

Low-frequency Ultrasound Treatment of Chronic Venous Leg Ulcers in an Outpatient Therapy

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Low-dose ultrasound seems to be an effective method to enhance wound healing, particularly in chronic venous leg ulcers. The aim of our investigation was to examine the effect of 30 kHz low-dose ultrasound in local treatment of chronic venous leg ulcers, when added to conventional therapy of outpatients. Twenty-four patients with chronic ulcerations of the leg due to chronic venous insufficiency were randomised in placebo-controlled parallel groups in a single-blind clinical study. Patients were randomised to conventional therapy with topical application of hydrocolloid dressings and compression therapy or conventional therapy with additional ultrasound treatment for 12 weeks. The ultrasound treatment consisted of 10 min of footbathing, with application of 30 kHz continuous ultrasound 100 mW/cm² three times a week. The ulcer area was measured by planimetry, using a millimeter grid before treatment and after 2, 4, 6, 8, 10 and 12 weeks of therapy. The ulcer radius and the daily ulcer radius reduction were calculated. Colour photographs of the ulcers were taken under standard conditions at the same time. After each treatment local findings and side effects were recorded. After 12 weeks of treatment the control group showed a mean decrease of 16.5% in the ulcerated area. In contrast the mean ulcerated area decreased by 55.4% in the ultrasound group ($p < 0.007$). The daily ulcer reduction in the ultrasound-treated patients was 0.08 mm ± 0.04 mm and in the placebo patients 0.03 mm ± 0.03 mm. Patients recorded only minor side-effects such as a tingling feeling and occasionally pinhead-sized bleeding in the ulcer area.

The application of low-frequency and low-dose ultrasound is a helpful treatment option in chronic venous leg ulcers, especially if they do not respond to conventional ulcer treatment. **Key word:** wound healing.

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Chronic venous leg ulcers are a major health problem in most countries with patients who suffer from chronic venous insufficiency. Apart from the suffering of the individual patient, who possibly becomes a recipient of long-term medical treatment, venous diseases also result in considerable economic costs. A conservative estimate cited costs of 2.3 billion marks in Germany (1, 2). In light of this situation, it is imperative that possibilities be sought which on the one hand would accelerate the slow healing processes in leg ulcers and on the other hand help to reduce the immense costs involved.

The therapy of leg ulcers is based, in current medical opinion, on four cornerstones: 1) compression treatment, 2) surgical measures 3) local therapy and 4) systemic treatment (3). But in spite of the multiple therapeutic possibilities, it often takes months before leg ulcers can be healed.

Ultrasound has been used as a therapeutic modality for

nearly 50 years (4). Several experiments using ultrasound have shown that the application of low-dose ultrasound in the treatment of skin wounds is more effective in cutaneous wound healing than high-dose ultrasound (5). Thirty kHz low-frequency ultrasound wound management is adjuvant to conventional therapy. Correctly used it is safe and simple to operate (6). The aim of our investigation was to examine the effect of 30 kHz low-dose ultrasound in local treatment of chronic venous leg ulcers, when given in addition to conventional therapy of a randomized outpatient population.

PATIENTS AND METHODS

Patients

Twenty-four patients who attended the outpatient clinic participated in the study after informed consent. There was no significant difference between the two groups in age, sex, initial ulcer area and radius or ulcer duration (Table 1). Due to non-compliance 2 patients of the control group dropped out after the 2nd week of placebo treatment. All subjects were affected by chronic venous leg ulcers, which had to be at least 2 cm² and of a duration for at least 3 months prior to the study. The clinical diagnosis of venous ulceration was confirmed by history, Doppler sonography and light-reflection-rheography. A concomitant arterial insufficiency was excluded by an ankle/arm index of over 0.8. Patients with diseases of the liver, cardiac or renal insufficiency, erosive haemorrhagic gastroduodenitis, colitis ulcerosa or leukemia, cerebral apoplex, diabetes, polyneuropathy, rheumatoid arthritis, Morbus Cushing, solid tumours or allergy to the standard treatment were excluded from the study. The study was performed from April 1994 to January 1996.

