

Evaluation of Clinical Effectiveness of MIST Ultrasound Therapy for the Healing of Chronic Wounds

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ABSTRACT

OBJECTIVES: (1) To determine the incidence of wound closure for chronic nonhealing lower extremity wounds of various etiologies using MIST ultrasound therapy, a 510(K)-approved, low-frequency, noncontact ultrasound device indicated for the cleansing and debridement of chronic wounds. (2) To determine the optimum treatment duration for therapy with this low-frequency, noncontact ultrasound device, quantifying end points that correlate with a maximal clinical response and identifying potential synergistic therapies that could be used in conjunction with this therapy. (3) To analyze the impact of low-frequency noncontact ultrasound therapy on the microcirculatory flow patterns within the wound bed.

DESIGN: A noncomparative clinical outcomes trial utilizing low-frequency, noncontact ultrasound.

SETTING: A tertiary-referral hospital-based wound clinic.

PATIENTS: Twenty-three 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.

INTERVENTIONS: During an 8-month period, a total of 29 lower extremity wounds in 23 patients who met criteria for inclusion were treated with low-frequency, noncontact ultrasound therapy. Standard of care was provided for 2 weeks for all wounds screened for the study. A failure to achieve an area reduction greater than 15% qualified the patient for enrollment to the trial and the addition of low-frequency, noncontact ultrasound therapy to the current treatment regimen.

MAIN OUTCOME MEASURES: Wound healing, area and volume reduction, and laser Doppler-derived mean voltage (a marker for microcirculatory flow) are the main outcome measures for the study.

RESULTS: Overall, 69% of the wounds in the study were healed using an intent-to-treat model. When low-frequency, noncontact ultrasound was used as a stand-alone device, median time to healing was 7 weeks. Historic controls were healed with a median time to healing of 10 weeks; however, a statistically significant

number of these patients required wound-related hospitalization and surgical procedures to achieve closure compared with the wounds in the present study.

CONCLUSIONS: Treatment with low-frequency, noncontact ultrasound achieved healing in chronic wounds when used as a stand-alone device or in combination with moist wound care in 69% of cases. Response to low-frequency, noncontact ultrasound was evident within 4 weeks of therapy. Earlier transition to secondary procedures and decreased utilization of inpatient care might result in more cost-effective wound healing than the current standard of care. A well-designed health economic-based trial is warranted to assess this technology.

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Significant clinician time and hospital resources are consumed when patients with chronic wounds are treated without a systematic approach.¹ Clinicians have a myriad of treatment options available; however, there is limited evidence with which to make decisions concerning timing and duration of treatment. In addition, treatment is often provided at multiple sites of care, which further results in costly, inefficient treatment. Without consistent, detailed medical records and communication from the various sites of care, overall care outcomes and healing rates are difficult to determine. Because clinicians tend to publish outcomes from their specific sites of care, healing rates often vary in the published literature.² True outcomes—clinical, humanistic, and economic—would require the coordination of care across the continuum and should include all relevant direct and indirect costs.

Of the many known factors that influence wound healing outcomes, wound duration has been reported by several authors as a predictor of poor healing.^{3,4} Another frequently reported negative prognostic marker for wound healing is a failure to respond to therapy within the first 2 to 4 weeks of treatment.^{5,6} As a result, many manufacturers have responded by introducing wound care products and treatment options that can stimulate the healing of so-called stunned wounds.⁷ Many

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of these treatments have undergone rigorous testing through randomized, controlled clinical trials (RCTs).^{8,9} Others rely on case reports, clinical effectiveness studies, and expert opinion.^{10,11} Unfortunately, the clinical efficacy achieved in many RCTs is rarely matched in subsequent clinical effectiveness studies, where trials are designed to emulate real world clinical settings.¹²

MIST ultrasound therapy (Celleration, Inc, Eden Prairie, MN) is a low-frequency, noncontact ultrasound therapy that has been cleared by the Food and Drug Administration (FDA) to promote healing through the cleansing and debridement of wounds. The release of this product correlates with an increased interest in the use of both diagnostic and therapeutic ultrasound within the wound healing community. Ultrasound is defined as a mechanical vibration transmitted at a frequency above the upper limit of human hearing (>20 kilohertz [KHz]).¹³ Diagnostic ultrasound intended for the anatomic analysis of skin relies on high-frequency (20-40 megahertz [MHz]) ultrasound devices.^{14,15} These units are used to assess the periwound skin, wound bed, and underlying soft tissue components. Therapeutic ultrasound, on the other hand, has been used for years by physical therapists for the treatment of a variety of musculoskeletal disorders, using devices that operate in the 1 to 3 MHz range.¹⁶ The current trend is toward using low-frequency ultrasound devices that operate in the kilohertz range.¹⁷

