Research Report

A Randomized Clinical Trial of Ultrasound in the Treatment of Pressure Ulcers

Background and Purpose. The purpose of this study was to assess the effects of ultrasound (US) therapy in the treatment of pressure ulcers as an adjunct to standardized treatment. Subjects. Eighty-eight patients from 11 nursing homes and one hospital participated. Subjects were randomly assigned to either a US group (n=45) or a sham US group (n=43). Methods. This was a multicenter placebo-controlled randomized trial. Wound survival, healing rates of wound surfaces, and changes on a clinical rating scale were measured over 12 weeks. Results. Comparison of the 12-week cumulative incidences of wound closure showed that 40% (18/45) of ulcers in the US group and 44% (19/43) of ulcers in the sham US group were closed. An analysis in which between-group baseline differences and the days of wound closures were accounted for showed that the wound closure probability per unit of time (ie, closure rate) was almost equal in the two treatment groups (Cox proportional-hazards ratio of 1.08). Mean absolute healing rates were 0.18 and 0.31 cm^2/wk in the US and sham US groups, respectively. Relative healing rates and healing speeds were similar in the two treatment groups. A panel scored slides of the ulcers with a report mark between 1 (bad) and 10 (excellent). The improvement was 0.71 and 0.46 points per week in the US and sham US groups, respectively. Conclusion and Discussion. These data do not support the idea that US speeds up the healing of pressure ulcers. [ter Riet G, Kessels AGH, Knipschild P. A randomized clinical trial of ultrasound in the treatment of pressure ulcers. *Phys Ther.* 1996;76:1301–1312.]

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In 1960, Paul et al[1] described the treatment of 23 patients with pressure ulcers using ultrasound (US) therapy. They concluded, "From our clinical observations, it would appear that a scientifically controlled study in this area would be richly rewarding."[1(p438)] Twenty-five years later, McDiarmid et al[2] published the first randomized trial of the effects of US on the healing of pressure ulcers. We were unable to find other randomized trials in the literature. Although McDiarmid et al[2] could not show an overall beneficial effect, they found that US therapy appeared to improve the rate of healing in a subgroup of patients with infected superficial ulcers.

Ultrasound has been used, mostly with positive results, in the treatment of animals with experimental wounds.[3–6] Negative results have also been reported.[7] Research on cultured fibroblasts indicates that US therapy can enhance collagen production.[8] These findings suggest a need to perform clinical trials of US therapy with human patients.

About 2,200 topical preparations alone have been recommended over the years for the treatment of pressure ulcers.[9] We chose to investigate US therapy because we found in a survey that one out of every five Dutch nursing home physicians and one out of every four Dutch supervisory nursing home nurses thought that US was effective in the treatment of patients with uncomplicated grade III pressure ulcers (full-thickness skin loss, damage of subcutaneous tissue) and almost one out of every two physicians and nurses thought that it was completely ineffective.[10]

We thought that the evidence of the usefulness of US in wound healing was, on balance, equivocal. Thus, we performed a controlled randomized trial, comparing US therapy with sham US therapy, which is currently considered the most valid method of approaching questions on efficacy. The purpose of our study was to determine to what extent application of US changes the healing pattern of pressure ulcers.

Patients and Methods

We recruited patients with grade II, III, or IV pressure ulcers (ie, partial-thickness skin loss or worse[11]) from 11 nursing homes and one hospital located in the south of the Netherlands. If a patient had multiple ulcers, we used two hierarchical criteria to choose one ulcer for inclusion in the trial. First, we preferred ulcers located on the trunk. Second, we chose the ulcer with the highest grade. The trial had a full factorial design. The second experimental intervention was twice-daily supplementation of either 500 or 10 mg of ascorbic acid (AA) by means of effervescent tablets. Thus, there were four treatment groups: (1) a US+high-dose AA group, (2) a US+low-dose AA group, (3) a sham US+high-dose AA group, and (4) a sham US+low-dose AA group.

In this article, we report on the US part of the trial exclusively. The results of the AA part of the trial were reported elsewhere.[12,13] Most of the exclusion criteria pertain to the AA part of the trial. Exclusion criteria were (rationale in brackets): difficulties with swallowing or frequent vomiting (poor compliance with AA regimen); osteomyelitis in the ulcer area (healing very unlikely); idiopathic hemochromatosis, thalassemia major, and sideroblastic anemia (in these three diseases, AA supplementation is contraindicated); and Cushing's syndrome or Cushing's disease, pregnancy, radiotherapy in the ulcer area, and the use of antineoplastic agents or systemic glucocorticosteroids (all because of hormonal alterations in collagen synthesis). A high probability to drop out within the 12-week follow-up period (terminally ill patients; patients for whom surgical treatment of the ulcer, other than debridement, had been planned) also led to exclusion. Furthermore, we excluded patients if they were already taking vitamin C supplements in excess of 50 mg per day. Patients with grade II ulcers (partial-thickness skin loss) could participate only if deepithelialization had persisted for at least 7 days without interruption. Patients with leg ulcers had to have a positive history of pressure on that site to be eligible. Written informed consent was obtained from each patient or his or her guardian before enrollment.