Ultrasound treatment and study procedure

Patients were randomised in parallel groups to conventional therapy with topical application of hydrocolloid dressings (Coloplast, Hamburg, Germany), compression therapy, using strong-quality elastic compression bandages (Beiersdorf, Hamburg, Germany) and a placebo procedure (control group, $n = 12$) or conventional therapy with additional ultrasound treatment for 12 weeks (treatment group, $n = 12$). For ultrasound treatment and placebo treatment, the patients placed their legs in a footbath containing 32–34°C water and no additives. The filling depth was about 10 cm above the leg ulcer. Then

Table 1. Comparison of placebo group and ultrasound group

	Placebo group	Ultrasound group
Number of patients	12	12
Sex ratio (male:female)	6:6	4:6
Mean age (SD)*	67.7 ± 15.6	68.3 ± 13.7
Mean ulcer area in cm ² (SD)*	19.94 ± 17.11	15.67 ± 19.91
Mean ulcer radius in cm (SD)*	2.03 ± 0.91	1.84 ± 1.02
Ulcer duration in months (SD)*	4.5 ± 1.1	5.5 ± 3.2
New ulcer	5	5
Recurrent ulcer	7	7

*NS between groups.

a flexible 30 kHz sound head transducer (Swen Sonic, Davenport, Illinois, USA) was immersed in the bath and placed in line with the ulcer, at a distance of about 5 cm. The continuous ultrasound treatment consisted of 10 min of footbathing with application of 30 kHz low dose ultrasound and an intensity of 0.1 W/cm^2 three times a week. The same procedure was selected for placebo treatment, but no ultrasound was generated during the 10 min footbath.

Clinical scoring

The ulcer area was measured using planimetry with OP Site Flexigrid (Braun-Smith & Nephew, Melsungen, Germany) prior to treatment and after 2, 4, 6, 8, 10 and 12 weeks of therapy. Based on the measured ulcer area, the initial ulcer radius (r_i) was calculated from the measured ulcer area (F) using the equation $r = \text{square root } F/\pi$, and the daily ulcer radius reduction (r_d) was determined using the equation $r_d = r_i - r_t/t$ (where r_t equals the radius after a certain treatment time and t equals the treatment time itself) (7). Wilcoxon ranks sum tests were used to compare the percentage change in ulcer area. At the same time photographs of the ulcers were taken under standard conditions (Macrolens with 50 mm focus, exposure 125 ms, shutter 16 or 19, distance from the ulcer 40 cm, overview or 30 cm, detail). At each visit, the physician assessed the ulcer with respect to the presence of slough and the formation of granulation tissue. Checks were made during and after the waterbath whether microbleeding occurred, and the subject was questioned concerning pain. At the end of the 12-week therapy, the patients were questioned about the occurrence of irritations and their duration, localisation and severity during or after the waterbath, the acceptability of treatment (pleasant, unpleasant, no opinion) and the therapeutic success (good, moderate, poor). Three months after completion of the ultrasound or placebo treatment, all patients were re-examined to determine the size and the radius of the ulcer, slough compared to week 12 and the general condition.

RESULTS

Planimetry

Significant decrease in leg ulcer area and daily ulcer radius reduction in the ultrasound group compared to the control group. Starting in week 8 of treatment, the ultrasound group showed a significantly better response to therapy than the control group. After 12 weeks of treatment the control group showed a mean decrease of 16.5% in the ulcerated area; the mean ulcerated area in the ultrasound group decreased by 55.4% ($p < 0.007$) (Fig. 1). Comparing the minimum with the maximum reduction of ulcer area after 12-week therapy, we observed values between 51% and 100% in the treatment group; complete healing was achieved only in 2 patients. The corresponding values in the placebo group ranged between no change of the ulcer area and a maximum reduction of 73%.

The mean change in initial ulcer radius prior to the start of therapy during the course of wound healing up to the 12th week of treatment under standardised treatment conditions was 7.0 mm in the 12 patients treated with ultrasound and 2.5 mm in the 10 placebo patients ($p < 0.015$). The daily ulcer reduction in the treatment group was $0.08 \text{ mm} \pm 0.04 \text{ mm}$ and in the placebo group $0.03 \text{ mm} \pm 0.03 \text{ mm}$.