The mechanism of action for ultrasound's impact on wound healing is based on the results of human, plant, and animal *in vitro* studies.¹⁸ One mechanism of action is known as acoustical cavitation.¹⁹ This involves the creation and oscillation of microscopic bubbles. When these bubbles, or vapor-filled voids, reach a size that resonates with the frequency of the sound field, they act as powerful concentrators of acoustic energy into shearing and microstreaming fields. The movement and compression of these bubbles can cause changes in cellular activities within the tissues subjected to ultrasound energy.²⁰

Microstreaming, another mechanism by which ultrasound generates biologic activity, is defined as the physical forces of sound waves that provide a moving force capable of displacing ions and small molecules.²¹ At the cellular level, organelles and molecules can be differentiated by their molecular weights. Although many of these structures are stationary, others are free floating and may be driven to move around the stationary structures.²² The mechanical pressure applied by the microstreaming wave produces a unidirectional movement of fluid along and around cell membranes.

The combination of cavitation and microstreaming, both of which occur more frequently with kilohertz than megahertz

ultrasound, provides a mechanical energy capable of altering cell membrane activity and, therefore, cellular activity.^{23,24}

The frequency resonance hypothesis is a relatively new theoretical model, which takes prior macroenvironmental ultrasound theories down to a molecular and genetic level.²⁵ The mechanical energy from an ultrasound wave is absorbed by an individual protein molecule, theoretically inducing a conformational change. Signal transduction pathways can also be stimulated from ultrasound-generated mechanical energy. This may result in a broad range of cellular effects that impact wound healing. Leukocyte adhesion, growth factor production, collagen production, increased angiogenesis, increased macrophage responsiveness, increased fibrinolysis, and increased nitric oxide levels are all examples of ultrasound-induced cellular effects.²⁶⁻³²

Historically, ultrasound in the megahertz range has been used to treat intact sclerotic, periwound skin; it is not frequently used to treat wound bed tissue. Infection control issues, the need to remove dressings, and the requirement to use a coupling gel are a few of the barriers encountered using traditional ultrasound. Recently, there has been a shift toward the use of low-frequency ultrasound (kilohertz range) to achieve vascular vasodilation, bone healing, and, with the use of cytotoxic chemicals as sonosensitizers, the treatment of malignant cells.^{17,33,34}

MIST ultrasound therapy has been shown to enhance angiogenesis and collagen deposition in a diabetic mouse model.³⁵ In a randomized, controlled, double-blinded, sham study of diabetic foot ulcers in human subjects, MIST therapy achieved statistically significant greater healing outcomes when compared with sham therapy (40.7% vs 14.3%, respectively).³⁶ The multicenter trial had more than 25 inclusion and exclusion criteria and required the investigators to use a prescribed dressing regimen throughout the study to maintain the rigid criteria for a randomized controlled trial.

The purpose of the present study was to evaluate healing outcomes, both initial and complete, in human subjects with wounds of multiple etiologies common to a typical outpatient wound clinic. The study was designed with limited inclusion and exclusion criteria to aid in predicting the performance of MIST therapy in an actual wound clinic setting. Laser Doppler (PIM 2 Perfusion Imager; Perimed, Inc, Stockholm, Sweden) image analysis was performed on all patients to assess the impact of ultrasound on angiogenesis and the microcirculation in a human model. Wound measurements were taken and the wounds were photographed weekly. Transcutaneous oxygen (TcPO₂) (Peri-flux system 5000, Multichannel TcPO₂; Perimed, Inc) was measured at the periwound tissue to assess tissue oxygenation at enrollment.

MATERIALS AND METHODS

Design

The trial was designed to evaluate the clinical effectiveness of a novel, low-frequency (kilohertz) noncontact ultrasound therapy for the treatment of recalcitrant chronic wounds. Patients were selected from those receiving wound care in a single, hospital-based, outpatient wound program located at Advocate Christ Medical Center in Oak Lawn, IL. The study was designed as a prospective, noncomparative, clinical outcomes trial. The absence of a positive clinical response to the clinic's standard of care (SOC) was used as criteria for inclusion. The approach to patients with chronic wounds in the clinic has been published and validated.³⁷ Patients are evaluated for tissue perfusion, bioburden, pressure, nutrition, and psychosocial issues, and a thorough evaluation of the wound bed tissue is performed. In addition, the authors used a previously published, prospective, intent-to-treat, healing outcomes database from the same clinic as a historic control.³⁸ Institutional Review Board (IRB) approval to conduct the study was obtained; the study was considered a nonsignificant risk study in accordance with the Code of Federal Regulations 21CFR 812.3.

