

Use of Noncontact Low-Frequency Ultrasound in the Treatment of Chronic Foot and Leg Ulcerations

A 51-Patient Analysis

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Background: A feasibility study was conducted to characterize the effects of noncontact low-frequency ultrasound therapy for chronic, recalcitrant lower-leg and foot ulcerations.

Methods: The study was an open-label, nonrandomized, baseline-controlled clinical case series. Patients were initially treated with the Mayo Clinic standard of care before the addition of or the switch to noncontact low-frequency ultrasound therapy. We analyzed the medical records of 51 patients (median \pm SD age, 72 \pm 15 years) with one or more of the following conditions: diabetes mellitus, neuropathy, limb ischemia, chronic renal insufficiency, venous disease, and inflammatory connective tissue disease. All of the patients had lower-extremity ulcers, 20% had a history of amputation, and 65% had diabetes. Of all the wounds, 63% had a multifactorial etiology, and 65% had associated transcutaneous oximetry levels below 30 mm Hg.

Results: The mean \pm SD treatment time of wounds during the baseline standard of care control period *versus* the noncontact low-frequency ultrasound therapy period was 9.8 \pm 5.5 weeks *versus* 5.5 \pm 2.8 weeks ($P < .0001$). Initial and end measurements were recorded, and percent volume reduction of the wound was calculated. The mean \pm SD percent volume reduction in the baseline standard of care control period *versus* the noncontact low-frequency ultrasound therapy period was 37.3% \pm 18.6% *versus* 94.9% \pm 9.8% ($P < .0001$).

Conclusions: Using noncontact low-frequency ultrasound improved the rate of healing and closure in recalcitrant lower-extremity ulcerations. (J Am Podiatr Med Assoc 97(2): 95-101, 2007)

Ultrasound delivers energy through mechanical vibrations (acoustic) in the form of sound waves at predetermined frequencies that are above detection by the human ear (>20 kHz). Therapeutic ultrasound has previously been used in wound healing by investigators using animal models and humans.¹⁻⁴

Therapeutic ultrasound requires the use of a gel or water interface as a medium between the transducer and the substrate.⁵ This medium is required to transfer the mechanical energy from the transducer to the substrate. High-frequency (megahertz) ultrasound has been used in clinical practice in physical therapy, physical medicine and rehabilitation, and sports medicine for many years.

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The noncontact low-frequency ultrasound system uses continuous ultrasonic energy to atomize saline and deliver continuous energy to the treatment site. The mechanism of action of ultrasound is thought to be through the processes of cavitation and microstreaming.⁶ Cavitation involves the production and vibration of micron-sized bubbles in the coupling medium and fluids in the tissues. Microstreaming is the movement of fluids along acoustic boundaries.^{7, 8} The combination of cavitation and microstreaming, which is more likely to occur with kilohertz ultrasound, provides a mechanical energy capable of altering cell membrane activity. Signal-transduction pathways are also stimulated from the ultrasound-generated mechanical energy, which results in a broad range of cellular effects.⁹ Multiple well-documented cellular effects of ultrasound therapy have direct implications for wound healing. Leukocyte adhesion, growth factor production, collagen produc-

tion, increased angiogenesis, increased macrophage responsiveness, increased fibrinolysis, and increased nitric oxide levels are all examples of ultrasound-induced cellular effects.¹⁰⁻¹⁶

The noncontact low-frequency ultrasound system (MIST Therapy; Celleration Inc, Eden Prairie, Minnesota) is a compact, portable unit consisting of a generator, a transducer, and a disposable applicator that has been designed to accept a prepackaged sterile bottle of saline (Fig. 1). This system provides a flow of saline to the tissue surface by the use of low-intensity (0.1–0.5 W/cm²), low-frequency (40 kHz) ultrasound. The disposable applicator contains an on/off valve that controls the flow of sterile saline to the ultrasound transducer surface. The generated mist has a relatively uniform droplet size of 55 to 60 μm. The noncontact low-frequency ultrasound system is designed to deliver therapeutic ultrasound to the wound bed without direct contact of the device with the body or the wound. One advantage of this system is that an external air supply is not required to atomize and propel the fluid and mist. The particles are uniform in size, and there is no contamination issue regarding the air supply. The purpose of this study was to characterize the effects of this novel noncontact low-frequency ultrasound therapy in a group of recalcitrant lower-leg and foot ulcerations.

