Expedited Wound Healing with Noncontact, Low-Frequency Ultrasound Therapy in Chronic Wounds: A Retrospective Analysis

Steven J. Kavros, DPM; David A. Liedl, RN; Andrea J. Boon, MD;
Jenny L. Miller, PT; Julie A. Hobbs, PhD; and Karen L. Andrews, MD

ABSTRACT

OBJECTIVE: To evaluate the clinical role of noncontact, low-frequency ultrasound therapy (MIST Therapy System; Celleration, Eden Prairie, Minnesota) in the treatment of chronic lower-extremity wounds.

DESIGN: A retrospective observational study.

SETTING: A multidisciplinary, vascular wound-healing clinic.

PATIENTS: One hundred sixty-three patients who received MIST Therapy plus standard of care (treatment group) and 47 patients who received the standard of care alone (control group).

INTERVENTIONS: All wounds in the control and treatment groups received the standard of wound care and were followed for 6 months. In the treatment group, MIST Therapy was administered to wounds 3 times per week for 90 days or until healed.

MAIN OUTCOME MEASURES: Proportion of wounds healed and wound volume reduction. Rate of healing was also quantified using 1-way analysis of variance to determine the slope of the regression line from starting volume to ending volume, where a steeper slope indicates a faster healing rate. Outcomes were evaluated in all wounds and etiology-specific subgroups.

MAIN RESULTS: A significantly greater percentage of wounds treated with MIST Therapy and standard of care healed as compared with those treated with the standard of care alone (53% vs 32%; $P = 0.009$). The slope of the regression line in the MIST arm (1.4) was steeper than the slope in the control arm (0.22; $P = .002$), indicating a faster rate of healing in the MIST-treated wounds.

CONCLUSION: The rate of healing and complete closure of chronic wounds in patients improved significantly when MIST Therapy was combined with standard wound care.

ADV SKIN WOUND CARE 2008;21:416–23

INTRODUCTION

Chronic wounds of the lower extremities are a frequent and persistent challenge in clinical wound care. One reason these wounds are difficult to treat is the multiple underlying pathologies that contribute to lower-extremity ulcers, the most common of which include venous insufficiency, arterial insufficiency, neuropathy (often from diabetes), and prolonged pressure and ischemia.[1] A second reason, which is common to chronic wound care in general, is the limited amount of high-quality research on advanced wound healing modalities.[2,3] For example, although there is some evidence to suggest that negative pressure wound therapy may improve wound healing, the methodologic quality of the studies overall is considered weak, and the evidence, to date, has been inconsistent.[4] Published studies also suggest that noncontact, low-frequency ultrasound therapy may expedite wound healing, but again, the studies, to date, have been relatively small and come with some methodology concerns.[5]

Wound chronicity results when the ordered cellular and molecular processes that lead to healing in acute wounds are disrupted,[6] typically by necrotic debris and associated bioburden.[7] A variety of debridement methods are used to remove necrosis and cleanse the wound bed, including autolytic, enzymatic, sharp/surgical, and mechanical techniques. Noncontact, low-frequency ultrasound therapy is a newer modality used to promote healing in chronic wounds by cleansing and maintenance debridement to remove yellow slough, fibrin, tissue exudates, and bacteria. The mechanisms by which low-frequency ultrasound energy stimulates wound healing have been previously described.[8,9] In brief, ultrasound initiates 2 processes that release energy to the tissues capable of inducing cellular change: surface cavitation (creation and dissipation of tiny bubbles in the tissues) and acoustic microstreaming

Steven J. Kavros, DPM, is Assistant Professor, College of Medicine, Department of Orthopedic Surgery and Gonda Vascular Wound Healing Center of the Mayo Clinic, Rochester, MN; David A. Liedl, RN, Gonda Vascular Wound Healing Center of the Mayo Clinic; Andrea J. Boon, MD, is Assistant Professor, College of Medicine; Jenny L. Miller, PT, is Physical Therapist, College of Medicine; Julie A. Hobbs, PhD, is Instructor, College of Medicine; and Karen L. Andrews, MD, is Assistant Professor, College of Medicine, Department of Physical Medicine and Rehabilitation and Gonda Vascular Wound Healing Center of the Mayo Clinic. **Acknowledgment:** The authors thank Laurie LaRusso, MS, ELS, for assistance in preparing this article with the educational support of Celleration, Inc.

