Treatment of Ischemic Wounds with Noncontact, Low-Frequency Ultrasound: The Mayo Clinic Experience, 2004-2006

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ABSTRACT

OBJECTIVE: To evaluate the clinical role of a novel, noncontact, low-intensity, low-frequency ultrasound therapy (MIST Therapy) in the treatment of nonhealing leg and foot ulcers associated with chronic critical limb ischemia.

DESIGN: Prospective, parallel-group, randomized, controlled trial.

SETTING: A multidisciplinary, vascular wound-healing clinic.

PATIENTS: Thirty-five patients who received MIST Therapy plus the standard of wound care (treatment group) and 35 patients who received the standard of wound care alone (control group).

INTERVENTIONS: Standard of wound care alone or standard of wound care plus MIST Therapy for 12 weeks or until fully healed. MIST Therapy was administered 3 times per week for 5 minutes per treatment.

MAIN OUTCOME MEASURE: Percentage of patients with greater than 50% reduction in wound size from the index measurement after 12 weeks of treatment. The relationship of transcutaneous oximetry pressure in the supine and dependent position was evaluated as a factor in assessing the potential to heal ischemic ulcerations of the foot and leg.

MAIN RESULTS: A significantly higher percentage of patients treated with the standard of care plus MIST Therapy achieved greater than 50% wound healing at 12 weeks than those treated with the standard of care alone (63% vs 29%; $P < .001$). Thus, failure to achieve the minimum wound healing requirement occurred in 37% of patients in the treatment group and 71% of patients in the control group. The predictive value of baseline transcutaneous oxygen pressure may benefit the clinician when assessing the potential to heal ischemic wounds.

CONCLUSION: The rate of healing of cutaneous foot and leg ulcerations in patients with chronic critical limb ischemia improved significantly when MIST Therapy was combined with the standard of wound care.

ADV SKIN WOUND CARE 2007;20:221–6

The prognosis for patients with nonhealing, lower-extremity ulcers associated with chronic critical limb ischemia is poor. These patients face a future of pain, disability, a high potential for amputation when wounds are recalcitrant, and unacceptable mortality rates after surgery.[1,2] Percutaneous and surgical revascularization procedures to restore adequate blood flow are options for only a small percentage of patients with critical limb ischemia.[2] Although both end-diastolic and non–end-diastolic intermittent pneumatic compression devices appear to improve wound healing and rates of limb salvage, published reports are limited.[3–6] Given the challenge of limb salvage in patients with chronic critical limb ischemia, novel, effective, wound healing modalities are of paramount importance.

Ultrasound as a wound healing modality has been studied in animal models and humans.[7–10] Therapeutic ultrasound devices deliver energy through mechanical vibrations in the form of sound waves at frequencies above detection by the human ear (>20 kHz). High-frequency (1 to 3 MHz) ultrasound has long been used in clinical practice in physical therapy, physical medicine and rehabilitation, and sports medicine. This therapy appears to offer unique benefits for chronic wound care as well.

Noncontact, low-intensity (0.1 to 0.8 W/cm^2), low-frequency (40 kHz) ultrasound therapy (MIST Therapy System; Celleration, Inc, Eden Prairie, MN) delivers continuous ultrasonic energy to the wound site via an atomized saline solution. The clinical benefit of MIST Therapy has been demonstrated in the improved healing of recalcitrant diabetic foot ulcers,[11] as well as chronic lower-extremity wounds of several etiologies.[12,13] These beneficial effects on wound healing appear to be achieved through 2 mechanisms: cavitation and microstreaming.[14] *Cavitation* involves the production and vibration of micron-sized bubbles within the coupling medium and fluids within the tissues. *Microstreaming* is the movement of fluids along acoustical boundaries.[15,16] The combination of cavitation and microstreaming, which are more likely to occur with kHz

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ultrasound than with MHz ultrasound, provides a mechanical energy capable of altering cell membrane activity.[17] The ultrasound-generated mechanical energy also stimulates signal-transduction pathways, resulting in a broad range of cellular effects,[17] including some with direct implications for wound healing, such as leukocyte adhesion; growth factor production; collagen production; and increases in angiogenesis, macrophage responsiveness, fibrinolysis, and nitric oxide.[18–24]

The authors conducted the present study to evaluate progression of wound healing associated with MIST Therapy for the treatment of lower-extremity wounds in patients with chronic critical limb ischemia.

