1%) had healed wounds by a mean of 6 weeks. A pooled analysis of four studies (N = 188) in the meta-analysis\textsuperscript{39} found a mean of 85.2% (95% CI: 64.7% to 97.6%) reduction in wound area by final follow-up. A major limitation of this meta-analysis was the lack of pooled comparisons of NCLFU therapy to optimal wound care alone or to an alternative intervention. Thus, conclusions cannot be drawn about the incremental benefit of NCLFU treatment over optimal wound care alone.

In summary, evidence to support the effectiveness of ultrasound therapy in the management of patients with chronic wounds is lacking, and reports of outcomes of using this method are controversial. Comparing NCLFU and HFU treatment is an initial step to settling debatable issues. To achieve reliable results, more controlled clinical trials and randomized clinical trials with larger samples size are needed to guide evidence-based practice.

Limitations

The small sample size of this study limits ability to draw firm conclusions, especially with respect to potential differences between the two methods of ultrasound therapy, because the difference in healing rates between these groups was smaller than those between standard care and the intervention groups. In addition, wound surface in this study was measured by tracing the margins of the open wound and measuring the two maximum perpendicular axes. Although this method is scientifically valid and reliable, use of more precise imaging and histopathological assessment methods may have enhanced study accuracy.

Conclusion

In this prospective, comparative clinical study, the effect of standard ulcer care alone was compared with high-frequency ultrasound and noncontact ultrasound therapy in the treatment of VLUs, and the two modes of ultrasound therapy also were compared. The results show wound healing was faster in ultrasound groups in comparison with standard treatment alone; ulcer size, mean degree of pain, and edema decreased more in the ultrasound than in the control groups. Although ulcers in the noncontact ultrasound therapy group had a slightly better response to treatment than those in the high-frequency group, the differences were not statistically significant.

References

7. Stücker M, Reich S, Robak-Pawelczyk B, Moll C, Rudolph