(movement of fluids along acoustic boundaries, such as cell membranes).[10] These processes are associated with a number of biophysical effects that are nonthermal and relevant to wound healing, including alterations in cellular protein synthesis and release, blood flow, and vascular permeability, angiogenesis, and collagen content and alignment.[11]

Although further research is needed to fully characterize the mechanisms by which low-frequency ultrasound may stimulate the wound healing process, prospective human studies of the one noncontact form of low-frequency ultrasound therapy (MIST Therapy System; Celleration, Eden Prairie, Minnesota) have demonstrated improved healing rates with adjuvant use of this therapy (ie, in addition to conventional wound care, including etiology-specific care). MIST Therapy has been shown to improve healing times in randomized, controlled studies of diabetic foot ulcers[12] and lower-extremity wounds complicated by chronic critical limb ischemia,[8] as well as nonrandomized studies of varied lower-extremity wounds.[9,13] Although the healing benefit of MIST Therapy seems to be fairly consistent across these studies, which range in size from 23 to 70 patients, assessments of larger patient populations are needed.

The primary objective of this study was to assess wound healing with the adjuvant use of the MIST Therapy System in a large population of lower-extremity wounds.

METHODS

Study Design

This retrospective, observational study was conducted in patients with below-the-knee, lower-extremity wounds of varied etiology. The healing outcomes of wounds treated with MIST Therapy in addition to standard wound care (MIST Therapy group) were compared with the outcomes of wounds treated with standard wound care alone (control group). MIST Therapy was administered 3 times per week for 90 days or until the wound healed. The Mayo Clinic institutional review board approved the research protocol.

All patients received standard wound care as appropriate to their specific cases, including moist wound healing, daily dressing changes, debridement, advanced wound care dressings (ie, silvers, collagens, antimicrobials), and etiology-specific care (ie, optimization of arterial perfusion, revascularization, compression, protective footwear, appropriate off-loading).

Setting and Patient Selection

The Vascular Ulcer Wound Healing Clinic, Gonda Vascular Center at Mayo Clinic, Rochester, Minnesota, is a multidisciplinary clinic offering wound care services to Gonda Vascular Center patients. Physicians, nurses, therapists, and clinical assistants from the departments of internal medicine, vascular medicine, vascular radiology, vascular surgery, podiatric medicine, dermatology, and physical medicine and rehabilitation are involved in patient care. The center provides wound care to patients from Olmsted County, Minnesota, as well as care to regional, national, and international patients.

Patient records from January 2005 through March 2007 (the study period) were reviewed to identify all patients who had received MIST Therapy on their wounds during this period. A total of 325 MIST-treated patients consented to the medical record review; 162 of these patients were excluded from the present analysis because they did not meet the criteria for ultrasound treatment 3 times per week, had significant discontinuity of treatments, did not complete the treatment regimen at the wound center, or had participated in a previous study of MIST Therapy in critical limb ischemia at the wound center.[8] The remaining 163 patients who met the inclusion criteria comprise the MIST Therapy group. Similarly, 92 matched control patients treated during the study period were identified. These patients had been suitable candidates for MIST Therapy but had been unable to accommodate the required thrice-weekly treatment visits. Forty-seven matched controls met the criteria for inclusion. Control and MIST-treated patients were matched based on patient characteristics (age, sex, comorbidities, etc) and wound etiology (ischemic, venous, neuropathic, etc). One target wound per patient was chosen at random for analysis purposes.