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Patients were randomly assigned to one of two treatment groups after stratification by nursing home[14] and according to whether muscle tissue was affected by the ulcer (ie, grade IV ulcer) (16 patients, yes; 72 patients, no) and whether 500-mg or 10-mg AA supplements were being given daily (43 patients, 500 mg; 45 patients, 10 mg). Randomly assigning patients to treatment groups after stratification by nursing home increased the likelihood that each treatment group received exactly half of the patients in any center, thus preventing confounding by differences (eg, in level of care) among centers. Randomization was carried out in random permuted blocks (n=4) prepared in advance with the help of a computer program.[14]

At baseline and after 2, 6, and 12 weeks, venous blood samples were collected. These samples were used to determine AA concentrations (to check compliance) and to adjust during data analysis for baseline differences in prognostic indicators such as albumin[15] and zinc.[16] The samples were frozen at −76°C and analyzed in one batch after data collection had been completed.

We worked with two identical US devices (Phyaction 796*). One of these devices was calibrated before the start of the trial by the Department of Biophysics at Maastricht University. We assumed the other device to be similar because it consisted of identical software and hardware. After completion of the data collection, 22 months later, both devices were calibrated by the biophysicists. Table 1 shows the features of US therapy in the trial. As a first-line quality control during the trial, the manufacturer of the US devices checked the power output of both devices approximately every 3 months by means of a beam pressure balance immersed in water.

Treatment duration was determined by defining a treatment area larger than the actual wound surface area. This was done by drawing, with a fine-tipped marker, a contour that ran parallel to the wound edge at a distance of approximately 0.75 cm on pieces of overhead transparency containing a grid of 1 × 1-cm squares. For each wound, the number of fully enclosed squares (N_f) and the number of partially enclosed squares (N_p) divided by 2 were added to obtain a treatment area (in square centimeters): $N_f + (N_p/2)$. In this way, we counted each partially enclosed square as 50% enclosed, although in reality some were enclosed to a larger extent and some to a lesser extent. On average, however, our estimate should have been about right using this rule.

We extended the wound radius by 0.75 cm because many physical therapists we talked to believe that the wound edge plays an important part in the healing of superficial wounds. We thought that direct treatment of the wound surface was likely to be most effective, but we decided to treat both the actual wound surface and the extended wound surface area. Circular movement of the transducer head across the wound results in insonating the central wound area more often than the areas at the periphery. By extension of the wound radius, we insonated the wound margins more, thereby complying with the physical therapists' wishes. Treatment duration was read from a table derived on the basis of the following formula: treatment area estimate ÷ effective radiating area (at the face of the transducer) × 3 minutes. The minimum treatment duration was 3 minutes 45 seconds. Wounds with a treatment area larger than 5 cm^2 were treated longer. A wound with a treatment area of 10 cm^2, for example, was treated for 7½ minutes. Surface estimations were repeated regularly, and treatment duration was adjusted accordingly. All patients were treated once daily, five times per week, not during the weekends. Full compliance over 12 weeks resulted in 60 treatments.

We used neutral Sonocol coupling gel (Franckline Products, Maurik†). Ultrasound therapy was guided by three main principles. First, using a thin layer of coupling gel, we tried to establish close contact between the transducer head and the wound. Second, we tried to establish contact between the transducer head and the wound at a right angle to ensure maximal absorption of sound energy. Third, the transducer head was moved in a circular fashion to average out intensity fluctuations in the near field. Transducers were cleaned with cold tap water and soap and put in a 2% lyorthol solution for at least 5 minutes after each treatment, as advised by the Department of Microbiology at Maastricht University.

Table 1.
Ultrasound Therapy Characteristics[a]

Frequency (MHz)	3.28[b]
Pulse duration (ms)	2
Pulse repetition frequency (Hz)	100
SATA intensity[c] (W/cm^2)	0.10
BNR	<4
ERA (cm^2)	4[d]

[a] SATA=spatial average temporal average, ERA=effective radiating area (at the face of the transducer), BNR=beam nonuniformity ratio (SPTA/SATA), Ptot=total acoustic power, SPTA=spatial peak temporal average, SATP=spatial average temporal peak, SATP=5 × SATA, Ptot=SATA × ERA, SPTA=SATA × BNR.
[b] The small transducers had frequencies of 3.42 and 3.29 MHz.
[c] Measurements at three monthly intervals showed that the SATA intensities ranged between the following values: device 1 (large transducer)=0.08–0.10 W/cm^2, device 2 (large transducer)=0.08–0.12 W/cm^2. The small transducers had SATA intensities of 0.10 W/cm^2 at all checks.
[d] The small transducers had an ERA of 1 cm^2.

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† Fysiomed, Doornstraat 78–9, B-2520 Edegem, Belgium.

Before using a transducer on another patient, any remaining lyorthol was washed off with tap water.

Ultrasound therapy with the characteristics mentioned in Table 1 cannot be distinguished from the sham US therapy, unless a few drops of water are put on an activated probe or the probe is immersed in a tray filled with water. We asked participating physical therapists not to do this, after explaining to them the importance of blind conditions. Instead of a switch button with two positions, each US device had 20 codes randomly divided over the two treatment options (10 active, 10 inactive). Obviously, inadvertent unblinding of one treatment code left the quality of the other codes hidden. This method guaranteed concealment of treatment allocation and, therefore, unbiased baseline measurements. The US therapy protocol was approved by a sample of Dutch education centers for physical therapy.

