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Akram Beheshti[1, A, C, F], Younes Shafigh[2, A, B], Hossien Parsa[2, E, F], Amir A. Zangivand[1, D]

Comparison of High-Frequency and MIST Ultrasound Therapy for the Healing of Venous Leg Ulcers

[1] Department of Dermatology, Qazvin University of Medical Sciences, Qazvin, Iran
[2] Department of General Surgery, Qazvin University of Medical Sciences, Qazvin, Iran

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Venous leg ulcers (VLUs) are a health problem in clinical care. Several options can be employed as adjuvant to standard treatment.
Objectives. We have aimed to analyze the effect of standard ulcer care alone with high-frequency ultrasound (HFU) and MIST ultrasound therapy on VLUs.
Material and Methods. Ninety patients with VLUs were assigned into the standard treatment, HFU and MIST ultrasound groups. All groups received the standard wound care. In the ultrasound groups, HFU and MIST ultrasound therapy was administered to wounds 3 times per week until the wound healed. Time of complete wound healing was recorded. Wound size, pain, and edema were assessed at baseline and after 2 and 4 months. Also, patients were instructed to contact our clinic monthly, and recurrence of VLUs was recorded for 6 months after complete wound healing. The data was analyzed using a Student's *t*-test, ANOVA, χ^2, or Fisher's exact test. $P < 0.05$ was considered significant.
Results. Mean time duration of complete wound healing in the first, second and third groups was 8.13 (SD 1.40), 6.10 (SD 1.47) and 5.70 (SD 1.57) months, respectively ($p < 0.0001$). Size of ulcer, mean degree of pain and edema in ultrasound therapy was decreased after the 4-month visit in comparison to the standard-treatment group ($p = 0.01$, $p < 0.0001$ and $p < 0.0001$, respectively). Also, our results don't show any significant differences between groups in the recurrence of VLUs during a 6-month follow up after complete wound healing ($p = 0.37$).
Conclusions. Our results in the present study show the significant effectiveness of ultrasound therapy in wound healing. Differences between the two ultrasound therapy groups were not statistically significant (**Adv Clin Exp Med 2014, 23, 6, 969–975**).

Key words: ultrasound therapy, venous leg ulcers.

Venous leg ulcers (VLUs) are wounds with long healing time and frequent recurrence in elderly adult clinics and affect approximately 1.1 to 1% of the world's population [1, 2]. Several hypotheses may help explain the origin of VLUs including insufficient veins or valves (dysfunctional valves in the veins that allow backward blood recirculation due to incomplete valve closure) or impaired muscle function which may lead to abnormal calf muscle pump function (elevated ambulatory venous pressure). These changes subsequently result in local venous dilatation and pooling, concomitantly trapping leukocytes that may release proteolytic enzymes that destroy tissue. Venous pooling also induces inter endothelial pore widening and deposition of fibrin and other macromolecules that "trap" growth factors within them, rendering them unavailable for wound repair [3–6].

High compression bandaging is the mainstay treatment, reducing edema, reversing venous hypertension, and improving calf muscle pump function [7]. Several treatment options can be employed as adjuvants to compression, e.g. systemic therapy with aspirin or pentoxifylline, autologous

grafts, tissue engineered skin, growth factor therapy and surgery [8].

Ultrasound has been used as a therapeutic modality for nearly 50 years [9]. In recent years, ultrasound therapy has been utilized for the management of chronic wounds in some centers [10]. Although high frequency ultrasound (HFU) (1–3 MHz) has been used in clinical practice in most studies, and shown to promote healing of some injuries [11–13], it can cause burns or endothelial injury and usage of it is limited in medical practice. On the other hand, several experiments using ultrasound have shown that the application of low doses in the treatment of skin wounds are more effective in wound healing than high dose ultrasound [14].

Thus, noncontact ultrasound therapy is among the newer modalities. Operating at a markedly lower frequency (40 kHz), it was approved for use in the wound care setting by the FDA in 2004 [15].

In our country, due to lifestyle modifications, ageing of the Iranian population and numerous chronic co-morbid conditions such as coronary heart disease, essential hypertension, diabetes mellitus, obesity, immobility, peripheral arterial disease, neuropathy etc., management of VLUs is estimated to become a leading cost on our national health system.

To control the previously described abnormalities and decrease further costly medical or surgical investigations, we need to identify accurate and appropriate strategies.