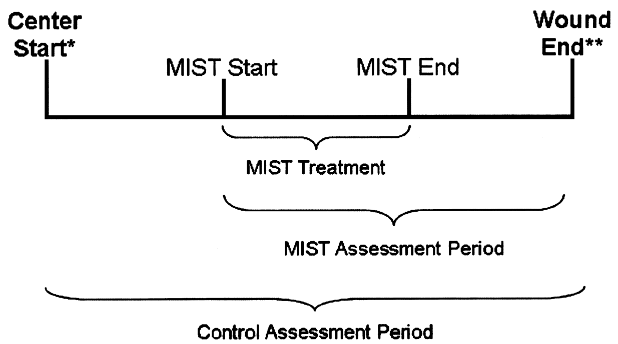
Therapeutic Ultrasound

The MIST Therapy System noncontact ultrasound device delivers low-intensity (0.1–0.8 W/cm^2), low-frequency (40 kHz) ultrasound energy via atomized, sterile saline mist to the wound bed without directly contacting the body or the wound. The device is a compact, portable unit consisting of a generator, transducer, and disposable applicator that uses prepackaged sterile saline. The disposable applicator contains an on/off valve that controls the flow of sterile saline to the ultrasound transducer surface. The product's recommended treatment algorithm is based on longer treatment times for greater total ulcer area, with treatment times ranging from 3 to 20 minutes for wound areas measuring less than 10 cm^2 to 180 cm^2. At our facility, the protocol is to treat wounds up to 4 × 4 cm with 4 minutes of MIST Therapy; larger wounds receive longer treatment times.

Assessments

Each patient's medical record, both paper and electronic, was reviewed, including all inpatient and outpatient care, relevant laboratory results, and noninvasive arterial studies. Data collected included patient demographics, risk factors, wound

Figure 1.
WOUND VOLUME ASSESSMENTS FOR CONTROL AND ULTRASOUND TREATMENT GROUPS



First measurement at Gonda Vascular Center
Last measurement during study period

etiology, frequency of treatments, wound discomfort, and wound size and duration.

Wound volumes were evaluated at the start and end of treatment. The primary outcomes of interest were the proportion of wounds healed and the rate of healing in each treatment group. A healed wound was defined as full epithelium covering the surface with no drainage. The rate of healing was calculated as a function of volume over time using analysis of variance (ANOVA) in which rate of healing is indicated by the slope of the regression line from starting volume to ending volume, where a steeper slope (higher numeric value) indicates a more rapid rate of healing. Because not all wounds would be expected to close during a given study period, percent volume reduction was calculated to quantify progress toward closure.

When drawing comparisons between treatment groups, it was necessary to differentiate between the start and end points of control and MIST therapies as illustrated in Figure 1. The assessment period for control patients began when they started treatment at the wound center (center start) and ended with the last wound measurement during the study period (wound end). Similarly, MIST Therapy patients were assessed at center start and wound end, but these patients were also assessed when MIST Therapy began (MIST start) and ended (MIST end). For the current analysis, comparisons were made using center start to wound end volumes for control patients and MIST start to wound end volumes for MIST Therapy patients. Using wound end rather than MIST end minimized the difference in duration of control and MIST treatment periods and allowed for evaluation of the complete healing trajectory associated with MIST Therapy rather than only the healing that occurred during MIST treatment. Wounds were followed for 6 months from the center start date.

Statistical Analysis

Quantitative analysis of baseline demographics and clinical characteristics were performed using the Mann-Whitney *U* test. Probability values for between-group comparisons of wound closure proportion and wound volume reduction were generated using the chi-square test, or where expected counts were small, Fisher exact test was used. A probability value of less than .05 was required for statistical significance. One-way ANOVA was performed to calculate 95% confidence intervals around the means. One-way ANOVA was also performed to quantify the rate of healing as represented by the slope of the regression line from starting volume to ending volume. All data were analyzed using JMP 4.0 statistical software (SAS Institute, Cary, North Carolina).

RESULTS

Patient Characteristics

Of the 210 patients in this study, 163 received MIST Therapy in addition to standard wound care, and 47 control patients received standard wound care only. As shown in Table 1, the