METHODS

Study Design and Patient Selection

The study was designed and conducted as a prospective, open-label, parallel-group, controlled trial of nonhealing foot, ankle, or leg wounds with documented chronic critical limb ischemia. Wounds were present for a minimum of 8 weeks before enrollment. Eligible patients had documented chronic critical limb ischemia as determined by transcutaneous oximetry (≤40 mm Hg) and included those with diabetes mellitus, chronic renal failure, prior vascular reconstructive surgery, and osteomyelitis. Although wound infection was not a criterion for exclusion from the study, no wounds had evidence of erythema or purulent discharge at enrollment. Patients undergoing chemotherapy and those who were unable or unwilling to attend 3 treatment sessions per week were not eligible for the study. Patients were treated at the Gonda Vascular Wound Healing Center, Mayo Clinic, Rochester, MN, by 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. The institutional review board approved the study protocol, and informed consent was obtained from all patients before enrollment in the study.

Seventy patients were randomly assigned to receive 12 weeks of treatment with either the standard of wound care (control group, n = 35) or MIST Therapy and the standard of wound care (treatment group, n = 35). The standard of care group was managed with daily dressing changes and weekly wound debridement, wound measurements, and digital photographs. This regimen included aggressive medical management to improve general and cardiovascular health and metabolic control,[8] moist wound healing, offloading, compression as appropriate, and aggressive weekly debridement when indicated. Compression of the lower extremity with a low-stretch wrap is an important part of the daily therapy to prevent edema in the compromised limb. Further venous congestion from dependency in a patient with chronic critical limb ischemia will impede arterial flow. In addition to the standard of care, the MIST Therapy treatment group received noncontact, low-intensity, low-frequency ultrasound therapy 3 times a week for an average duration of 5 minutes per treatment.

Therapeutic Ultrasound Device

The MIST Therapy System delivers low-intensity (0.1 to 0.8 W/cm^2), low-frequency (40 kHz) ultrasound energy via atomized saline mist (droplet size 45 to 65 micrometer) to the wound bed without directly contacting the body or wound. The device, shown in Figure 1, 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.

Assessments

Baseline assessments included complete blood count with differential; glycosylated hemoglobin; serum creatinine; foot radiographs; transcutaneous oxygen pressure ($TcPO_2$) in the supine, elevated, and dependent positions; and wound cultures if indicated. Transcutaneous oxygen pressure levels were measured using an electrode that warms the skin to 45° C to overcome vasoconstriction. Electrodes were attached for 20 minutes to the skin of interest and to the skin of the chest as a control. The standard placements were 2 on the leg (proximal and distal tibia) and 2 on the foot (hind foot and forefoot). An electrode was placed in the periulcer area to assess the degree of cutaneous ischemia to help predict the healing of clean ischemic wounds.

The primary end point of the study was the incidence of wound healing at 12 weeks in patients treated with the standard of care plus MIST Therapy compared with those treated with the standard of care alone. Wound measurements and digital photographs of wound beds were obtained weekly in both groups. Wound volume was based on ruler measurements, using length by width by depth calculations. Depth measurements were obtained using a sterile, cotton-tip applicator and ruler. The proportion of patients with greater than 50% wound healing, as defined by reduction of wound volume, in the 2 groups was compared.