The focus of this study was to compare the effect of standard ulcer care alone, with HFU and with noncontact ultrasound therapy. Therefore, in a comparative study, we measured the mean time duration of complete wound healing, edema, pain, size of ulcers and recurrence rate of VLUs in all groups.

Material and Methods

Protocol of the Study

From April 2011 to August 2012, 90 patients diagnosed with VLUs were enrolled in this study after obtaining informed consent. All chosen patients received wound care in only one hospital-based, outpatient wound program that was located at the vascular clinic of Shahid Rajaii Hospital (Qazvin, Iran).

The exclusion criterion were allergy to ultrasound contact gel, pregnancy, or with any of the known contraindications to ultrasound including ankle or knee prosthesis or metal in the lower leg, suspected or confirmed local cancer or metastatic disease and neuropathy, no clinical evidence of infections including active cellulites, suspicious thrombophlebitis and no history of antibiotic therapy at the time of enrollment. The original protocol also stated the study would not recruit people with peripheral arterial disease, diabetes or rheumatoid arthritis. VLUs that had the following characteristics were included for study: wound duration longer than 4 weeks and no clinical improvement after using the clinic's standard care (SOC) for healing during a 2 week period [16].

All patients were randomly assigned into the standard treatment group, HFU and MIST ultrasound group. Randomization was performed by means of sealed opaque envelopes containing computer generated random numbers. In the first clinical visit, a baseline assessment of wound size, pain and edema was performed, and also treatments starting in this visit. All groups received compression therapy as the standard of wound care. In the ultrasound groups, HFU therapy and MIST therapy were administered to wounds 3 times per week until the wound healed.

Afterwards, monthly clinical visits were performed and the size of the ulcer, pain and edema were recorded at 2nd and 4th month after the initial study. Also, the time duration of complete wound healing was recorded during the monthly visit in this study. After complete healing in each patient, a 6-month clinical follow up was performed for the patient and the rate of recurrence of VLUs calculated (Fig. 1 summarizes the protocol of the study).

Ultrasound Therapy

HFU therapy was applied with a SoLo Therasonic 355 machine (EMS Physio, Wantage, UK). The ultrasound transducer head was sterilized with alcohol wipes. Ultrasound was then applied to the skin surrounding the reference ulcer, using a water based contact gel recommended by the manufacturer, for 5–10 min by moving the transducer head in a slow, controlled manner around the edges of the ulcer in overlapping circles to cover the skin evenly. Ulcers of area < 5 cm^2 received ultrasound for 5 min, those of ≥ 10 cm^2 received 10 minutes' ultrasound. For ulcers between 5 cm^2 and 10 cm^2, treatment time in min equaled the ulcer area in cm^2 (ulcer of 7 cm^2 area = 7 minutes' treatment).

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 unit consisting of a transducer, generator and disposable applicator that uses prepackaged sterile saline. The applicator contains