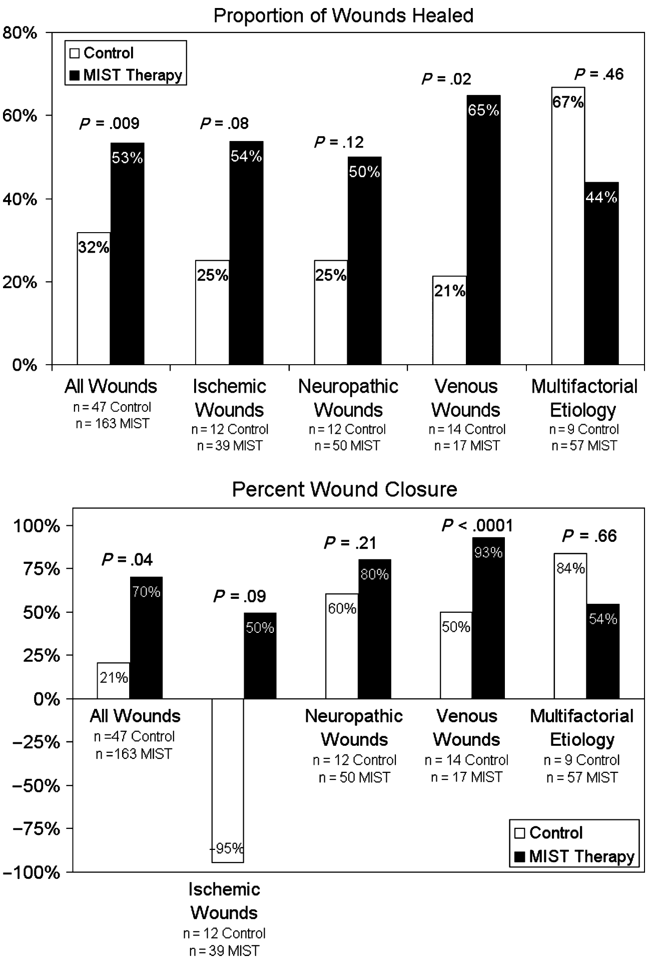
Table 1.
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WHO RECEIVED ADJUVANT MIST THERAPY AND MATCHED CONTROL PATIENTS WHO RECEIVED NO ULTRASOUND THERAPY

Characteristics	MIST Therapy (n = 163)	Control (n = 47)
Age, median (range), y	70.6 (41–101)	71.9 (45–97)
Men, no. (%)	82 (50)	27 (57)
Coronary artery disease, no. (%)	78 (48)	20 (43)
Diabetes mellitus, no. (%)	125 (77)	31 (66)
(a) Insulin dependent	38 (30)	10 (21)
(b) Non–insulin dependent	87 (70)	21 (47)
Glycosylated hemoglobin 8, no. (%)	122 (97)	45 (95)
Median (range)	5.5 (4.28–9.8)	5.2 (4.5–8.8)
Hypertension, no. (%)	132 (81)	31 (66)
Dyslipidemia, no. (%)	109 (67)	24 (51)
Treated with statins, no. (%)	98 (90)	20 (88)
Smoking, no. (%)		
Current	25 (15)	7 (15)
Former	89 (55)	29 (62)
Never	49 (30)	11 (23)
Serum creatinine, median (range)	1.2 (0.7–4.4)	1.4 (0.7–4.3)
Hemodialysis, no. (%)	18 (11)	4 (9)
Osteomyelitis, no. (%)	12 (7)	6 (13)
Previous amputations, no. (%)	24 (15)	6 (13)
Amputations post treatment, no. (%)	5 (3)	8 (17)

No statistically significant differences were observed between treatment groups.

Figure 2.

PROPORTION OF WOUNDS HEALED (A) AND PERCENT WOUND CLOSURE (B) IN ALL WOUNDS AND ETIOLOGY-SPECIFIC SUBGROUPS



MIST and control groups were well matched on the demographic and clinical characteristics collected (ie, no statistically significant differences between groups). The mean patient age was approximately 71 years old with a near-equal representation of men and women. Diabetes mellitus and hypertension were present in most patients. Dyslipidemia was also present in a majority of patients, and coronary artery disease was present in nearly half of the patients. Serum creatinine levels were on the higher end of the normal range. Among individuals with end-stage renal disease, 11% (n = 18) of the MIST group and 4% (n = 9) of the control group were on hemodialysis. Major or minor lower-extremity amputation had been performed before study enrollment in 15% (n = 24) of the MIST group and 13% (n = 6) of the control group. The proportion of patients who required amputation after treatment was greater in the control group than the MIST group (17% [n = 8] vs 3% [n = 5]), although the difference did not reach statistical significance.

Of the 210 wounds evaluated, 51 (24%) were of ischemic origin, 62 (30%) were associated with neuropathy, 31 (15%) were of venous stasis origin, and 66 (31%) were of multifactorial etiology.

In the primary analysis, wound outcomes are reported based on comparison of control group wound sizes at center start and wound end versus MIST group wound sizes at MIST start and wound end (Figure 1).

Wound Healing

As shown in Figure 2A, of 163 wounds treated with thrice-weekly MIST Therapy, 53% healed over a mean 147 days. In comparison, 32% of the 47 wounds treated with the standard of care alone healed over a mean 134 days (*P* = .009). In the wounds of ischemic, neuropathic, and venous origin (also shown in Figure 2A), this pattern of proportionately more wounds healed with MIST Therapy than without is evident, although the difference is only significant for wounds of venous origin. Means and confidence intervals for the proportion of wounds healed are shown in Table 2.