Materials and Methods

The trial was designed and conducted as an open-label, nonrandomized, baseline-controlled, single-center clinical case series. The Mayo Clinic was the first center in the United States to have the opportunity to



Figure 1. Noncontact low-frequency ultrasound system consisting of a generator, a transducer, and an applicator.

use the noncontact low-frequency ultrasound system in patient care for recalcitrant cutaneous ulcerations. Patients were seen and treated at the Gonda Vascular Wound Healing Center, Mayo Clinic, Rochester, Minnesota. A team of physicians (internal medicine, vascular medicine and surgery, podiatric medicine, interventional radiology, dermatology, and physical medicine and rehabilitation), physician assistants, nurses, and physical therapists provide patient care. In addition to providing primary wound care to patients from Olmsted County, Minnesota, the clinic provides ulcer care to regional, national, and international patients.

Fifty-one patients presenting to the Gonda Vascular Wound Healing Center with lower-leg or foot ulcerations were considered for the study, and their medical records were reviewed. Many of these individuals had ongoing wound care at outside institutions before being seen at the Mayo Clinic. These individuals had chronic, nonhealing wounds of 3 to 18 months' duration. Patients' comorbidities or previous failure in ulcer therapy did not exclude them from this feasibility study. Informed consent was obtained from patients before they entered this study, and institutional review board approval was granted by the Mayo Clinic.

Patient assessments included wound cultures, radiographs, transcutaneous oximetry, glycosylated hemoglobin levels, and serum creatinine concentrations. Plain film radiographs were used to screen for osteomyelitis. If bone infection was suspected, magnetic resonance imaging was performed to confirm or exclude the presence of osteomyelitis. Patients were not excluded if osteomyelitis was identified. Appropriate antibiotic drug therapy was administered for the medical management of osteomyelitis. Table 1 summarizes the demographics and baseline characteristics of the 51 patients. Wounds were predominantly multifactorial; a large proportion of the patients had a component of limb ischemia and diabetes mellitus.

Table 2 characterizes the wound etiology and the transcutaneous oximetry levels in the distal foot. Sixty-five percent of the patients had transcutaneous oximetry levels less than 30 mm Hg, and 22% had levels less than 20 mm Hg.^{17, 18} Fourteen patients had positive deep culture findings, with *Staphylococcus aureus* and *Pseudomonas aeruginosa* being the most common pathogens noted.

All of the patients first received the standard of care protocol followed by noncontact low-frequency ultrasound therapy when the investigator deemed it appropriate. The mean ± SD time patients received the standard of care protocol was 9.8 ± 5.5 weeks. The standard of care regimen included aggressive

Table 1. Baseline Characteristics of the 51 Study Patients

Characteristic	Value
Age (median [range]) (years)	72 (22–98)
Men	29 (57)
Race	
White	50 (98)
American Indian	1 (2)
Smoking	
Current	13 (25)
Former	24 (47)
Never	14 (27)
History of previous limb revascularization	18 (35)
History of previous amputation	5 (10)
Diabetes mellitus	
Type 2 diabetes	38 (75)
Treated with insulin	33 (65)
Glycosylated hemoglobin level $\leq 8.0\%$	31 (82) ^a
Arteriosclerosis of lower extremity	29 (57)
Hypertension	47 (92)
Albuminuria	22 (43)
Osteomyelitis	8 (16)
Dyslipidemia	32 (63)
Treated with statins	26 (51)
Use of immunosuppressives or corticosteroids	11 (22)

Note: Data are given as number (percentage) except where indicated otherwise.