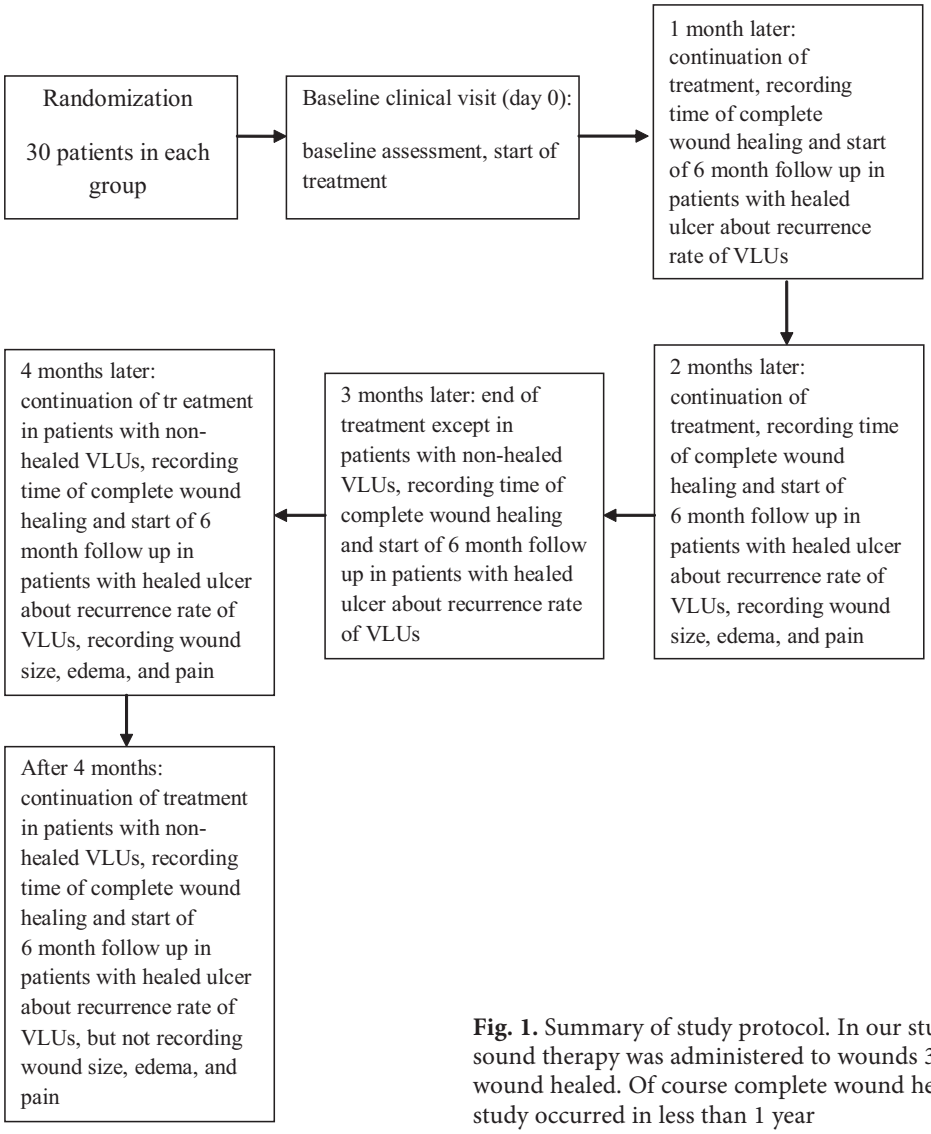

Fig. 1. Summary of study protocol. In our study, HFU and MIST ultrasound therapy was administered to wounds 3 times per week until wound healed. Of course complete wound healing in all patients in this study occurred in less than 1 year

a valve that controls the flow of saline to the transducer surface. The product's recommended treatment algorithm is based on longer treatment times for greater total ulcer area. At our facility, the protocol is to treat wounds up to 4 cm^2 with 4 min of MIST therapy; larger wounds receive longer treatment times (max treatment time = 12 min for wounds larger than 10 cm^2).

Data Collection and Variable Definition

Pain was assessed by a numerical rating scale in which the patient was instructed to choose a number from 0 for "without pain" to 20 for "unbearable pain" [17]. To assess leg edema [18], the examiner pressed his fingertip against a bony prominence for 5 s, and then removed it. A residual indentation indicated pitting edema, which was graded on a scale of 1 (mild) to 4 (severe).

Ethical Approval

The study was approved by the ethics committee of the university before its initiation, and the protocols used conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Statistical Analysis

The statistical evaluation was performed by computer analysis with SPSS Software (Statistical Package for the Social Sciences, version 11.0, SPSS Inc, Chicago, Ill, USA). The Student's *t* test, ANOVA, $\chi 2$, or Fisher's exact test were used, where appropriate, for comparing clinical data between all groups. Continuous data was recorded as mean ± standard deviation. P value less than 0.05 was considered significant.

Results

Ninety patients diagnosed with VLUs (46 men and 44 women), aged 58.5 (SD 11.6) took part in this study. Inspections of background characteristics between study groups showed a generally good balance of the demographic and clinical characteristics collected and mean age of patients, wound duration and mean initial size of ulcer, and even the distribution of men and women was not significant.

Mean time duration of complete wound healing in the first, second and third groups was 8.13 (SD 1.40), 6.10 (SD 1.47) and 5.70 (SD 1.57) months, respectively ($p < 0.0001$; Table1). The results between the duration of complete wound healing in the ultrasound treatment groups was not a statistically significant difference ($p = 0.22$; Table 1).

Edema at the first clinical visit was mild to severe in all groups and after treatment had subsided in all groups. In spite of the fact that edema was not statistically significantly different in all groups at baseline and 2-month visits, after 4 months the edema was more subsided in the 2nd and 3rd groups in comparison to the standard treatment, and recovery from edema was statistically significantly better in the ultrasound groups ($p = 0.02$; Table 2). Also, the assessment of leg edema between HFU and MIST ultrasound therapy didn't show any significant differences.