Eligibility

Chronic wounds of any etiology on the lower extremity were considered for enrollment if they had been present longer than 4 weeks and had failed to improve despite using the clinic's standard approach for wound care during a 2-week period. Failure to improve was defined as less than a 15% reduction in wound area. The principal investigator evaluated the patient's wound for clinical signs of infection, such as periwound erythema, odor, and purulent drainage.

To provide a homogeneous population, the investigator had to ensure the patient had no clinical signs of infection and was not taking antibiotics at the time of enrollment. Although it is difficult to determine the presence or absence of clinical infection in the diabetic population, other studies have used this exclusion criteria, making study comparisons more likely.^{8,36} Ultrasound therapy is not contraindicated for infected wounds; however, due to the fact that consensus on clinical signs and symptoms that define wound infection are inconsistent in the literature, it was decided to exclude these patients from the study.³⁹ Potential patients were informed of the 3-times-per-week treatment protocol to increase the chance of successful study completion. Patients were enrolled despite the presence of multiple comorbidities, such as peripheral vascular disease, coronary heart disease, and hypertension. The patients were older than 18 years and able to read, understand, and sign an IRB-approved consent form. During the 8-month period of recruitment, 75 new patients were screened by the lead author

(WJE). Some of the reasons for nonenrollment included patients with pressure ulcers that required surgical flap closure, the inability to achieve 3 visits per week (ie, nursing home residents), or the need for urgent revascularization. Twenty-four patients with 30 wounds were screened for enrollment. In total, 32% of new patients seen in the clinic were selected for the trial.

Screening

Patients who were considered for the trial continued to receive moist wound dressings, compression as indicated, and debridement as required; they were also maintained on prior systemic medications for the 2 weeks from initial screening until possible enrollment. If no improvement was seen—defined by greater than a 15% reduction in area—after 2 weeks of SOC provided at the clinic, patients were enrolled in the study and began MIST therapy. Twenty-three of 24 patients screened failed to improve after 2 weeks of SOC therapy. The study results are based on this 23-patient, 29-wound cohort.

Enrollment

After enrollment, MIST therapy was performed 3 times per week for treatment intervals that were dependent on wound area (Table 1). A moist wound environment was maintained using advanced wound care dressings selected by the investigator (eg, alginates, hydrogels, and foam dressings). Patients whose wounds produced a large amount of exudate were allowed to perform dressing changes at home in addition to those performed in the clinic. The clinic staff demonstrated dressing change techniques and viewed patients performing the dressing change before allowing home dressing changes. Digital photography, wound measurements, and local debridement as required were performed weekly.

Table 1.

TREATMENT TIME ACCORDING TO ULCER AREA

Ulcer Area (cm ²)	Treatment Time (minutes)
<10	3
10-19	4
20-29	5
30-39	6
40-49	7
50-59	8
60-69	9
70-79	10
80-89	11
>90	12

To simulate real clinical practice, it was decided that patients should be transitioned from MIST therapy to another treatment protocol if they had a healing trajectory that either had not been established or had reached a plateau (ie, 2-4 consecutive weeks without area or volume reduction). This approach is followed by the authors for all other treatment modalities, (eg, electrical stimulation and traditional ultrasound therapy), making these MIST trial results comparable to those seen in the historic control group. The incidence of complete healing using the MIST device followed by a subsequent therapy has been termed "MIST-assisted healing" for the purposes of this study. In this trial, a maximum of 20 weeks of MIST therapy could be used; however, it was anticipated that a shorter treatment course would be used. Secondary end points included area and volume reductions. MIST treatments should optimally be delivered no less than 24 or no more than 72 hours apart. It was determined that patients who missed 3 consecutive visits or 7 total visits during the study would be dropped from the study. However, this was not a factor during the present study; all patients adhered to the treatment schedule. A maximum of 30 wounds were to be enrolled.

Macrovascular and microvascular testing

Baseline TcPO₂ testing was performed to assess microcirculation and tissue oxygenation. Patients were stabilized for 15 minutes in a recumbent position followed by the application of a Clarke electrode over the periwound tissue, defined as being within 5 mm from the wound edge. An infraclavicular electrode was placed at the midclavicular line to provide a patient-specific control value for TcPO₂ values and to create a regional perfusion index (defined as the periwound TcPO₂ value divided by the chest wall control; normal values are >0.65).⁴⁰

A dime-sized, Clarke-type, solid-state polarographic electrode (E5280) containing a platinum cathode with a reference electrode of silver chloride is housed in a probe tip along with a heater and a thermistor. The tip of the probe is covered with a permeable membrane. The electrode is attached via a fixation device to the immediate periwound skin and heated to 43° C to 45° C, which induces hyperemia and the dissolution of keratin lipids, thereby increasing gas permeability. The final TcPO₂ result may be influenced by capillary temperature, blood flow, and metabolic oxygen consumption. Although there is a short distance from the probe tip to the capillary (0.3 mm), the oxygen has to pass through metabolically active tissue and is, therefore, partially consumed. The TcPO₂ value does not directly correlate to the arterial blood gas, often causing confusion among health care providers working with this equipment. The technique generates a value that is more reflective of the

difference between oxygen delivery and utilization than an approximation of arterial PO₂.