A secondary analysis evaluated the degree of wound healing associated with $TcPO_2$ levels of 20 to 40 mm Hg and levels less than 20 mm Hg in both the supine and dependent positions. Transcutaneous oxygen pressure levels reflect the degree of

Figure 1.
MIST THERAPY SYSTEM

The photo on the left shows the MIST Therapy System, a unit consisting of a generator, a transducer, and a disposable applicator. The photo on the right shows the disposable applicator discharging saline solution.

mismatch between oxygen delivery (low in critical arterial and arteriolar insufficiency) and oxygen consumption (a reflection of the local metabolic rate, which increases with trauma or infection) at a wound site.[25] Thus, $TcPO_2$ levels quantify the degree of cutaneous ischemia and may help predict the likelihood of healing in clean ischemic wounds. Bacharach et al[26] demonstrated the predictive value of baseline $TcPO_2$ levels for healing of surgical amputation sites. Essentially, a supine $TcPO_2$ of greater than 40 mm Hg reliably predicted healing, and a value of less than 20 mm Hg universally predicted failure of healing. In the Bacharach study,[26] supine $TcPO_2$ between 20 and 40 mm Hg appeared to be a borderline zone in which $TcPO_2$ measurement after leg elevation could improve predictability of outcome. In the present study, the authors also sought to determine whether baseline $TcPO_2$ in the dependent position (foot and leg lowered 90 degrees) would predict healing success in patients with chronic critical limb ischemia.

Statistical Analysis

Quantitative analyses of baseline demographic and clinical characteristics were performed using the Mann-Whitney *U* test. Transcutaneous oximetry values were compared with the Wilcoxon sum-rank test. The Chi-square test was used to compare proportions of patients healed between groups. A probability value of <0.05 was required for statistical significance. All data were analyzed using JMP 4.0 statistical software (SAS Institute, Cary, NC).

RESULTS

Demographic and baseline clinical characteristics of the 70 patients (Table 1) did not differ significantly between groups. A majority of patients were men (77%), with a mean age of 75 years. Comorbid medical conditions were common in this population: 76% had coronary artery disease, 67% had diabetes mellitus, and 80% had hypertension or dyslipidemia. Most (82%) were current or former smokers. Mean serum creatinine values were not indicative of renal failure. Osteomyelitis was present in only a small proportion of patients.

Measures of baseline arterial status did not differ significantly between groups (Table 2). The prevalence of peripheral vascular disease in this population is demonstrated by the median ankle-brachial index of 0.72 and 0.73 in the treatment and control groups, respectively. Prior arterial reconstruction and femoro-distal bypass procedures were also common.

Table 1.

BASELINE PATIENT CHARACTERISTICS

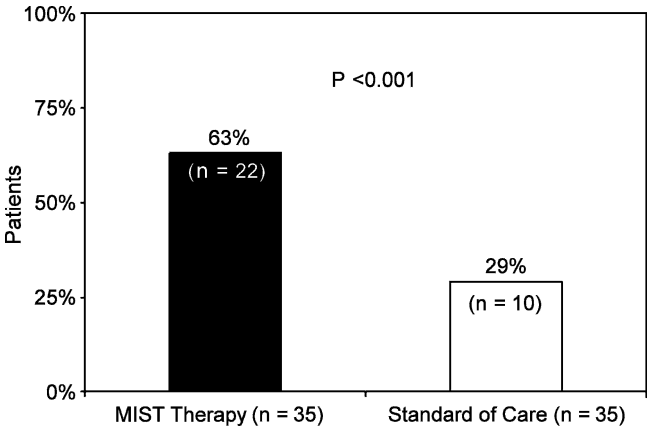
Patient Characteristics	MIST Therapy (n = 35)	Standard of Care (n = 35)
Age, median (range), years	74 (72.2–76.5)	76 (73.4–81.2)
Men, no. (%)	28 (80)	26 (74)
Coronary artery disease, no. (%)	26 (74)	27 (77)
Prior revascularization, no. (%)	24 (69)	28 (80)
Diabetes mellitus, no. (%)	22 (63)	23 (66)
Insulin dependent	12 (55)	9 (36)
Non-insulin dependent	10 (29)	14 (56)
Glycosylated hemoglobin (≤8%), no. (%)	16 (73)	20 (80)
Median (range)	7 (6.72–7.85)	6.9 (6.2–7.98)
Hypertension, no. (%)	26 (74)	30 (86)
Dyslipidemia, no. (%)	29 (83)	27 (77)
No. (%) treated with statins	22 (63)	25 (71)
Smoking, no. (%)		
Current	5 (14)	4 (11)
Former	26 (74)	22 (63)
Never	4 (11)	9 (26)
Chronic renal failure		
Serum creatinine, median (range)	1.2 (1.1–1.8)	1.2 (1.17–1.85)
No. (%) on hemodialysis	3 (8)	4 (11)
Osteomyelitis, no. (%)	4 (11)	5 (14)