The wounds of multifactorial etiology present some interesting observations (Figure 2A), although the findings should

Table 2.

MEAN VALUES AND ASSOCIATED 95% CONFIDENCE INTERVALS FOR WOUND HEALING AND RATE OF HEALING

	MIST Therapy (n = 163)	Control (n = 47)	*P*
Proportion of wounds healed	% (95% CI)		
All patients (n = 210)	53 (46–61)	32 (18–46)	.009
Ischemic etiology (n = 51)	54 (38–70)	25 (−4 to 54)	.08
Neuropathic etiology (n = 62)	50 (36–64)	25 (−4 to 54)	.12
Venous etiology (n = 31)	65 (42–88)	21 (−4 to 47)	.02
Multifactorial etiology (n = 66)	44 (25–62)	67 (7–126)	.46
Rate of healing	Slope[a] (95% CI)		
All patients (n = 210)	1.4 (1.0–1.7)	0.22 (−0.4 to 0.9)	.002
Ischemic etiology (n = 51)	1.5 (0.3–2.7)	−1.0 (−3.2 to 1.2)	.049
Neuropathic etiology (n = 62)	1.4 (1.0–1.8)	0.6 (−0.2 to 1.4)	.08
Venous etiology (n = 31)	1.6 (1.0–2.2)	0.5 (−0.2 to 1.1)	.02
Multifactorial etiology (n = 66)	0.9 (0.4–1.4)	1.3 (−0.4 to 3.0)	.66

CI indicates confidence interval.

95% CI = the upper and lower boundaries between which the true treatment effect is expected to fall in 95 out of 100 cases.

[a]The slope of the regression line from starting volume to ending volume indicates the rate of healing, where a steeper slope indicates a more rapid rate of healing.

be interpreted with caution, given the very small number of wounds in the control group (n = 9) and the lack of statistical significance. First, the percentage of control wounds that healed is 2 to 2.5 times greater than for control wounds in the overall study population and for every other subgroup reported. This exceptionally high proportion of healed wounds in the control group was also greater than that observed in multifactorial wounds treated with MIST (n = 57). What is particularly interesting from a clinical decision-making perspective is that clinicians were 6 times more likely to administer MIST Therapy to wounds of multifactorial etiology than they were to stay with the standard of care in these wounds. In addition, the mean starting wound volume in the multifactorial wounds treated with MIST was more than 4 times greater than that in the control group. Based on these observations, it seems that clinicians tended to use MIST Therapy on larger wounds with more complex etiology.

Analysis of percent closure (ie, percent of wound surface closed) showed a similar pattern of benefit associated with MIST Therapy. Again, the benefit is statistically significant for analysis of all wounds ($P = .04$) and for those of venous origin ($P < .0001$), but represents only a nonsignificant trend for ischemic and neuropathic wounds. Also consistent with the percent-healed analysis, the few control wounds of multifactorial etiology seem to progress toward healing better than the other wound-type subgroups. Figure 2B also shows that while 50% wound closure was observed in ischemic wounds treated with MIST Therapy, the ischemic wounds treated with the standard of care got larger on average, although the difference between groups was not statistically significant. It is important to note that many patients with ischemic wounds in this study had not yet received treatment to alleviate their ischemia.

Wound Volume

As shown in Figure 3, the percent reduction in mean wound volume from the start of treatment (center start or MIST start) to the end of the study (wound end) is greater in wounds treated adjuvantly with MIST Therapy. This was observed for all wounds and wounds of ischemic and venous etiology. Mean volume reduction in neuropathic wounds was greater in the control arm than the MIST arm. Volume reduction was comparable between treatment groups in the multifactorial wounds. The range of wound volumes in both treatment groups at each time point is quite broad, which resulted in median values substantially lower than the means for all wounds and the subgroups analyzed. Median wound volume for control wounds at center start was 368 mm^3 and at wound end was 68 mm^3; median volume for MIST-treated wounds at MIST start was 304 mm^3 and was 0 mm^3 at wound end.