Microvascular status was also evaluated at baseline and at each clinic visit using the Perimed PIM 2 scanner. This non-invasive device generates mean voltage values from the entire surface of the wound bed. Laser Doppler imaging (LDI) corrects for spatial variations noted in single periwound measurement devices by imaging a larger surface area and calculating average perfusion values. Two mirrors guide a He-Ne laser beam sequentially over the skin surface. At each measurement site (40% maximum), a tissue volume of a few hundred micrometers is illuminated. A photodetector records backscattered Doppler-broadened light, which is created by the interaction of the beam with the moving blood cells. The light signal is converted into an electrical signal and transferred to a signal processor and stored in computer memory. An image matrix is created by dividing the full range of values into 6 color-coded intervals. This process results in a multicolored picture (using a color printer), which represents the microvascular perfusion in the scanned region. By converting the image matrix to an ASCII format, the data may be analyzed by any spreadsheet or statistical software package.

Macrovascular status was determined by hand-held Doppler analysis and angiography when indicated.

MIST therapy system

The MIST therapy system is a low-frequency, noncontact ultrasound device. The generator converts voltage to high-frequency electrical energy. The electrical energy is transmitted to a piezoelectric transducer (lead zirconate titanate PZT), where it is changed to mechanical energy. The transducer operates at 40 KHz with a distal displacement of 60 to 70 microns. The mechanical energy is transferred to a transducer horn (titanium alloy) that vibrates longitudinally, creating an acoustic pressure output. When the leading edge of the applicator tip touches tissue (10 mm), the maximum transducer intensity at a distal displacement of 65 microns is 1.25 W/cm². Sterile saline in a disposable reservoir is used to create the vaporized mist, which acts as a conduit, or coupler, for delivery of the ultrasound energy to the wound bed without the need for direct patient contact.

The atomized saline is directed at the wound bed, with the device held perpendicular to the wound. It is passed horizontally and vertically multiple times during a 4-minute period. The device has a fixed frequency; therefore, the intensity at the wound is a function of the distance from the radiating surface of the transducer to the wound surface. The leading edge of the disposable applicator is held at a distance of 5 to 15 mm from the wound bed during treatment. It is also 10 mm from the

transducer's radiating surface, allowing the actual treatment range to be 15 to 25 mm from the transducer's radiating surface. Therefore, at a distal displacement of 65 microns, the treatment intensity within the therapeutic range is 0.1 to 0.5 W/cm².

MIST treatment

After removal of the dressing and irrigation of the wound with saline, the MIST device was opened and a new sterile saline bottle was attached to the transducer. The treatment was conducted holding the device perpendicular to the wound bed and moving the device in an up and down pattern across the wound bed, as described above. After treatment, the wound was covered with an appropriate dressing that provided a moist environment, and the patient was given discharge instructions.

RESULTS

Twenty-three patients with 29 wounds were enrolled in the study. The overall group demographics are presented in Table 2. To compare this therapy with the authors' previously published clinical outcomes, the clinic database was filtered to search the most recent 3 years for wounds with a duration between 1 and 30 months, which was the range obtained in the present 29-wound study. In addition, the database was filtered to include only the wound etiologies that were represented in the present trial. There were almost twice as many men as women in this study, although that was not statistically significant. The average age of the patients was 61 years, and they suffered from numerous chronic comorbid conditions. Patient demographics were comparable between patients included in the present study and the historic control group.

Wounds with a variety of clinical etiologies were included in this study (Table 3). The wounds were recalcitrant, with a mean duration of 9.86 months. Venous and ischemic ulcers in this

trial had a statistically significant longer wound duration on enrollment compared with historic controls. Diabetic ulcers were significantly larger in the historic control group. The most common wound etiology, diabetic foot ulcers, comprised 41% of the total wounds treated in the present study. Although diabetic wound etiology was the most predominant in this study, in the authors' published experience, there has been no statistically significant difference in healing rates from wounds of various etiologies.⁴¹ Wound size ranged from 0.3 to 45 cm² at enrollment, with a mean of 5.5 ± 1 cm².

The clinician performed sharp/surgical debridement when indicated at each visit. Venous and ischemic ulcers were less likely than wounds with other etiologies (*P* < .05) to be debrided during this trial.