More than 75% of the treatments were given by the main investigator (GtR) and his nurse assistant, who received training from a consultant physical therapist. All patients lay on water beds.[‡] Staff were instructed to reposition patients once every 3 hours. We provided flotation pads[§] if patients sat up and their chairs permitted installation. Local wound care was standardized and consisted of once-daily (exceptionally twice-daily) gentle cleansing or rinsing with sterile saline (0.9%) or chlorhexidine (0.1%) on gauze or in a syringe. We performed surgical debridement and used Elase®[‖] when indicated. Ulcers were covered by neutral paraffin gauze, followed by hydrophilic gauze, and fixated with tape. Use of topical antibiotics was left to the treating physician, but discouraged by us. The investigators, nursing staff, and patients were blinded as to treatment allocation. The main investigator and a research nurse performed most (weeks 1–6 and then all even weeks to week 12, except during weekends) of the topical wound care themselves. Success of blinding was checked after 2 and 12 weeks through the use of brief interviews.

Effect Measurements

The wound areas were photographed on Fuji™ chrome 100 film[#] with a 35-mm camera (Nikon™ F601[**]). All films had an identical emulsion number. Each wound was photographed twice on each occasion from a point perpendicular to the main plane of the wound. Perpendicularity was estimated as adequately as possible without instruments. Shadowless illumination was obtained by two flash lamps mounted on the right and left sides of the camera (Nikon™ AS21[**] in combination with a Nikon™ AS14 controller[**] fed by four rechargeable batteries). To minimize geometric distortion, a 105-mm focal-length lens was used (Nikon™ AF105[**]). Focusing was done at full aperture on a standard gray card (Kodak™[††], 9 cm^2) at a right angle to the lens with a code for patient and time of photography. This gray card was mounted on a steel rod fixed to the camera. The focusing distance was 78 cm. After focusing on the gray card, the rod (which was marked at 78 and 75 cm from the site at which the gray card was attached) was pulled to the 75-cm mark to prevent the rod from touching the patient during photography. Thus, the factor of magnification was identical for all slides. The equipment was supported by a tripod on a mobile dolly. Subsequent focusing on the wound edge was done by adjustment of the lens-to-object distance by moving the dolly. All exposures were done at f/11 aperture. The main investigator and the nurse took the color slides at baseline and after 1, 2, 4, 6, 8, 10, and 12 weeks. We argued that the US effects, if any, must be clear within 12 weeks. To ensure a fair number of surface measurements for each patient, we spaced them equally over that period. We expected small wounds, which were prevalent, to heal quickly; therefore, we included one measurement at week 1.

We measured, when possible, ulcer volumes using the method described by Berg et al.[17] Briefly, volume measurement was carried out before US therapy to avoid remains of coupling gel reducing the readings. Tegaderm® transparent dressing[‡‡] was applied tightly over the ulcer and the surrounding skin. The ulcer was then filled with sterile physiological saline by injection through the film. Another needle was placed at the highest point of the ulcer to allow air to escape. If necessary, air bubbles hidden under an ulcer margin were gently massaged out of the ulcer. We did every measurement twice, also scoring the quality of the measurements on a three-point scale (1=low, 2=moderate, 3=high).

The slides were projected (in random order per patient and magnified 6.2 times) and the wound contours drawn by two co-workers (data analysts with a background in dietetics and human nutrition) who had been trained by the main investigator and who were unaware of treatment allocation and follow-up week. Wound contours were scanned (Hewlett-Packard Scanjet[§§]), and surface areas were calculated with a computer program. This method has been shown to have high precision (coefficient of variation=.06).[18,19] In addition to absolute healing rates (in centimeters per week) and relative healing

[‡] Semperit Technische Produkte GmbH, Modecenterstrasse 22, A-1031 Wien, Austria.
[§] Jobst Ire Ltd, Industrial Estate, Thurles, County Tipperary, Ireland.
[‖] Fujisawa USA Inc, Parkway North Center, 3 Parkway N, Deerfield, IL 60015-2548.
[#] Fuji Photo Film Co Ltd, 26–30, Nishiazabu 2-chome, Minato-ku, Tokyo 106, Japan.
[**] Nikon Corp, 2–3, Maronouchi 3-chome, Chiyoda-ku, Tokyo 100, Japan.
[††] Eastman Kodak Co, Rochester, NY 14650.
[‡‡] 3M Medical-Surgical Div, St Paul, MN 55101.
[§§] Hewlett-Packard BV, PO Box 667, 1180 AR Amstelveen, Netherlands.

rates (percentage of change), this program enabled us to calculate healing rates (in centimeters per week), indicating at which rate the wound edges were growing toward the center. These rates take into account that wounds with a large contour might have more healing potential than smaller wounds because they have a greater number of dividing epithelial cells along their edge.

Two nursing home physicians and two senior staff nurses in nursing homes, who had an interest in pressure ulcers but were unaware of treatment allocation, were invited as members of a panel. A brief training session was held to improve interrater consistency (also called "inter-observer reliability"). During this training session, the investigator showed about 10 typical color slides representing the extreme and some intermediate values of items to be scored. Sometimes, a brief discussion followed about the score proposed by the investigator. During the actual scoring sessions, panel members were allowed to consult photographs showing typical examples of pressure ulcers. The four panel members independently scored all slides on four visual items (color of the surrounding skin, necrotic tissue, granulation tissue, and deepest tissue involved), each on a four-point scale, and then gave an overall report mark between 1 and 10 (1=bad, 10=excellent) for each ulcer. For this purpose, we prepared slide carousels carrying the slides of eight patients (four from each treatment group). In each carousel, the slide order was random. Signs with regard to follow-up week were masked. In addition, panel members scored the overall clinical change (between −100% and +100%), comparing each follow-up slide with the corresponding baseline slide. In that session, which was also preceded by a training session, the slide order for each patient was again random, except for the baseline slides. Again, signs on the follow-up week were masked. All scores were assigned within 8 hours on the same day.