^aPercentage is based on the 38 patients with diabetes mellitus.

medical management to improve general and cardiovascular health and metabolic control,² moist wound healing, off-loading and compression as appropriate for the diagnosis, and aggressive routine debridement when clinically appropriate. In addition, biologically active products (such as growth factors) and adjunctive wound-care modalities (such as the Circulator

Table 2. Wound Characteristics

Characteristic	Patients (No. [%])
Total cutaneous ulcers	51 (100)
Ulcers of the foot	39 (76)
Ulcers of the leg	12 (24)
Predominant etiology	
Multifactorial	32 (63)
Arterial	8 (16)
Small-vessel disease	5 (10)
Other—neuropathic, venous, traumatic	4 (8)
Transcutaneous oximetry levels (mm Hg)	
<30	33 (65)
<20	11 (22)

Boot [Circulator Boot Corp, Malvern, Pennsylvania] and noncardiac gaited intermittent compression pumps) were routinely incorporated into their care. Patients were followed on a weekly basis during the standard of care period. The baseline standard of care period was continued until the investigator determined that the patient's wounds were no longer progressing. At this point, patients were switched to or had the noncontact low-frequency ultrasound therapy added to their treatment regimen. During the noncontact low-frequency ultrasound treatment period, patients were seen and treated three to five times per week for a mean \pm SD of 5.5 ± 2.8 weeks. Wound measurements and digital photographs of the index wound were obtained on a weekly basis during both periods. Wound measurements were obtained using length \times width \times depth calculations.

Results

Table 3 summarizes the starting and ending wound volume measurements for the baseline standard of care control period and the noncontact low-frequency ultrasound treatment period. Given the study design, the starting wound volumes in the baseline standard of care period were larger than those in the noncontact low-frequency ultrasound treatment period. In addition, as defined by the study design, the ending wound volume for the baseline standard of care period was the same as the initial wound volume for the noncontact low-frequency ultrasound treatment period. An analysis of covariance showed that there was a significant difference between the baseline standard of care and noncontact low-frequency ultrasound treatment periods ($P < .05$). Analysis of covariance is the appropriate model selection for this experiment because the starting wound size was smaller for noncontact low-frequency ultrasound therapy and analysis of covariance can control for such baseline measures when modeling treatment differences. Although no statistical method can discount entirely the potential for bias in the observed results, this analysis suggests that the order of treatment was not responsible for the results obtained.

Table 4 summarizes a variety of additional key wound closure parameters. In the noncontact low-frequency ultrasound treatment period *versus* the baseline standard of care period, the mean percent reduction in wound volume and weekly rate of volume reduction were significant ($P < .0001$ and $P < .0237$, respectively). The mean \pm SD treatment times for the baseline standard of care and noncontact low-frequency ultrasound treatment periods were 9.8 ± 5.5 and 5.5 ± 2.8 weeks, respectively ($P < .0001$). During

Table 3. Wound Volumes During the Control and Treatment Periods

Variable	SOC	MIST	P Value
Starting wound volume (mean [SD]) (mm ³)	2,477 (4,979)	1,609 (3,395)	<.0011
Ending wound volume (mean [SD]) (mm ³)	1,609 (3,395)	144 (470)	<.0009
Ratio of starting to ending volumes	1.54:1	11.2:1	

Abbreviations: SOC, standard of care; MIST, a noncontact low-frequency ultrasound system.

Table 4. Wound Closure Statistics During the Control and Treatment Periods

Variable	SOC	MIST	Difference	P Value (Paired <i>t</i> Test)
Wound volume reduction (%)	37.3 ± 18.6	94.9 ± 9.8	-57.6 ± 17.5	<.0001
Treatment (weeks)	9.8 ± 5.5	5.5 ± 2.8	4.25 ± 4.49	<.0001
Volume reduction per week (mm ³)	91 ± 160	318 ± 747	-227 ± 694	.0237

Abbreviations: SOC, standard of care; MIST, a noncontact low-frequency ultrasound system.

Note: Data are given as mean ± SD.

the baseline standard of care period, no wound closures were noted. However, 26 of the chronic wounds proceeded to closure during the noncontact low-frequency ultrasound treatment period. Both of these findings were significant ($P < .05$).

In addition to the previously mentioned wound closure parameters, we observed in patients without closure during the noncontact low-frequency ultrasound treatment period that treatment with the ultrasound therapy system stimulated the wound bed to develop robust granulation tissue to act as an excellent substrate for skin substitutes, which was not apparent during the baseline standard of care period.