The mean value for the baseline periwound TcPO₂ measurement was 30, which is considered a borderline low value for healing⁴² (Table 4). The mean regional perfusion index was also low at 0.56; it is generally accepted that a perfusion index of 0.7 is required for normal healing.⁴²

Three patients, each with 1 wound, were lost to follow-up because they transferred to a different care setting during the course of the study. One patient was transferred due to insurance purposes and the other 2 were hospitalized at outside facilities. Another patient with 2 wounds died from a hemorrhagic stroke unrelated to the study device, leaving 2 wounds unhealed. Another patient experienced acute thrombosis of a peripheral leg bypass graft. Subsequently, this patient suffered a myocardial infarction and lost the leg to amputation, leaving 2 wounds unhealed. Two additional wounds were unhealed at the conclusion of the trial, for a total of 9 wounds that did not achieve closure. The data are reported on all 29 wounds, however, in an intent-to-treat approach. In addition, all area and volume reduction values are included for patients lost to follow-up as part of the Kaplan-Meier analysis. Those lost to follow-up, death, or amputation are included in the MIST-only group if they only received MIST therapy during the study. The final outcomes are described as those healed by MIST alone and those healed by MIST assisted by a secondary procedure.

Table 5 describes the final outcomes for the 29 wounds subdivided into their various etiologies. An overall healing rate of 69% was achieved during a maximum treatment time of 27 weeks (2 wounds) and a mean treatment time of 13 weeks in this study, despite the loss of 7 wounds from patients lost to follow-up, death, or amputation. Removing these cases results in a 91% healing rate, although this would not represent the intent-to-treat analysis, which is accepted as standard for reporting scientific reports.

A subgroup analysis of outcomes stratified to either those treated with MIST therapy alone or with MIST therapy

Table 2.

PATIENT DEMOGRAPHICS

Demographics	Current Trial		Historic Control	
	(n = 23)	%	(n = 122)	%
Gender				
Male	15	65.22	53	43.44
Female	8	34.78* NS	69	56.56
Average age (years)	61.06 ± 3		66.5 ± 16	
Comorbidities				
Hypertension	12	52.17	64	52.46
Diabetes	12	52.17	53	43.44
Coronary heart disease	8	34.78	13	10.66
Smoker, active	3	13.04	20	16.39
Peripheral vascular disease	9	39.13	32	26.23

**P* > .05; NS = not statistically significant.

Table 3.

WOUNDS BY ETIOLOGY

Wound Etiology	Number of Wounds		Total Number of Debridement Episodes/ Wound During Study (mean ± SEM)	Wound Duration (months; mean ± SEM)		Initial Wound Area (cm ² ; mean ± SEM)	
	Current Trial n (%)	Historic Control n (%)		Current Trial	Historic Control	Current Trial	Historic Control
Diabetic	12 (41.38)	30 (13.76)	1.75 ± 0.5	8.83 ± 1	5.81 ± 0.9	3.02 ± 1	8.44 ± 2*
Venous	3 (10.34)	96 (44.04)	0.67 ± 0.3	18.33 ± 6 [†]	6.4 ± 0.6	5.66 ± 3	4.65 ± 0.8
Ischemic	5 (17.24)	22 (10.09)	0	11.40 ± 2 [†]	4.12 ± 1	3.37 ± 1	5.60 ± 2
Pressure	1 (3.44)	46 (21.10)	0	8.00	6.25 ± 0.9	7.50	13.19 ± 4
Postoperative	4 (13.79)	24 (11.00)	1.5 ± 1	5.50 ± 2	3.87 ± 0.8	12.94 ± 10	7.47 ± 2
Inflammatory	4 (13.79)	0 (0)	0.25 ± 0.2	9.50 ± 4	NA	7.56 ± 4	NA
Total	29 (100)	218 (100)	1.03 ± 0.3	9.86 ± 1 [†]	5.84 ± 0.4	5.50 ± 1	7.55 ± 1

*Significant at $P = .03$ [†]Significant at $P \leq .007$

SEM = standard error of the mean; NA = not applicable.

followed by another treatment protocol yields noteworthy results (Table 6). Wound volume reduction was achieved to a statistically significant greater degree in wounds treated by MIST therapy alone than wounds treated with MIST therapy assisted by a secondary procedure ($P = .04$). Volume reduction appears to be an indicator of therapeutic benefit from MIST therapy. Wounds that achieved total closure using only MIST therapy were older in duration and smaller in size than those that healed in the MIST-assisted group, although there was no statistical significance noted.

Wounds achieving closure by MIST therapy alone were healed in a mean of 8 weeks compared with 18.71 weeks (Kaplan-Meier method) for those patients healed with MIST therapy followed by an additional modality ($P = .0005$; Table 7). Again, it was expected that wounds that required additional therapy post-MIST treatments would take longer to heal, but the relatively short treatment time to healing was surprising in the MIST-only group.