Statistical Analysis

We carried out an intention-to-treat analysis and a per-protocol analysis. Intention-to-treat analysis is an approach in which all eligible patients, regardless of compliance with the study protocol, are included in the analysis whenever possible (ie, when outcome data are not missing). We defined per-protocol analysis as an analysis restricted to those patients who had never had US therapy on their ulcer before, who had an overall compliance of at least 80%, who received no major cointerventions (except our standardized treatment consisting of repositioning once every 3 hours, water bed, flotation pad, and topical wound care), and whose effect measurements were relatively unproblematic. Per-protocol analysis aims at estimating pure efficacy, but it may violate the principles underlying randomization. Therefore, intention-to-treat analysis, although fair, may be somewhat conservative due to the possible diluting effects of bad compliers and measurement problems. For all calculations, we used SPSS-PC 5.0 for Windows.[III]

Covariables

The plethora of covariables prevented the standard use of multivariate analysis. Therefore, we grouped baseline variables into eight clinically cogent clusters and used these clusters to control confounding.[20] The Appendix (page 1312) shows the eight clusters and their most important component variables. The partitioning code was broken only after all cluster variables and outcome variables were defined and cutoff points for independent variables were chosen. We estimated 14 missing values on independent variables using information on relevant baseline data from cases that had complete information on those variables. To do this, we used linear regression, in which continuous variables were trichotomized to avoid unnecessary assumptions of linearity. For instance, to estimate a missing value on height (one case), information on gender, weight, and age (the latter two in tertiles) was used. The estimation of missing values seems hazardous; however, the default strategy of deleting these variables from the analysis may also be hazardous if there is an association between the reasons for the data being missing and chances of wound healing. Such an association is not unlikely in more severely debilitated patients in whom even the most dedicated investigator may be reluctant to measure body weight or scapular skinfolds.

Outcome Variables

Surface reductions (in square centimeters) and actual wound closure (yes or no) both are interesting end points. Therefore, we used different outcome measures to operationalize these end points. In addition to a comparison of the proportions of wounds healed after 12 weeks (12-week incidences), we used life-table methods (Kaplan-Meier method)[21] to calculate wound survival times and Cox proportional-hazards analysis[21] to calculate the ratio of the wound closure probabilities per unit of time. In contrast to the Kaplan-Meier method, Cox regression allows adjustment for between-group imbalances in multiple baseline variables simultaneously. In all other multivariate analyses, we used straight-line regression analysis.

Absolute mean surface reductions (in square centimeters per week) were calculated by fitting a straight line through the surface area values for each patient. We calculated the relative changes in surface area (percent per week) by subtracting a patient's baseline value from his or her last value. This difference was then divided by

[III] SPSS Inc, 444 N Michigan Ave, Chicago, IL 60611.

Table 2.
Results of Intention-to-Treat Analysis of Outcome Variables of Surface, Volume, and Changes on the Clinical Rating Scales for the Ultrasound (US) and Sham US Groups[a]

	US Group (n=45)	Sham US Group (n=43)	US Group Minus Sham US Group	Adjusted Difference CI[b]	P (One-tailed)
Mean surface reduction (cm^2)	0.18	0.31	−0.13	−0.12 (−0.27, 0.03)	.09
Mean surface reduction (%)	22.91	13.82	9.09	8.27 (−2.31, 18.85)	.10
Mean healing rate (cm)	0.18	0.13	0.05	0.05 (−0.04, 0.13)	.18
Mean volume reduction[c] (mL)	−0.29	0.42	−0.71	−0.72 (−1.22, 0.22)	.01
Mean volume reduction[c] (%)	−4.12	15.84	−19.96	−17.41 (−51.35, 16.53)	.19
Overall clinical assessments from slides					
Mean improvement in report mark[d]	0.71	0.46	0.26	0.22 (−0.14, 0.57)	.16
Mean clinical improvement[e] (%)	27.40	16.51	10.90	9.15 (−1.44, 19.73)	.08

[a] All values represent mean weekly changes.
[b] CI=90% confidence interval; other intervals are shown in Figure 3.
[c] Volume measurements were available for 11 and 14 patients in the US and sham US groups, respectively.
[d] Improvements (changes) were scored on a scale from 1 (bad) to 10 (excellent).
[e] Improvements (changes) were scored on a scale from −100% to +100%.