Discussion

This study demonstrated a significant improvement in the rate of healing in the noncontact low-frequency ultrasound therapy period compared with the baseline standard of care period. Although this was not a randomized, concurrently controlled, parallel-group clinical study and could have some degree of bias owing to the baseline-controlled design, the results indicate that noncontact low-frequency ultrasound therapy may be effective in the treatment of recalcitrant lower-extremity leg and foot ulcers. In addition, we saw benefits in preparing the wound bed for the utilization of bioengineered skin substitutes in wounds that did not primarily close with noncontact low-frequency ultrasound therapy. It seems that noncontact low-frequency ultrasound therapy develops robust granulation tissue and reduces dense fibrous tissue in the wound bed, facilitating acceptance of the bioengi-

neered skin substitute. In addition, one can consider that the destruction of microbes by the noncontact low-frequency ultrasound may have a cleansing effect on the wound bed.

The soundness of these statistical results is supported by the original trial design. Only wounds that were progressing slowly with baseline standard of care received noncontact low-frequency ultrasound treatment. Although the baseline standard of care wounds exhibited some degree of healing, the mean ± SD percent volume reduction was significantly less than during the noncontact low-frequency ultrasound treatment (37.3% ± 18.6% versus 94.9% ± 9.8%). Although the choice of a baseline-controlled study design prevents a statistical argument claiming that noncontact low-frequency ultrasound therapy is the only factor that could have affected healing, inspection of the clinical trial design, coupled with the observed results, shows that noncontact low-frequency ultrasound therapy played a substantial role in wound outcomes.

Pecoraro et al¹⁹ outlined the risk factors associated with lower-extremity limb amputation, including cutaneous ulcerations, faulty wound healing, initial minor trauma, ischemia gangrene, infection, and neuropathy. The triad of minor trauma, cutaneous ulceration, and wound-healing failure led to 72% of nontraumatic amputations. By altering or improving any of the components of this triad, one may potentially decrease the unfavorable outcomes leading to amputation.¹⁹ This new technology may minimize the deleterious effect of morbidity and mortality due to nontraumatic lower-extremity amputations in the diabetic popula-

tion.²⁰ These patients were especially challenging owing to poor peripheral circulation and, therefore, wound-healing potential. As stated earlier, 65% of the patients had transcutaneous oximetry levels less than 30 mm Hg, and 22% had levels less than 20 mm Hg. In our experience, individuals with chronic critical limb ischemia can be challenging with respect to limb salvage.^{21, 22}

During the baseline standard of care period, patients were seen once per week. During the noncontact low-frequency ultrasound treatment period, those same patients were seen either three or five times per week for treatment. The product is recommended for use three times per week but can be used more frequently depending on the patient's ability to return to the clinic for treatment. One may speculate that the patient seen three to five times per week for therapy may have a more rapid closure rate as a result of increased contact with medical personnel. In our experience, we continue to use other modalities such as the Circulator Boot and intermittent compression pumping when patients are routinely seen three to five times per week.^{21, 22} However, we have not seen the type of response with the use of those products as has been demonstrated with noncontact low-frequency ultrasound therapy.

The wound bed cleansing effect led to evaluation of the effect of noncontact low-frequency ultrasound therapy on microbes. A total of 5×10^6 CFU of *S aureus*, *P aeruginosa*, methicillin-resistant *S aureus*, and vancomycin-resistant enterococci was inoculated onto a tryptic soy agar (TSA) surface for noncontact low-frequency ultrasound therapy using sterile saline applied to agar plates for 2.5 min. Control TSA plates were treated with the same volume of saline *via* the drip method using calibrated pipettes at the same distance from the substrate for 2.5 min. Specimens were collected and prepared for electron microscopy. This simulated the treatment process that was commonly accomplished regarding *in vivo* patient care. Scanning and transmission electron micrographs of bacteria were obtained from treated and control TSA plates to characterize the morphological effect on the organisms treated with noncontact low-frequency ultrasound therapy. In Figures 2 to 5, scanning and transmission electron micrographs show the effects of noncontact low-frequency ultrasound therapy on bacteria. It is clear that there is cell wall destruction of the bacteria after the application of noncontact low-frequency ultrasound therapy, as demonstrated in the scanning and transmission electron micrographs.