DISCUSSION

Many modalities are available for managing wounds, and the wound care clinician often selects a therapy based on anecdotal

experience. The authors have utilized physical therapy-based wound modalities throughout the past 10 years for patients with wounds that fail to improve during an initial 2 to 4 weeks of SOC. The database used in this study was prospectively collected and includes all patients seen more than once. Patients in the present study had an average wound duration of 9.86 months prior to presenting to the wound care clinic. Patients were further stratified by using a 2-week washout period to ensure that only wounds that did not respond to treatment were included in the study.

Patient demographics, wound size, and duration were matched without any statistically significant differences. The overall percentage of wounds healed in the present study was 69%, compared with 72% of wounds in the historic control group, which was not statistically significant ($P > .05$). The historic control group was treated with electrical stimulation, megahertz-based ultrasound, or a combination of the 2 if patients failed to improve with 2 to 4 weeks of SOC; this occurred in 12% of the cases. Further analysis of the treatments performed in the historic control group revealed that another 20% of patients were admitted to the hospital, and 17% of those underwent surgical debridement and/or closure of the wound, compared with 3.3% and 0%, respectively, of the patients in the present study ($P = .04$). The statistically significant trend toward increased surgical intervention in the historic control group resulted in shorter median healing times. There are striking differences in the healing rates of the MIST-only group compared with the MIST-assisted group. MIST-only therapy resulted in healing with a Kaplan-Meier mean of 8 weeks, which is highly significant compared with MIST-assisted healing ($P = .024$). For practicing clinicians with a

Table 4.

VASCULAR STATUS

TcPo ₂ Probe Location	Number of Patients (n = 22)*
Periwound TcPo ₂ (mean)	30.0
Chest wall TcPo ₂ (mean)	58.6
Regional perfusion index	0.56

Regional perfusion index = TcPo₂ periwound/TcPo₂ chest wall control

*Data available from 22 of 24 patients

Table 5.

FINAL DISPOSITION BY WOUND ETIOLOGY

Wound Etiology	Total in Current Study, n (%)	Healed MIST-Only, n (%)	Healed MIST-Assisted, n (%)	Not Healed, n (%)	Lost to Follow-Up, n (%)	Overall Healing, Current Study, n (%)	Historic Controls, n (%)
Venous	3 (10.3)	2 (66.7)	1 (33.3)	NA	NA	3 (100)	71 (73.19)
Diabetic	12 (41.1)	4 (33.3)	4 (33.3)	3 (25.0)	1 (8.3)	8 (66.6)	23 (76.66)
Ischemic	5 (17.2)	NA	2 (40.0)	3 (60.0)	NA	2 (40.0)	12 (75.0)
Pressure	1 (3.4)	NA	NA	NA	1 (100)	0 (0)	33 (64.70)
Postoperative	41 (3.8)	3 (75.0)	1 (25.0)	NA	NA	4 (100)	18 (75.0)
Inflammatory	4 (13.8)	NA	3 (75.0)	NA	1 (25.0)	3 (75.0)	NA
Total	29 (100)	9 (31.0)	11 (37.9)	6 (20.7)	3 (10)	20 (68.9)	157 (72.02)

NA = not applicable.

myriad of treatment options available, having a quantitative parameter such as this that could be used to determine treatment duration and, ultimately, its success would be helpful.

Laser Doppler imaging was performed at each visit during the study. The laser system is able to generate a digital image of the wound that can then be used for planimetric analysis in addition to measuring microcirculatory flow. A sterile string is applied to the perimeter of the wound, which marks the outline of the wound and allows for easy recognition on the digital image. Wound area can then be planimetrically calculated by adding the sum of pixels within the outlined region. Wound volumes in this study were calculated using standard length, width, and depth measurements. Figure 1 shows the volume reduction over the first 10 weeks of the trial. There is an immediate separation between MIST-only and MIST-assisted cases within the first 4 weeks. The MIST-only cases achieve a

20% volume reduction compared with essentially no change in the MIST-assisted cases. The area reduction is also predictive, with a 40% reduction in area compared with a 15% reduction in area noted in the MIST-assisted group (Figure 2).

Although volume is difficult to measure accurately, it is an important parameter in wound healing, especially if the modality under investigation stimulates healing through the production of granulation tissue. There are also reasons to consider volume reduction as a surrogate end point for patients with end-stage disease and/or in palliative medicine.⁴³ To help understand this phenomenon, the microcirculation data were analyzed. In both MIST-only and MIST-assisted cases, there was an early rise in overall mean wound voltage (Figure 3). The authors propose that existing capillary recruitment via nitric oxide release is responsible for the initial increase seen in the first 2 weeks of MIST therapy. From week 4 through week 8,

Table 6.