Clinical findings

Marked formation of granulation tissue depending from decrease of slough and only occasionally small pinhead bleedings in the ultrasound group. The clinical findings prior to therapy and after 2, 4, 6, 8, 10 and 12 weeks of therapy with respect to slough and the formation of granulation tissue

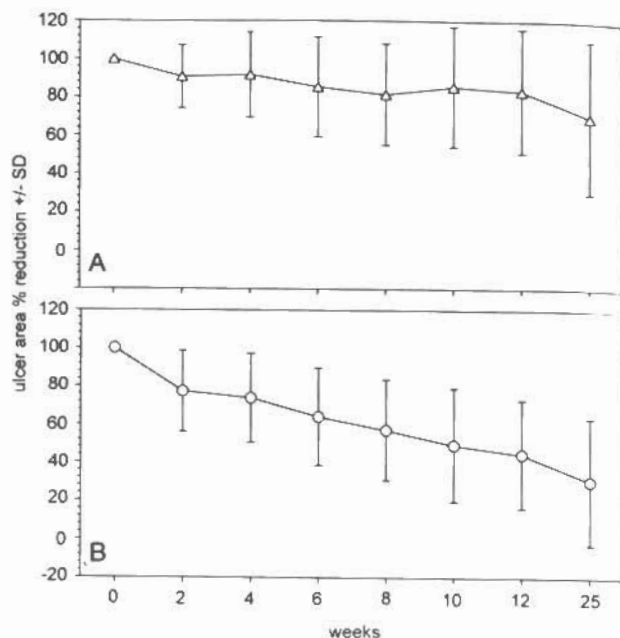


Fig. 1. Eight-week 30 kHz low-frequency ultrasound treatment results in a significant decrease of leg ulcer area compared to controls. In 22 patients with venous leg ulcers the reduction of the ulcer area (%) was determined by planimetry during a 25-week study procedure. (A) control group ($n=10$). (B) treatment group ($n=12$).

showed marked differences between the two groups. All ulcers prior to therapy showed partial or completely fibrinous or necrotic slough in both groups. No granulation tissue was visible except in one patient of the treatment group. Among the 12 patients in the treatment group, there was a visible decrease in slough after the 4th week of treatment in 7 patients and in the remaining 5 patients after the 8th week of treatment. This finding correlated with the formation of fresh granulation tissue at the same time or 2–4 weeks previously, which increased continuously to the end of treatment. Three of the 10 placebo patients showed no increase or decrease in slough during the entire treatment period, while the other 7 patients showed a decrease in slough after the 6th week, accompanied by discrete granulation around the ulcer up to the end of treatment. The occurrence of microbleeding during or after the waterbath was not observed in any patient in the placebo group at any time during the study. Microbleeding around the ulcer occurred in 5 patients of the treatment group from the start of therapy until week 6. Differences were noted in the responses of patients concerning pain in the ulcer before and after therapy. Four of 10 placebo patients were free from pain before and during the entire treatment period. Of the other 6 patients one patient reported no change in pain over the entire period, 2 patients complained of pain once in week 10, and 3 patients from week 8 to the end of therapy. Three patients in the treatment group remained completely free from pain, one patient reported no change in the pain, which had existed from the beginning. Eight patients complained of pain in the ulcerated area prior to treatment; pain was no longer reported by any patients starting in week 4.

Questioning of the patients at the end of the treatment

Questioning of the 22 patients after completion of the 12-week therapy with respect to the occurrence of irritations during or

after the waterbath, acceptability of the treatment and therapeutic success showed the following results: irritation in the ulcerated area was experienced by no placebo patient at any time. The treatment was rated as pleasant by 9 patients, except one patient who voiced no opinion. Therapeutic success was rated as poor by 7 patients and moderate by 3 patients. Four patients in the treatment group reported no irritations during treatment. Eight patients reported a tingling feeling in the ulcerated area during ultrasound application. Treatment was considered pleasant and soothing. The therapeutic success was rated as good by all patients treated with ultrasound. In addition, one patient reported that the itching in the leg disappeared completely for about 2 h following each treatment.