Of the 15 patients who received noncontact low-frequency ultrasound therapy three times per week, six (40%) experienced wound closure, and of the 36

patients who received it five times per week, 20 (56%) experienced closure ($P < .05$). These data suggest that more frequent treatments with noncontact low-frequency ultrasound might have an added benefit.

The median age of patients in this study was 72 years (range, 22–98 years). If one looks at mean patient age in relation to the outcome of wound closure, no difference is found. In the 26 wounds that closed, the mean patient age was 71.3 years (range, 22–98 years), and in the 25 wounds that did not close, the mean patient age was 70.0 years (range, 42–90 years). These data support the positive effect of noncontact low-frequency ultrasound therapy across all age groups.

Additional findings during the noncontact low-frequency ultrasound treatment period were more observational. Many of these lower-extremity wounds contained dense fibrous adherent tissue that was generally difficult to remove using sharp debridement techniques without significant damage to the wound bed. During treatment with the noncontact low-frequency ultrasound, this tissue was much less adherent and easier to remove, with minimal damage to the wound bed using similar or identical debridement techniques.

A 30-month survivorship questionnaire was sent to all 51 patients in the study. There were eight deaths and 43 survivors among participants since completion of the study. Six of the eight patients who died had documentation of death in the medical records at the Mayo Clinic. Of the 43 surviving patients, 100% responded and 38 (88%) did not have an incident of further ulceration. Five patients (12%) developed a subsequent ulcer; however, this ulcer was in a different location than the index ulcer. The ulcers of three individuals with ulcer recurrence were neuropathic and those of two were ischemic. The time to repeated ulceration was 6 to 18 months after final treatment.

No serious adverse effects were noted with the use of noncontact low-frequency ultrasound therapy. Tingling in the periulcer area was occasionally noted after treatment. This finding was seen in three patients with leg ulcers with close approximation to the subcutaneous border of the tibia. The tingling was transient and did not prevent continuation of care. One may speculate that the cause of this tingling was the periosteal stimulation from the noncontact low-frequency ultrasound (similar effects are seen with therapeutic ultrasound for musculoskeletal therapy).²³

Our experience using this noncontact low-frequency ultrasound system was very positive. The noncontact low-frequency ultrasound system seems to be an effective modality for the treatment of wounds. This modality has demonstrated a reduction in healing

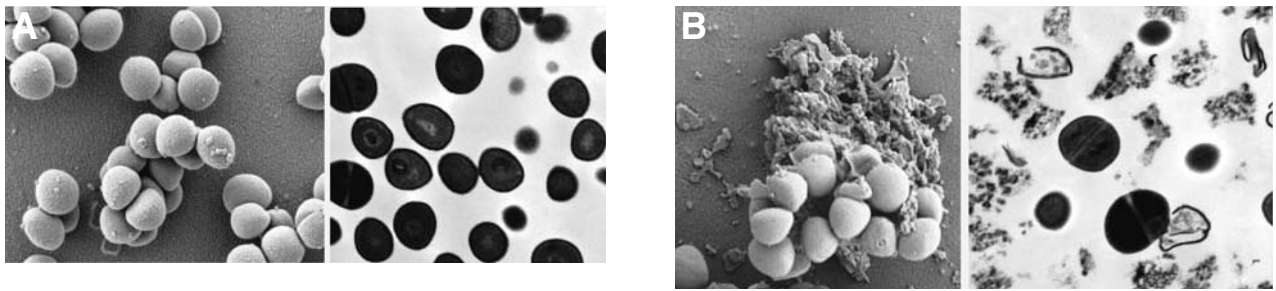


Figure 2. Scanning (left) and transmission (right) electron micrographs of *Staphylococcus aureus* during the control (A) and experimental (B) periods ($\times 40,000$).