OUTCOMES

	Current Study	MIST Only	MIST-Assisted	Significance Between MIST-Only and MIST-Assisted	Historic Control
Total wounds	29	14	15		218
Number of healed wounds	20	9	11		157
Total % healed	68.97	31.04	37.93		72.01
% Area reduction MIST	61.84	75.84	47.83	NS	
% Area reduction overall	80.36*	79.15	81.58	NS	62.00
% Volume reduction MIST	61.83	74.44	10.05	<i>P</i> = .04	
% Volume reduction overall	69.75	78.31	61.20	NS	76.89
Wound duration mean (months)	9.86 ± 1 [†]	13 ± 2	7.67 ± 1	NS	5.84
Initial mean baseline area	5.50	4.62	6.32	NS	7.55
Mean area post-MIST therapy	1.51	1.69	1.35	NS	
Weeks MIST treatment/number of individual MIST treatments	8.71/24.6	6.82/18.64	10.47/30.33	<i>P</i> = .01	

*Not significant at *P* = .09 compared with historical control†Significant at *P* = .007 compared with historical control

NS = not statistically significant.

Table 7.

KAPLAN-MEIER RESULTS

	Current Study						Historic Control		
	MIST-Only		MIST-Assisted						
Wounds	n = 14	Mean ± SEM	Median ± SEM	n = 15	Mean ± SEM	Median ± SEM	n = 218	Mean ± SEM	Median ± SEM
Weeks of treatment		8.06 ± 1	7.00 ± 1		18.71 ± 1	19.00 ± 2		12.86 ± 0.7	10.00 ± 0.7
Disposition									
Healed (%)		9 (64.29)			11 (73.33)			157 (72.02)	
Not healed (%)		5 (35.71)			4 (26.67)			61 (27.98)	
Total Wounds	29						218		

Significance for weeks of treatment: *P* = .0005

Log rank between MIST-only and MIST-assisted if it is calculated without the historical control

SEM = standard error of the mean

there is a significant increase in voltage in those wounds that subsequently went on to heal without the need for an additional therapy. Wounds in the MIST-assisted group had a flat response, related to microcirculatory flow, compared with wounds in the MIST-only group after the initial small increase. This delayed increase in voltage or microcirculation is likely secondary to an absence of angiogenesis and subsequent granulation tissue formation.

The spike in angiogenesis activity directly correlates with wound volume reduction. If the wound is filling from the base with new granulation tissue, one would expect the volume to decrease and anticipate that this new tissue has increased microcirculation. This type of analysis might allow clinicians in the future to predict the clinical effectiveness of a treatment at

an earlier point in the treatment course, which could lead to improved overall healing rates, fewer complications, and improved cost effectiveness.

Another noteworthy finding in this trial is the synergistic effect noted when Apligraf (Organogenesis, Inc, Canton, MA) was used following initial MIST therapy. Within the MIST-assisted group, 12 wounds were treated with Apligraf. Nine (75%) of these wounds healed using an intent-to-treat model, with a Kaplan-Meier mean of 19 weeks. The average number of weeks of MIST therapy before using Apligraf was 10 weeks. This means that 75% healing was achieved, on average, in 9 weeks after Apligraf was placed. Two wounds that were treated with Apligraf were located on a patient who died during the trial. The third wound treated with Apligraf became infected