The mean degree of pain was recorded in all groups and changes in pain after 2 and 4 months were shown in this study. Our results indicate the mean degree of pain decreased more in the 2nd and 3rd groups and these decreases was statistically significant ($p < 0.0001$; Table 3). There were not any significant differences between HFU and MIST ultrasound therapy. The analysis of wound surface and size of ulcer showed the mean size of the ulcer at the 1st clinical visit and 2 months after the baseline clinical visit were not statistically significantly different, but after 4 months our results showed significant differences ($p = 0.01$; Table 4). On the other hand, our results showed VLU recurrence 6 months after complete wound healing was seen in 4 cases in the standard group, 2 cases in the HFU and 2 cases in the MIST ultrasound group ($p = 0.37$; Table 5).

Discussion

VLUs are one of the main burdens for patients and healthcare service centers. Traditional wound healing intervention such as compression

Table 1. Mean time duration of complete wound healing

P-value	SD	Mean (months)	Number	Group
< 0.0001*	1.40	8.13	30	standard treatment
	1.47	6.10	30	high-frequency ultrasound
	1.57	5.70	30	MIST ultrasound

* p-value between high frequency ultrasound and MIST ultrasound was calculated at 0.22.

Table 2. Changes in edema

P-value	Staging of edema				Number of patients in each group	Time
	4 plus	3 plus	2 plus	1 plus		
0.31	7	8	5	10	standard treatment	visit 1
	3	8	7	12	high-frequency ultrasound	
	8	8	5	9	MIST ultrasound	
0.64	5	6	7	12	standard treatment	2 months after
	3	4	9	14	high-frequency ultrasound	
	5	4	7	14	MIST ultrasound	
0.02*	5	5	12	8	standard treatment	4 months after
	1	1	5	23	high-frequency ultrasound	
	4	2	3	21	MIST ultrasound	

* p-value between high frequency ultrasound and MIST ultrasound therapy in visit 1, 2 months after and 4 months after was calculated at 0.13, 0.63 and 0.21, respectively.

Table 3. Changes in pain

P-value	SD	Mean (cm^2)	Number of patients	Group	Time
0.38	3.69	9.90	30	standard treatment	visit 1
	2.52	8.50	30	high-frequency ultrasound	
	5.23	9.43	30	MIST ultrasound	
< 0.0001*	3.54	7.80	30	standard treatment	2 months after
	2.30	4.93	30	high-frequency ultrasound	
	3.19	4.46	30	MIST ultrasound	
< 0.0001*	2.09	6.56	30	standard treatment	4 months after
	2.12	4.20	30	high-frequency ultrasound	
	2.70	4.20	30	MIST ultrasound	

* p-value between high frequency ultrasound and MIST ultrasound therapy in visit 1, 2 months after and 4 months after was calculated at 0.38, 0.16 and 0.98, respectively.

Table 4. Changes in mean of ulcer size

P-value	SD	Mean (cm^2)	Number of patients	Group	Time
0.98	3.07	8.96	30	standard treatment	visit 1
	2.37	9.03	30	high-frequency ultrasound	
	2.27	9.10	30	MIST ultrasound	
0.16	2.42	5.63	30	standard treatment	2 months after
	2.35	4.76	30	high-frequency ultrasound	
	3.19	4.46	30	MIST ultrasound	
0.01*	2.95	4.80	30	standard treatment	4 months after
	2.16	3.70	30	high-frequency ultrasound	
	1.93	3.30	30	MIST ultrasound	

* p-value between high frequency ultrasound and MIST ultrasound therapy in visit 1, 2 months after and 4 months after was calculated 0.91, 0.68 and 0.45, respectively.

Table 5. Recurrence of VLUs after 6-month follow up

Group	Number (%)	P-value
Standard treatment	4 (13.3)	0.37
High-frequency ultrasound	2 (6.6)	
MIST ultrasound	2 (6.6)	

bandages are the mainstay and standard treatment for chronic venous ulcers. Today, several systemic adjunctive treatments, for example application of ultrasound etc., may be used in conjunction with compression therapy. HFU has been used in clinical practice in musculoskeletal disorders, primarily by physical therapists, wound healing, and sports medicine with both thermal and mechanical effects for many years. The therapeutic effect of ultrasound therapy in the kilohertz (low frequency) range has been approved for use in the wound care setting in recent years.