No statistically significant differences were observed between treatment groups.

Figure 2.

PROPORTION OF PATIENTS WITH GREATER THAN 50% WOUND HEALING AFTER 12 WEEKS OF TREATMENT

As the graph illustrates, 63% of patients treated with MIST Therapy achieved greater than 50% wound healing at 12 weeks; only 29% of patients receiving the standard of care alone achieved greater than 50% wound healing at 12 weeks.



Baseline $TcPO_2$ levels differed between the groups, with patients in the treatment group more likely to have baseline $TcPO_2$ values greater than 20 mm Hg than patients in the control group (69% vs 57%), although this difference did not reach statistical significance.

A significantly higher proportion of patients treated with MIST Therapy and the standard of care achieved greater than 50% wound healing at 12 weeks than those treated with the standard of care alone (63% vs 29%; $P < .001$; [Figure 2]). Table 3 illustrates the value of $TcPO_2$ measurement in the dependent position for predicting healing outcomes in both groups. Of the 32 patients with greater than 50% wound healing at 12 weeks (22 treatment group patients and 10 control group patients), only 1 patient (treatment group) had a baseline $TcPO_2$ less than 20 mm Hg with dependency. In contrast, the majority of patients in both groups who did not achieve greater than 50% healing within 12 weeks had baseline dependent $TcPO_2$ values of less than 20 mm Hg.

Table 2.

BASELINE ARTERIAL STATUS

	MIST Therapy (n = 35)	Standard of Care (n = 35)
Supine $TcPO_2$, no. (%)		
0–20 mm Hg	11 (31)	15 (43)
21–40 mm Hg	24 (69)	20 (57)
Dependent $TcPO_2$, no. (%)		
0–20 mm Hg	12 (34)	19 (54)
21–40 mm Hg	23 (66)	16 (46)
Ankle-brachial index, median (range)	0.72 (0.66–0.83)	0.73 (0.65–0.81)
Prior arterial reconstruction, no. (%)	27 (77)	26 (74)
Femoro-popliteal bypass, no. (%)	4 (15)	6 (23)
Femoro-distal bypass, no. (%)	15 (56)	10 (38)

No statistically significant differences were observed between treatment groups.
$TcPO_2$ = transcutaneous oximetry pressure

Table 3.

ANALYSIS OF $TcPO_2$ WITH DEPENDENCY BASED ON POSITIVE OR NEGATIVE WOUND HEALING OUTCOME AFTER 12 WEEKS OF TREATMENT

	MIST Therapy (n = 35)	Standard of Care (n = 35)	*P* Value
Positive outcome (>50% healing in 12 weeks), no. (%)	22 (63)	10 (29)	$P < .001$
$TcPO_2$ with dependency, no. (%)			
<20 mm Hg	1 (0.05)	0 (0)	NS
20 to 40 mm Hg	21 (96)	10 (100)	NS
Negative outcome (<50% healing in 12 weeks), no. (%)	13 (37)	25 (71)	$P < .01$
$TcPO_2$ with dependency, no. (%)			
<20 mm Hg	11 (85)	19 (76)	NS
20 to 40 mm Hg	2 (15)	6 (24)	NS