Post-treatment study follow-up

Conventional therapy (without ultrasound application) was continued after termination of ultrasound therapy, and the patients were re-examined to determine the size and radius of the ulcer 3 months after the last visit. Examination of the treatment group showed a further decrease of the ulcer area. The mean ulcer size was 30.6% of baseline. The healed ulcers were non-recurrent. The mean change in initial ulcer radius up to the 25th week of treatment under standardised treatment conditions was 9.9 mm in the 12 patients treated with ultrasound and 5.3 mm in the 10 placebo patients ($p < 0.012$). The placebo group showed a mean ulcer size of 70.2% of baseline. The daily ulcer radius reduction from the end of the 12th week up to the 25th week in the ultrasound treated as well as in the placebo patients was $0.04 \text{ mm} \pm 0.04 \text{ mm}$. All re-examined patients, except for 2 patients of the treatment group, whose ulcers were healed, continued to show fibrin slough. The general condition of the 12 patients treated by ultrasound was good, and in the placebo group good in 5 patients and reduced in 5 patients.

DISCUSSION

There is considerable evidence that ultrasound can increase the rate of wound healing in experimental wound studies (8,9) pressure sores (10) and in leg ulcers (11–13). Considering our clinical data this is to our knowledge the first study that proves an increased response rate of wound healing in leg ulcers, contributing to low-frequency and low-dose ultrasound in patients who attended the outpatient clinic. However, Lundeberg et al. (14) showed, in a controlled study, that there were no significant differences in the proportion of healed ulcer area in the pulsed ultrasound group as compared with the placebo group, demonstrating that the healing rates in previous studies may reflect an effect of extra care given during ultrasound treatment. Among leg ulcer studies there is additionally a considerable variation in response concerning the healing of ulcers, possibly depending on the manner in which ultrasound has been applied. The question of which ultrasound conditions should be used is a matter requiring further investigation. In this study the daily ulcer radius reduction during the 12-week study procedure was approximately 0.08 mm in patients treated with ultrasound versus 0.03 mm in placebo patients. The average rate of radius reduction in the time period from week 12 to week 25, however, showed values of 0.04 mm in both groups, suggesting a positive influence of 30 kHz low-dose ultrasound on ulcer healing. The initial

ulcer area and radius were larger in the control group than in the actively treated group; however, this difference was not statistically significant (Table I). Therefore we do not expect any influence of this difference on shown healing results. Our rates are virtually identical to the rates seen by Cordts et al. (15) (0.049 cm/week) and by Margolis et al. (16) (0.062 cm/week). Various experimental and clinical studies have been conducted, showing positive effects of ultrasound on wound healing. In contrast to high-dose ultrasound it is extremely unlikely that low-dose ultrasound (intensity $< 0.5 \text{ W/cm}^2$, frequency $< 100 \text{ kHz}$) shows any thermal effect on biological tissues, contributing to enhanced wound healing (17). Its main effect is probably a mechanical and piezoelectric effect, which is created through the shearing action of stable microbubbles in alternating high- and low-pressure waves that are generated by the ultrasonic transducer (17, 18). This phenomenon, called stable cavitation, is most important in making low-dose ultrasound a potential tool for debridement without damaging vital structures within the wound (19, 20). Our results show that a decrease of slough by application of 30 kHz low-dose ultrasound is associated with an increased formation of granulation tissue. Furthermore, low-dose ultrasound is involved in the mechanism of stimulation of protein synthesis (21, 22), stimulation of fibroblasts and macrophages (23, 24) and in an increased collagen deposition (17). It was also shown to stimulate angiogenesis (25) and have a bactericidal effect (20, 26). Low-dose ultrasound has been demonstrated to increase the TcPO_2 and to decrease the TcPCO_2 during insonation, probably due to an improvement in skin capillary blood flow (27). In this study microbleedings occurred only in patients treated with low-dose ultrasound, suggesting a possible improvement in capillary blood flow. Pain relief was found in patients treated with low-dose ultrasound, and partly in placebo-treated patients, confirming the thesis that especially low-dose ultrasound might improve the well-being of leg ulcer patients during insonation and shortly after treatment, possibly because of a mechanical action on larger nerve fibres which could close the "pain-gate" (28, 29). In contrast, pain relief following treatment with placebo is a well-recognized phenomenon, on which may be due to changes in pain perception mediated by circulating opioids (29). Awareness of irritation and assessment of the acceptability of the treatment, in human beings, are highly subjective. Questioning of the patients at the end of the treatment in our study shows similar results as described previously (30).

In conclusion, the application of 30 kHz low-dose ultrasound in ambulant patients seems to be a helpful treatment option in addition to the established therapy modalities in chronic venous leg ulcers, especially if they do not respond to conventional ulcer treatment.

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