Table 3.
Results of Per-Protocol Analysis of Outcome Variables of Surface, Volume, and Changes on the Clinical Rating Scales for the Ultrasound (US) and Sham US Groups[a]

	US Group (n=30)	Sham US Group (n=31)	US Group Minus Sham US Group	Adjusted Difference (CI)[b]	P (One-tailed)
Mean surface reduction (cm^2)	0.20	0.30	−0.13	−0.14 (−0.35, 0.07)	.14
Mean surface reduction (%)	26.94	16.01	10.92	13.13 (−1.61, 27.87)	.07
Mean healing rate (cm)	0.21	0.14	0.07	0.07 (−0.04, 0.18)	.16
Mean volume reduction[c] (mL)	−0.16	0.48	−0.33	Not enough data	
Mean volume reduction[c] (%)	−29.17	11.09	−18.08	Not enough data	
Overall clinical assessments from slides[d]					
Mean improvement in report mark[e]	0.79	0.52	0.27	0.31 (−0.17, 0.78)	.15
Mean clinical improvement[f] (%)	30.11	17.54	12.57	13.32 (−0.84, 27.49)	.06

[a] All values represent mean weekly changes. This analysis was restricted to those patients in whom compliance was at least 80% and no major cointerventions (except our standardized treatment consisting of three hourly repositionings, water bed, flotation pad, and topical wound care) occurred and whose effect measurements were relatively unproblematic. Decisions on exclusions were made before the partitioning code was broken.
[b] CI=90% confidence interval.
[c] Volume measurements were available for only 3 and 6 patients in the US and sham US groups, respectively.
[d] These measurements pertain to 32 and 32 patients in the US and sham US groups, respectively.
[e] Improvements (changes) were scored on a scale from 1 (bad) to 10 (excellent).
[f] Improvements (changes) were scored on a scale from −100% to +100%.

baseline value and time interval. The potential to epithelialize is related, at least in superficial wounds, to the length of the wound edge (ie, the number of dividing epithelial cells). Therefore, we also calculated mean healing rates (in centimeters per week), indicating how rapidly the edge moves toward the center of the wound. Mean changes per week in report marks were calculated by fitting a straight line through the report marks for each patient. Mean overall clinical changes per week were calculated by taking the mean of the panel's judgments for each patient.

The influence of loss to follow-up on the study outcome was tested in a sensitivity analysis in which a patient's trend was extrapolated either using the sham US group (sham US+10 mg AA) trend or the trend of the group to which the patient had been allocated. Deletion was a third option. We prefer using the sham US group trend for extrapolation because it is the best estimate of the natural course (placebo effects included) in these patients. We present results from that analysis in Tables 2 through 4.

We report differences with their 90% confidence intervals (CIs), allowing easy one-tailed testing of the null hypothesis with $P=.05$. Readers can choose any desired confidence interval for two important outcome variables using the probability-value curve shown in Figure 1.

Table 4.
Results of Three Multivariate Subgroup Analyses of Mean Surface Reduction for Ultrasound (US) and Sham US Groups

	No. of Patients		Adjusted Difference (CI)[a]	*P* (One-tailed)
	US Group	Sham US Group		
Baseline surface area (cm^2)				
≤1	19	15	0.21 (0.00, 0.42)	.05
1.01–10	25	24	−0.15 (−0.31, 0.01)	.06
Spontaneous body movements				
At least some (nondestructive)	10	13	−0.01 (−0.32, 0.29)	.48
None or destructive	35	30	−0.17 (−0.35, 0.00)	.06
Wound				
Clean	7	6	0.14 (−0.29, 0.57)	.28
Infected	38	37	−0.16 (−0.33, 0.00)	.06

[a] CI=90% confidence interval.

Results

Eighty-eight patients were randomly assigned to the US and sham US groups in 1991 and 1992. We examined the successfulness of maintaining double-blind conditions. After 2 and 12 weeks, nurses, physical therapists, and the main investigator and his assistant were invited to guess the treatment allocation and to indicate their certainty on a scale from 1% to 100%. In about 85% of the cases, the three groups of workers indicated maximal doubt. In the remaining cases, the number of incorrect guesses exceeded the number of correct guesses, although the correct guesses were made with slightly more certainty. After 12 weeks, nurses' guesses did not indicate any unblinding. Physical therapists correctly guessed allocation in eight cases and incorrectly guessed allocation in five cases with, on average, 92% and 75% certainty, respectively, indicating no large problems in blinding. Due to jamming of radios and other technical problems, the main investigator and his assistant had broken the code in 7 patients with near certainty. In two other cases, they made an incorrect guess.

There were five deaths and one withdrawal in the US group and three deaths and two withdrawals in the sham US group. Two patients, one in each group, complained of the US therapy being painful at times. Other side effects were not reported. Seven patients died and two patients withdrew before effect measurements at 6 weeks. One patient died and one patient withdrew after 6 weeks of follow-up. For these two patients, we estimated missing outcome variable values by extrapolating their own trend instead of using the group trend substitution mentioned earlier.

Intention-to-Treat Analysis

Table 5 shows the extent of baseline similarity of the treatment groups at the level of the cluster variables, and Table 6 shows distributions of a selection of separate baseline variables. A crude analysis in which baseline differences in the covariables are not accounted for showed that after 12 weeks, 40% (18/45) of ulcers in the US group and 44% (19/43) of ulcers in the sham US group were closed (CI of the difference=−21 to 13; *P*=.43 [one-tailed]). This analysis, using the 12-week cumulative incidence of wound closure, did not take