Figure 1.
PERCENTAGE AREA REDUCTION OVER TIME

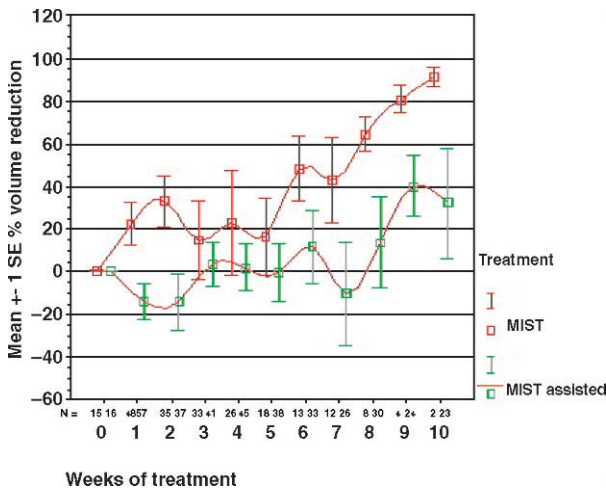


Figure 2.
PERCENTAGE VOLUME REDUCTION OVER TIME

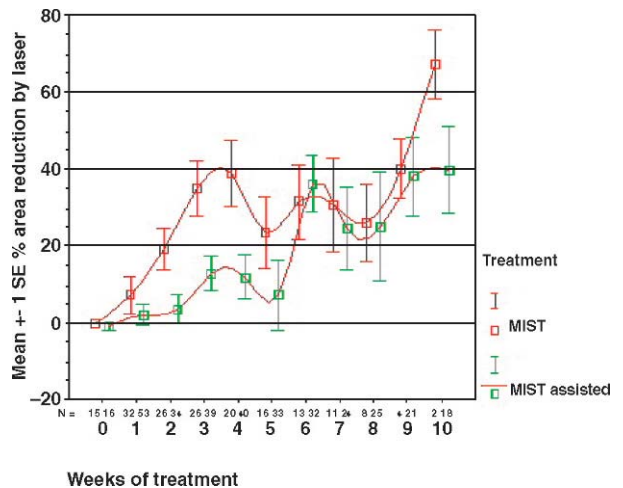
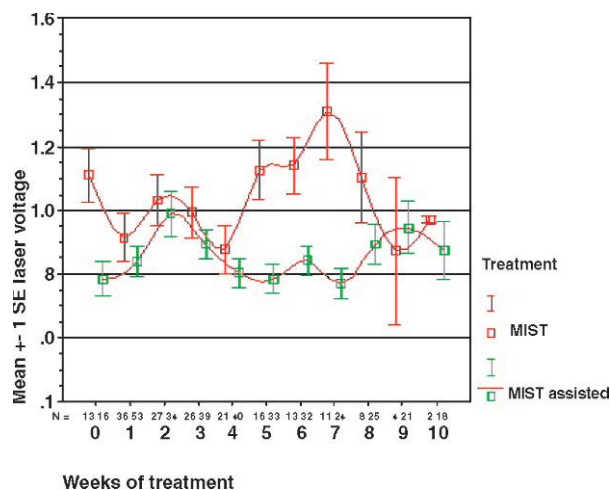


Figure 3.
LASER DOPPLER-MEASURED MICROCIRCULATORY FLOW OVER WEEKS OF TREATMENT



after the Apligraf had resulted in near closure of the wound. The patient was found to have infected underlying hardware and the wound healed completely after the hardware was removed. These results are exceptional, and the clinical appearance of the Apligraf construct over the weeks following application was unusual. The investigators were able to identify intact, viable grafts 6 weeks after placement. It is the authors' theory that MIST therapy effectively lowers the bioburden and therefore improves the biochemical impact from the large number of growth factors known to be viable in Apligraf. The authors are planning a study of this apparent synergistic effect in the future.

There are a few limitations to this study that need to be addressed. First, it was not a randomized controlled trial. The study's design was intended to emulate the scope and variety of cases seen in most outpatient wound care centers. Historic control data are a second best option to a prospectively gathered control data pool. All wounds in the historic control group used in this study were treated by the authors utilizing a published wound care clinical pathway.

Another limitation is the fact that the principle investigator was able to transition the patient to another modality based on clinical impressions and not a rigidly prescribed time frame. This might make reproducing the results more difficult; however, it helps align the data in this study with the historic controls.

Using wounds of various etiologies may also complicate the analysis of the results. The authors have, however, published data that support the concept that wounds of multiple etiologies will heal within similar time frames if they are approached in a routine and systematic fashion.⁴¹ Future work with this and other wound care technologies needs to address the overall episode of care cost of healing. Quantifiable, reproducible markers are needed to assist clinicians in their treatment decisions. Much practice variation exists with regard to modalities used, timing of treatments, and transition patterns from one therapy to another. The preliminary results of the present study point to determining the clinical effectiveness of an ultrasound therapy within 4 weeks of treatment. The use of this office-based therapy may help reduce overall costs of care if admissions and surgical interventions could be reduced, even if overall treatment times were slightly increased.

SUMMARY

MIST ultrasound therapy was shown to be clinically effective in a recently published randomized, controlled, multicenter trial for the healing of diabetic foot ulcers.³⁶ The present study extends the application of the product to common wound types that are seen in a typical outpatient wound center. The authors have found the treatment to be quick, painless, and clinically effective, as evidenced by the 69% healing rate found in the present study. In addition, results of the present study indicate that a subgroup of wounds will go on to complete healing without the need for any additional treatments (ie, MIST therapy only). These cases were identified by area and volume reductions over the first 4 weeks of treatment. Early reduction in wound size seems to correlate with an increase in angiogenesis in the wound bed. The wounds that healed with the use of MIST therapy only healed in a statistically significant reduced time frame compared with wounds treated with MIST therapy and an assisted modality (8 weeks vs 18.7 weeks, respectively; $P = .0005$). If patients could be identified as early responders for MIST therapy, a cost savings could be realized through the significant reduction in treatment times. Further work on cost-effective outcomes and mechanisms of action are planned for the future. ●

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