Rate of Healing

The rate of healing can be calculated as a function of volume over time using the 1-way ANOVA. The slope of the regression line from starting volume to ending volume indicates the rate of healing, where a steeper slope indicates a more rapid rate of healing. For the analysis of all wounds, the slope of 1.4 in the MIST arm compares favorably with the slope of 0.22 in the control arm ($P = .002$), indicating a faster rate of healing associated with MIST Therapy. Similarly, rates of healing in ischemic (1.5 vs −1.0; $P = .049$), neuropathic (1.4 vs 0.63; $P = .08$), and venous (1.6 vs 0.5; $P = .02$) wounds were greater for MIST-treated wounds than for wounds treated with the standard of care. Similar to the findings for wound closure and volume, the rate of healing in the multifactorial wounds favored the standard of care without reaching statistical significance (MIST 0.9 vs control 1.3; $P = .66$).

Because MIST Therapy was administered for a maximum of 90 days within the entire treatment period, the authors also analyzed the slope of volume reduction from MIST start to MIST end. Again, a steeper slope of volume reduction for MIST Therapy was observed (1.7 vs 0.22; $P = .002$).

Alternative Analyses

Although not reported in this article, results of analyses using MIST start to MIST end data rather than MIST start to wound end data (as in the primary analysis) did not differ substantially.