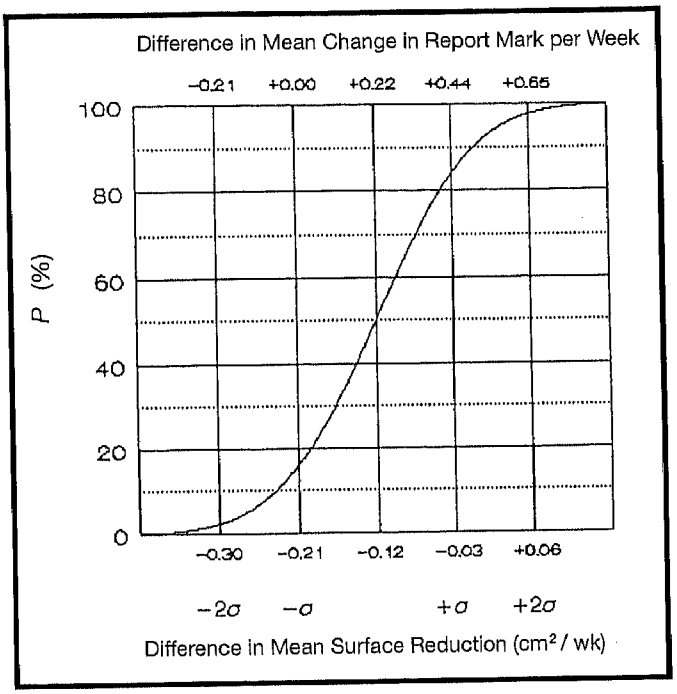

Figure 1.
Probability value curve from the intention-to-treat analysis. The x-axis represents the surface reduction (in square centimeters per week) (bottom) as well as the change in report marks on a scale between 1 and 10 (top). The sigmas below the figure indicate the location of treatment differences (intervention minus control) one and two standard deviations (to both sides) from our estimate and facilitate the construction of 68% and 95% confidence intervals, respectively. The point estimate (*P*=.5) of the adjusted difference in surface reduction was −0.12 cm^2/wk, and the point estimate of the adjusted change in report mark was +0.22. For example, for the hypothesis of a true difference of +0.06 cm^2/wk (or +0.65 report mark points), the figure shows that the probability of finding the measured or a larger difference is 95%. In this figure, probability values higher than 50% should be subtracted from 100%, which leads to a value of 5% in this example.

Table 5.
Distribution of Patients (in Percentages) Over the Levels of the Prognostic Cluster Variables for the Ultrasound (US) and Sham US Groups[a]

	US Group (n=45)	Sham US Group (n=43)
Wound status		
Bad	35.6	32.6
Moderate	53.3	53.5
Good	11.1	14.0
Nutritional status		
Bad	68.9	72.1
Usual	31.1	27.9
Vitamin C (mg/L)		
≤2	24.4	27.9
2–4	24.4	37.2
>4	51.1	34.9
Mobility		
Bad	35.6	46.5
Usual	64.4	53.5
Subcutaneous cushioning		
Bad	11.1	27.9
Usual	88.9	72.1
Care level		
Bad	31.1	39.5
Usual	68.9	60.5
Concomitant diseases		
Bad	17.8	23.3
Usual	82.2	76.7
Overall pressure ulcer status		
Bad	73.3	69.8
Usual	26.7	30.2

[a] Each cluster is constructed of separate baseline variables (see Appendix).

Table 6.
Distributions of a Selection of Separate Baseline Variables for the Ultrasound (US) and Sham US Groups[a]

	US Group (n=45)	Sham US Group (n=43)
Age of patients (y)	82 (79–87)	80 (75–86)
Gender		
Women	77.8	72.1
Men	22.2	27.9
Age of ulcer at randomization (d)	92 (45–224)	86 (27–200)
Grades II and III (%)	80.0	83.7
Ulcers located on the trunk (%)	60.0	58.1
Report mark (1=bad, 10=excellent)	6.5 (5.5–7.0)	6.0 (5.5–7.0)
Wound surface area (%)		
0.01–1.00 cm^2	42.2	34.9
1.01–5.00 cm^2	40.0	44.2
5.01–10.00 cm^2	15.6	11.6
>10 cm^2	2.2	9.3
Wound volume[b] (%)		
0.01–1.00 mL	36.4	50.0
1.01–5.00 mL	45.5	35.7
5.01–10.00 mL	18.2	0.0
>10 mL	0.0	14.3
Body mass index (kg/m^2)	21.4 (18.2–23.1)	20.8 (18.9–24.8)
Serum albumin (g/L)	31.0 (28.6–33.9)	31.3 (29.3–33.2)
Serum zinc (μmol/L)	11 (11–13)	12 (10–13)
Hemiplegia (%)	11.1	25.6
Diabetes mellitus (%)	13.3	32.6
Time in bed (h/24 h)	17.2 (14.4–24.0)	16.0 (14.0–20.5)
Exposure to feces (min/24 h)	26 (5–62)	30 (13–120)
Exposure to urine (min/24 h)	180 (0–510)	120 (0–480)

[a] For continuous variables, the median (and, in parentheses, the 25th and 75th percentiles) is given.
[b] Available for 11 and 14 patients in the US and sham US groups, respectively.

into account the exact days on which wound closure occurred. Life-table analysis remedied this defect. Figure 2 shows the wound survival times by means of Kaplan-Meier curves. The two curves do not reveal differences between the groups. Unfortunately, Kaplan-Meier analysis does not allow for correction of between-group imbalances in multiple baseline variables simultaneously. This defect was remedied by a Cox proportional-hazards analysis in which the wound survival ratio was adjusted for differences at baseline. It yielded a proportional-hazards ratio of 1.08 (CI=0.56–2.06), indicating no larger wound closure probability per unit of time in the US group. Thus, the outcome of the simple analysis was confirmed by the outcomes of the more sophisticated analyses.