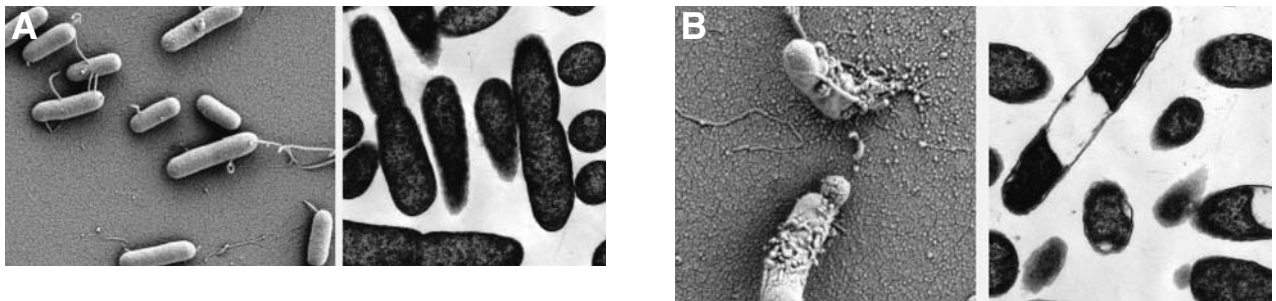


Figure 3. Scanning (left) and transmission (right) electron micrographs of *Pseudomonas aeruginosa* during the control (A) and experimental (B) periods ($\times 40,000$).

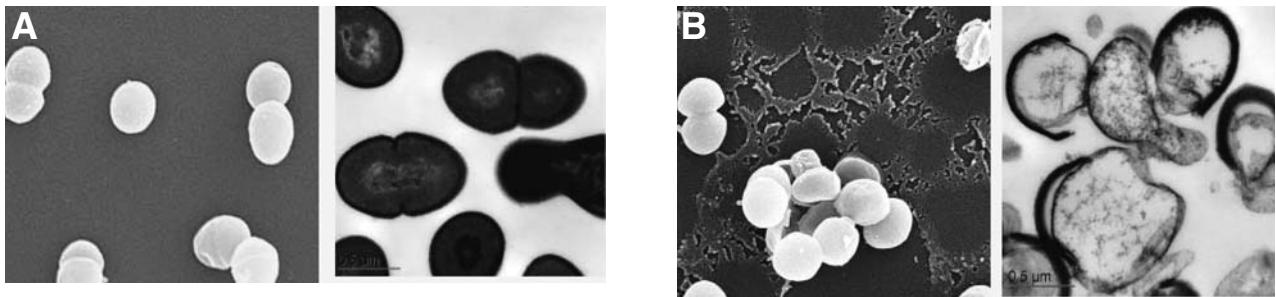


Figure 4. Scanning (left) and transmission (right) electron micrographs of vancomycin-resistant enterococci during the control (A) and experimental (B) periods ($\times 40,000$).

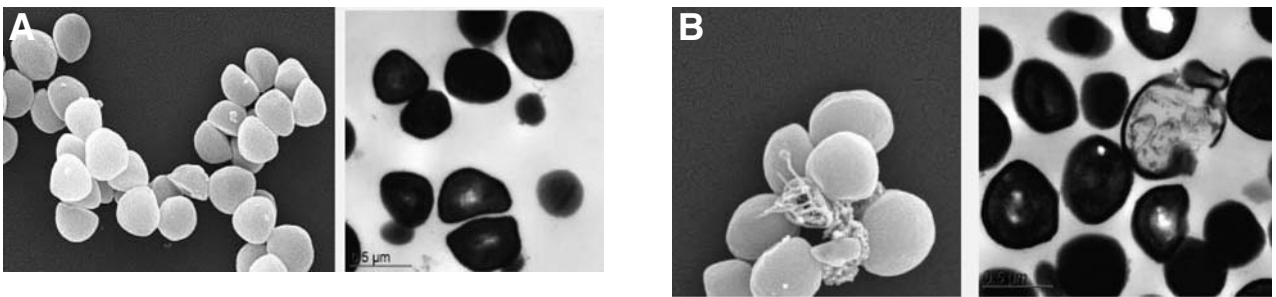


Figure 5. Scanning (left) and transmission (right) electron micrographs of methicillin-resistant *Staphylococcus aureus* during the control (A) and experimental (B) periods ($\times 40,000$).

time and has brought many recalcitrant wounds to closure after the standard of care regimen had failed to do so. It may also assist in preparing the wound bed for advanced wound-healing modalities, such as bioengineered skin substitutes. One may speculate that the bacterial burden or biofilm in the wound bed may be cleansed and removed with noncontact low-frequency ultrasound therapy. Further clinical and basic science investigations using this technology are warranted.

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Conflict of Interest: None reported.

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