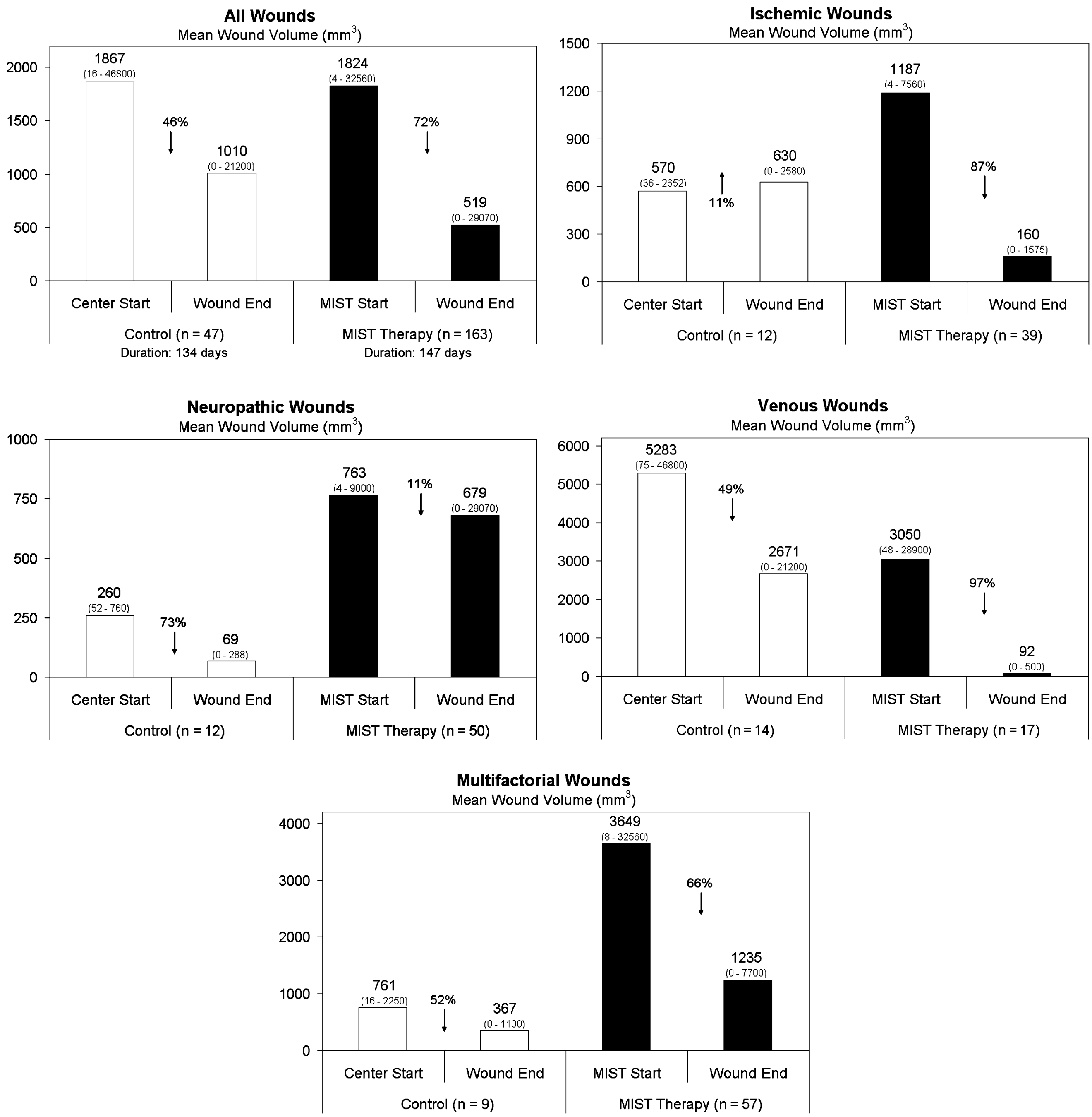
DISCUSSION

The principal objectives of noncontact, low-frequency ultrasound in wound care are to reduce the microbial bioburden from the wound surface, debride and stimulate local autolysis of necrotic tissue, and enhance the formation of granulation tissue. Previous studies have suggested a role for noncontact, low-frequency ultrasound (MIST Therapy) in the treatment of chronic wounds.[8,9,12,13]

In this retrospective observational study, a significantly greater proportion of wounds treated adjuvantly with MIST Therapy healed compared with the standard of care alone. Furthermore, progress toward closure was significantly greater, and the rate of healing (represented by the steeper slope of regression line) significantly increased with the addition of MIST Therapy to standard wound care. Among the wound subgroups studied, venous wounds seem to benefit the most from adjuvant MIST Therapy, although improvements were also observed for ischemic and neuropathic wounds. The finding of modestly better prognosis among multifactorial wounds treated with the standard of care, although limited by the very small sample (n = 9), suggests the need for further research into clinician treatment choices and healing outcomes in these more complex wounds.

Figure 3.

WOUND VOLUME IN ALL STUDY WOUNDS AND ETIOLOGY-SPECIFIC SUBGROUPS (A–E)



When interpreting ANOVA, the confidence interval provides insight into the clinical relevance of research findings beyond the statistical significance represented by the *P* value. While the *P* value indicates with 95% certainty that a difference in treatment effect is a true difference rather than a chance finding, the 95% confidence interval tells the clinician between which upper and lower boundaries the true treatment effect lies. For the clinician, this means that 95 times out of 100, the treatment effect will fall within this upper and lower limit. Based on the confidence intervals shown in Table 2, a clinician could expect 46% to 61% of wounds treated with 90 days of MIST Therapy to heal within 147 days, whereas only 18% to 46% of patients in the control group would likely heal in a similar time frame (134 days). In terms of healing rate, the slope of the regression line (ie, the slope of volume reduction) was consistently steeper for MIST-treated wounds (Table 2). Furthermore, the 95% confidence intervals in the MIST group are all greater than zero, indicating volume reduction rather than the possibility of an increase in volume. In contrast, the 95% confidence intervals in the control group all have a negative value for the lower boundary, indicating the possibility of a volume increase. The confidence intervals presented in Table 2 illustrate the rather consistent, clinically relevant healing benefit of MIST Therapy as opposed to the control group, where there appears to be either comparatively poorer healing or inconsistent healing based on wide confidence intervals.

Although retrospective, this analysis contributes, by far, the largest patient cohort to the published research on MIST Therapy for healing of chronic wounds. Although this analysis did not include controlling for comorbidities or other treatments, the matching of control patients based on patient characteristics and wound etiology provides some added rigor to offset the inherent limitations posed by the retrospective, observational design. In addition, comparing outcomes across treatment groups where start and end points differ between groups presents inherent challenges for analysis and interpretation of results. It is reassuring, however, that the impact of MIST Therapy on wound healing seems to be consistent regardless of whether the analysis included the period from MIST start to wound end or only the MIST treatment period (not reported). The larger study population allowed for analysis of specific wound types, although small patient numbers in some subgroups require that subgroup results be interpreted with caution.