Table 2 shows the crude results and the adjusted results for the other outcome variables. Figure 1 provides extra data for absolute surface reductions and changes on the clinical rating scales. There are no clear indications that US treatment is different from sham US treatment. The results of two analyses in which we dealt with missing values on outcome variables differently (sensitivity analysis) were almost identical to the results presented here.

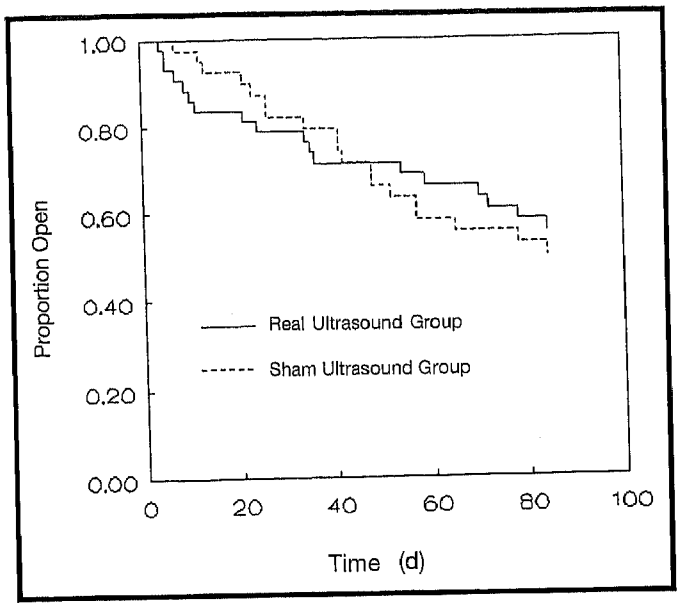

Figure 2.
Kaplan-Meier wound survival curves for all 88 patients (intention-to-treat analysis). The solid line and the broken line represent the survival curves for the ultrasound and sham ultrasound groups, respectively (P=.61 [log rank test, one-tailed]).

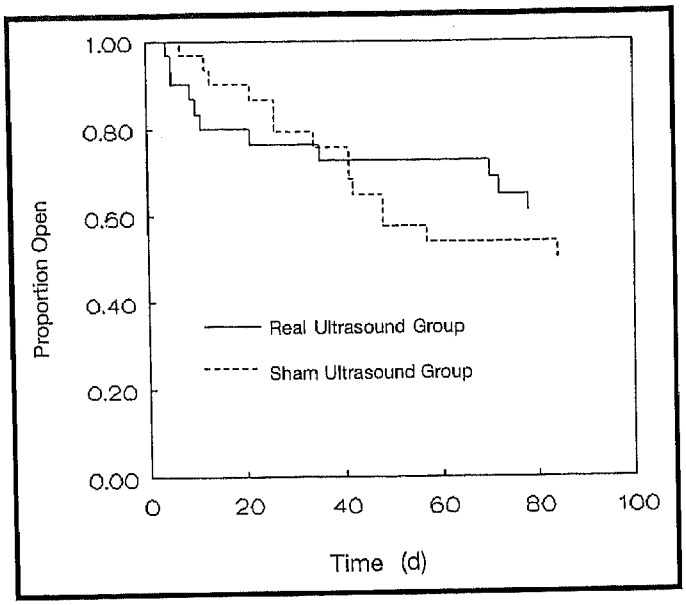

Figure 3.
Kaplan-Meier wound survival curves for 64 patients (per-protocol analysis). The solid line and the broken line represent the survival curves for the ultrasound and sham ultrasound groups, respectively (P=.71 [log rank test, one-tailed]).

Per-Protocol Analysis

We restricted the per-protocol analyses to 64 patients. Three patients were excluded only from analyses pertaining to wound surface areas. We decided on the exclusions before the partitioning code was broken. Four patients had had some form of US therapy before randomization, 1 patient was found later to be ineligible, 13 patients had received less than 80% of the US treatments, 8 patients had received a potentially powerful cointervention during the trial (eg, specially adapted wheelchairs in cases of sacral ulcers), and effect measurements were considered unreliable for 5 patients, usually due to the wound surface areas depending considerably on the degree of traction applied to the wound edge during photography. Four patients were excluded for more than one reason.

Figure 3 and Table 3 show that this analysis broadly confirms the results of the intention-to-treat analysis. The Kaplan-Meier curves are not different between the groups. The Cox proportional-hazards ratio was 1.08 (CI=0.44–2.66; P=.44 [one-tailed]). Again, the results of two analyses in which we dealt with missing values on outcome variables differently were almost identical to the results presented here.