The main effect of low frequency ultrasound is a mechanical property [19]. Also, it has been proposed that low frequency ultrasound in the KHz range may improve wound healing *via* the production, vibration, and movement of micron-sized bubbles in the coupling medium and tissue.

The results of the present study show that the size of the ulcers in ultrasound therapy were smaller in the visits after 4 months. Also, mean time duration of complete wound healing 4 months after the initial study was very fast in comparison to standard treatment alone. However, these differences were not significantly different between HFU with MIST therapy.

Our results emphasize similar results in other studies. For example, in a randomized, controlled, double-blinded study, Ennis et al. examined the effectiveness of MIST ultrasound therapy after 12 weeks of care for the healing of recalcitrant diabetic foot ulcers. The authors concluded, the proportion of wounds healed in the active ultrasound therapy device group was significantly higher than that in the control group (40.7% vs. 14.3%, p = 0.0366, Fisher's exact test) [20].

Also Ennis et al., in another non-comparative study, used MIST ultrasound during an 8-month period and ultimately concluded that 69% of the wounds were healed and median time to healing was 7 weeks when MIST ultrasound was used as a stand-alone therapy [19].

In another study, Kavros et al. assessed MIST ultrasound therapy in the treatment of non-healing leg and foot ulcers associated with chronic critical limb ischemia. The subjects included 35 patients who received MIST ultrasound therapy plus the standard of wound care for 12 weeks (treatment group) and 35 patients who received the standard of wound care alone (control group). The main outcome measurements showed a significantly higher percentage of patients treated with the treatment group achieved greater than 50% wound healing at 12 weeks than those treated with the standard of care alone (63% vs. 29%; $p < 0.001$) [21]. Also, this author et al. in another study indicated healing time reductions (9.8 ± 5.5 weeks vs. 5.5 ± 2.8 weeks ($p < 0.0001$)) and wound volume percent improvement (37.3% ± 18.6% vs. 94.9% ± 9.8% ($p < 0.0001$)) in comparing the clinic's standard care with MIST ultrasound therapy [22].

Our results about changes in pain after 2 and 4 months of the initial of study also showed decreases in the ultrasound treatment groups in comparison to standard treatment alone. Of course in this item, the differences were not significant between MIST and HFU therapy. In similar literature, Gehling and Samies reviewed and recorded pain scores of 15 consecutive patients (7 men and 8 women, age range of 28 to 88 years) with painful, non-healing, lower-extremity wounds treated for 2 to 4 weeks with MIST ultrasound therapy. Mean pain scores decreased from 8.07 ± 1.91 pre-treatment to 1.67 ± 1.76 post-treatment (p = 0.0003) [23].

The recurrence rate of VLUs in our study was 13.3% in the standard treatment group and 6.6% in the ultrasound group. The recurrence rate of this disorder in previous studies was variable between 26% and 69% [24]. Our results were lower than similar studies but we believe the 6-month follow up is very short to truly decide about the potential of prevention of recurrence in patients treated with ultrasound therapy.

Overall, our results in the present study are similar to other published literature in the world and show the significant effectiveness of ultrasound therapy, especially MIST therapy, in wound healing as an adjuvant therapy. This method prepares the wound bed for healing by reducing the bioburden, enhancing angiogenesis, assisting in debridement of necrotic and devitalized tissues, and stimulating cellular activity. From another perspective, the tissue repair and wound healing process has 3 phases: inflammatory, proliferative and remodeling. Application of the MIST therapy system for tissue repair in the initial inflammatory stage could cause a promotion of it. However, we bear in mind that the MIST therapy system does not have only anti-inflammatory properties. In the proliferative phase, it also affects ultrasound induced edema resolution, cellular element migration and division, accelerated granulation tissue formation and stimulated fibroblasts for collagen production. At the last phase of wound healing, the scar tissue that is exposed to the MIST therapy system may be stronger and more elastic compared to normal scar tissue.

In conclusion, according to the very limited effects identified in individuals in the MIST therapy group, which showed earlier response to therapy based on wound area and volume reductions, it could give us a cost savings through a prominent reduction in therapeutic times. Additional work on cost-effective outcomes and planning are greatly needed for the future.

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Address for correspondence:

Hossien Parsa
Clinical Research Development Unit
Qazvin University of Medical Sciences
Qazvin
Iran
Tel.: +98 281 334 74 96
E-mail: parsahossien@gmail.com

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