However, some of the smaller, prospective studies have demonstrated that MIST Therapy is beneficial in patients with diabetes and chronic critical limb ischemia. In a sham-controlled study of 55 patients with diabetic foot ulcers, 40% more wounds treated with MIST Therapy healed completely by 12 weeks than wounds treated with standard wound care alone.[12] In a randomized study of 70 patients with chronic critical limb ischemia, 54% more wounds treated with MIST Therapy reached more than 50% closure in 12 weeks than wounds treated with only standard wound care.[8] Compared with a historical control group treated with standard wound care, Ennis et al[13] observed a statistically significant 30% reduction in mean healing time in a prospectively analyzed group of patients with varied wound etiology treated with MIST Therapy. Also in a heterogeneous wound cohort, MIST Therapy was associated with a 44% reduction in time to healing compared with a baseline standard-of-care period.[9]

As an adjuvant therapy to hasten wound closure, MIST Therapy prepares the wound bed for healing by reducing bioburden, enhancing angiogenesis, assisting in debridement of necrotic and devitalized tissues, and stimulating cellular activity. In many cases, such preparation will be sufficient to stimulate formation of adequate granulation tissue, ultimately leading to complete epithelialization and wound closure. However, such robust wound bed preparation can also be particularly valuable for patients considered candidates for a skin graft procedure. One may consider that enhanced vascularity, decreased bioburden, and decreased dense fibrin and necrotic tissue in the wound bed would improve the chances of obtaining a positive result with an autologous or bioengineered, human-equivalent skin graft. Closing chronic wounds as quickly as possible, with or without grafts, minimizes the opportunity for infection or complication to further hinder healing. For some patients, this will ultimately result in limb salvage. The trend toward fewer posttreatment amputations among MIST-treated patients in this study, however, must be interpreted with caution, given the very small number of wounds and the lack of statistical significance.

CONCLUSIONS

The addition of MIST Therapy to standard wound care seems to expedite healing of chronic wounds in the lower extremities. Further research on the healing impact of MIST Therapy in specific wound types will provide additional clinical insight into the use of this noncontact, low-frequency ultrasound therapy. ●

REFERENCES

1. de Araujo T, Valencia I, Federman DG, et al. Managing the patient with venous ulcers. Ann Intern Med 2003;138:326-34.
2. Vacuum-Assisted Closure for the Management of Wounds: An Accelerated Systematic Review. ASERNIP-S Report No. 37: Australian Safety and Efficacy Register of New Interventional Procedures—Surgical, The Royal Australasian College of Surgeons; December 2003.
3. Negative Pressure Wound Therapy Update: Health Technology Policy Assessment. Toronto, Ontario: Medical Advisory Secretariat, Ministry of Health and Long-Term Care; 2006.
4. Gregor S, Maegele M, Sauerland S, et al. Negative pressure wound therapy: a vacuum of evidence? Arch Surg 2008;143:189-96.

5. Unger PG. Low-frequency, noncontact, nonthermal ultrasound therapy: a review of the literature. Ostomy Wound Manage 2008;54:57-60.
6. Enoch S, Harding K. Wound bed preparation: the science behind the removal of barriers to healing. Wounds 2003;15:213-29.
7. Ennis WJ, Meneses P. Factors impeding wound healing. In: Kloth LC, McCulloch JM, eds. Wound Healing: Alternatives in Management. Philadelphia, PA: F. A. Davis Co; 2002:68-96.
8. Kavros SJ, Miller JL, Hanna SW. Treatment of ischemic wounds with noncontact, low-frequency ultrasound: the Mayo clinic experience, 2004-2006. Adv Skin Wound Care 2007;20:221-6.
9. Kavros SJ, Schenck EC. Use of noncontact low-frequency ultrasound in the treatment of chronic foot and leg ulcerations: a 51-patient analysis. J Am Podiatr Med Assoc 2007;97:95-101.
10. Sussman C, Dyson M. Therapeutic and diagnostic ultrasound. In: Sussman C, Bates-Jensen B, eds. Wound Care: A Collaborative Practice Manual for Physical Therapists and Nurses. 2nd ed. Gaithersburg, MD: Aspen Publications; 2001:596-616.
11. Hess CL, Howard MA, Attinger CE. A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrostimulation. Ann Plast Surg 2003;51:210-8.
12. Ennis WJ, Foremann P, Mozen N, et al. Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomized, double-blind, controlled, multicenter study. Ostomy Wound Manage 2005;51:24-39.
13. Ennis WJ, Valdes W, Gainer M, Meneses P. Evaluation of clinical effectiveness of MIST ultrasound therapy for the healing of chronic wounds. Adv Skin Wound Care 2006;19:437-46.