Subgroup Analyses

We carried out three additional analyses to explore the possibility that the effects of US therapy differed for special subgroups of patients. We focused on baseline surface area (≤1 versus 1–10 cm^2), mobility (no spontaneous body movements or movements that are destructive with regard to the ulcer versus at least some nondestructive spontaneous body movements), and infection (color of the surrounding skin is red or any degree of necrosis versus otherwise). The latter variable was suggested by the positive results in infected wounds in the trial by McDiarmid et al.[2] In these analyses, the influence of other variables was adjusted for by means of the cluster variables. Table 4 shows four differences of marginal statistical significance. Three of those were negative differences, for which we do not have a reasonable explanation. Surprisingly, we found a positive difference in small wounds. Actually, we conjectured that US therapy would be more effective in larger wounds only, because in such wounds US therapy would have a greater potential to produce its beneficial effects (more fibroblasts, more granulation tissue). Therefore, we find the tendency for US therapy to be more effective in small wounds difficult to explain. We believe that these subgroup findings are due to chance, but it would be interesting to see whether future research will provide a new context for these findings.

Discussion and Conclusions

Table 6 shows that the sham US group had a greater proportion of patients with very large ulcers, hemiplegia, and diabetes, which might be a prognostic disadvantage. Baseline similarity on the level of the cluster variables was good for four out of eight clusters, leaving some room for confounding. When we used the clusters in a multivariate analysis to correct for potential confounding, however, the adjusted differences were close to the crude differences.

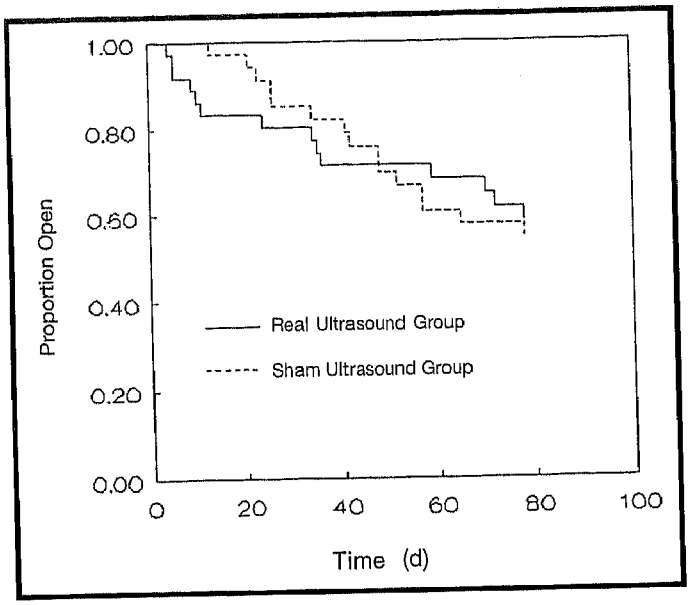

Figure 4.
Kaplan-Meier wound survival curves for 75 patients with an infected wound. The solid line and the broken line represent the survival curves for the ultrasound and sham ultrasound groups, respectively ($P=.46$ [log rank test, one-tailed]).

Measurement errors may have occurred in some of the variables requiring judgment that were used to form the cluster variables (eg, "destructive movement" [scored as "yes" or "no"], "mobility"). Because the observers were blinded with regard to treatment, such errors would be nonsystematic. Furthermore, because the results from the multivariable analyses confirm those from the simple unadjusted analyses, we do not think that major confounding was introduced due to these potential misclassifications.

Compliance was higher than 80% in 75 patients. We tried to establish similar circumstances, apart from the intervention, in both treatment groups by standardizing body support measures and topical wound care and by strict blinding. Because the main investigator and the nurse assistant personally carried out topical wound care most of the time, the blinding was standardized to a high degree. Measurement bias was eliminated by working under blinded conditions, which was almost completely successful. Where blind conditions were compromised, standardized procedures probably prevented major bias.

We assessed the impact of loss to follow-up, which was 12.5%, by doing the analyses under three different assumptions (ie, a sensitivity analysis). The results of these analyses were almost identical. In conclusion, we believe that our trial is internally valid.

The evidence from randomized trials on humans on the efficacy of US therapy in wound healing and the healing of pressure ulcers in particular is scarce and contradictory. To a lesser extent, this also applies to laboratory research. There are three randomized trials of US therapy in venous ulcers. Callam et al[22] reported positive results in a trial where the control group received only standard treatment, no sham US therapy. Lundeberg et al[23] and Eriksson et al[24] unsuccessfully tried to reproduce Callam and colleagues' findings in two trials that were similar to that of Callam et al, but controlled with sham US therapy. We found two controlled, but nonrandomized, trials in this area[25,26] showing positive results.

The only randomized trial in pressure ulcers that we know of was fairly similar to ours in the choice of the US therapy variables. McDiarmid et al[2] were unable to show an overall beneficial result, but they reported a positive result in a subgroup of patients with infected ulcers. With hindsight, they reasoned that slowly healing infected wounds offer scope for improvement in contrast to clean sores that are already healing at a near-maximum rate. We could not confirm their findings in a subgroup analysis. A Kaplan-Meier analysis in this subgroup showed no treatment differences, either (Fig. 4).

Just as in the trial by McDiarmid et al,[2] we judged infection from wound inspection (red edge or necrosis). No cultures were made. Our subgroup of patients with infected wounds consisted of 75 persons.

A problem with formal testing of US therapy is the large number of treatment variables (Tab. 1), each of which can be varied. By using the literature and asking experts on physical therapy in the Netherlands, we tried to choose the variables with the highest chance of producing beneficial effects. We gave the therapy a maximal chance to show its efficacy. However, we could not demonstrate clear beneficial effects under optimal circumstances. This result probably reflects the low therapeutic potential of other forms of US therapy in the treatment of pressure ulcers, as well.

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