$TcPO_2$ = transcutaneous oximetry pressure; NS = not statistically significant

DISCUSSION

In this prospective, randomized, controlled trial of patients with chronic critical limb ischemia, the addition of noncontact, low-intensity, low-frequency ultrasound therapy (MIST Therapy) to the standard of care was associated with a significant improvement in wound healing at 12 weeks compared with the standard of care alone. These findings bolster prior findings of wound healing benefits with MIST Therapy in recalcitrant diabetic foot ulcers[11] and various chronic lower-extremity wounds[12,13] in the critical limb ischemia population. A randomized, double-blind, sham-controlled analysis of MIST Therapy for 55 patients with recalcitrant diabetic foot ulcers demonstrated a higher proportion of wound healing (defined as complete epithelialization without drainage) compared with the standard of care.[11] In a baseline-controlled analysis of 51 patients with a range of lower-extremity wounds, MIST Therapy significantly reduced wound volume compared with the standard of care.[13] Additionally, faster healing in chronic lower-extremity wounds of various etiologies (diabetic, venous, ischemic, pressure-related, postoperative, and inflammatory) has been observed with MIST Therapy compared with a group of historical controls from the same clinic and receiving the clinic's standard of care.[12]

As a randomized, parallel-controlled trial, the present study supports the findings of enhanced wound healing associated with MIST Therapy compared with the standard of care reported in the earlier baseline- and historically controlled analyses.[12,13] Despite the strengths of this design, there are limitations on what can be learned from the present study. For example, the effect of MIST Therapy on wound pain was not routinely evaluated using a standardized pain assessment scale, such as a visual analog scale. In earlier studies, however, pain was not reported in association with this ultrasound therapy.[11–13] In addition, because wound infection was not present in this study population, the authors were unable to assess the potential effects of MIST Therapy on bacterial burden. Earlier analyses, however, have demonstrated a reduction in exudate associated with MIST Therapy[11] and the destruction of bacterial cell walls subjected to MIST Therapy,[13] suggesting that this treatment may have a deleterious effect on organisms that infect chronic wounds. Further basic scientific investigations of bacterial burden and cellular stimulation are warranted. Another limitation of the present study is that the measurement technique is subject to human error. Although measurements were done by skilled wound care professionals, the potential for error always exists.

The analysis of transcutaneous oximetry in the present study indicates that $TcPO_2$ measurements are a helpful adjunct to clinical assessment in determining the likelihood of wound healing in patients with chronic critical limb ischemia, regardless of the assigned treatment. Similar to Bacharach's observation that baseline supine $TcPO_2$ values greater than 40 mm Hg predict better healing of clean leg amputation sites,[26] the observation of the authors of the present study was that baseline dependent $TcPO_2$ values in the 20 to 40 mm Hg range, as opposed to those below 20 mm Hg, are associated with markedly higher healing rates among chronic critical limb ischemia patients. In concordance with Bacharach et al,[26] patients in the present study with baseline $TcPO_2$ values below 20 mm Hg were unlikely to achieve the study threshold for positive outcome (>50% healing). These findings illustrate the clinical value of assessing $TcPO_2$ in both the dependent and supine positions in patients with chronic critical limb ischemia and chronic lower-extremity wounds.

Two findings of this study have important implications for the care of patients with chronic critical limb ischemia. First, this novel, noncontact, low-intensity, low-frequency ultrasound therapy seems to offer a nonsurgical option for wound healing and limb salvage in chronic critical limb ischemia patients, a population known to have poor prognosis and largely regarded as candidates for amputation. Second, determination of $TcPO_2$ in the dependent position can provide valuable information regarding a patient's likelihood of healing.

Patients with chronic critical limb ischemia are especially challenging because of poor peripheral circulation and, therefore, poor wound healing potential. Limb salvage can be challenging in these patients.[3,6] This new nonsurgical therapy may well minimize the effects of morbidity and mortality resulting from nontraumatic lower-extremity amputations in the chronic critical limb ischemia population.[2]

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