The effect of stochastic electrical noise on hard-to-heal wounds

• **Objective:** To evaluate the effect of electrical stochastic noise stimulation on hard-to-heal wounds.
• **Method:** This open-label observational case series aimed to evaluate the effect of the Bioelectrical Signal Therapy (BST) device on the treatment of hard-to-heal (recalcitrant) wounds. The study group comprised nine patients (three males and six females), with a total of 11 ulcers that had not healed (ulcer duration range: 18 months to 20 years) despite being treated with other standard methods. Ulcer aetiologies were: EPUAP grade IV pressure ulcers (n=6) and grade III pressure ulcer (n=1), vasculitic ulcer (n=1), post-actinic lesion (n=1), ischaemic (n=1) and post-surgical lesion (n=1). The median patient age was 75. Treatment was delivered for 30 minutes, three times a day for 60 days.
• **Results:** Four patients (five ulcers) closed completely. Ulcers in three patients reduced in size with signs of epithelialisation. No improvement was observed in one patient (who had paraplegia). One patient stopped treatment due to skin irritation at electrode sites. No other adverse effects were observed and all of the treated patients defined the treatment as painless.
• **Conclusion:** Stochastic white noise applied to hard-to-heal ulcers for 60 consecutive days reduced the wound surface area by an overall mean closure rate of 82.5% (SD=25.2%). This open-label observational case series provides preliminary indication of the possible role of stochastic resonance in wound healing.
• **Declaration of interest:** This study was supported by Vivisol (Italy), a distributor of Lifewave's BST.

wound healing; electrical stimulation; stochastic resonance

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Chronic, 'hard-to-heal' wounds can be defined as those that fail to heal with 'standard therapy' in an orderly and timely manner. In many cases, these wounds can last for years with no improvement.[1-3] Such wounds are prevalent in older people, in those with diabetes and those with venous insufficiency.[4-7] Consequently, the economic burden on the health sector is huge, and patients have a reduced quality of life.[8-10]

Practitioners therefore require an alternative or adjunct therapy to existing treatment modalities for chronic wounds. We report on the use of an easy-to-use, non-invasive, painless treatment on a selected series of patients with hard-to-heal wounds that had undergone standard treatment without improvement over 1.5 to 20 years.

Electrical stimulation in wound healing

The use of electrical stimulation as an adjunct treatment for chronic wounds such as diabetic foot ulcers (DFUs), venous leg ulcers (VLUs) and pressure ulcers (PUs) has been explored.[11-13] Indeed, the recent international pressure ulcer guidelines (EPUAP and NPUAP) rated electrical stimulation as the only treatment for pressure ulcers (PUs) with the highest strength of evidence A.[14] However, the exact mechanism of action of different modalities of electrical stimulation remains controversial and unresolved.[15-17]

Certain electrical currents, mainly direct current (DC) or pulsed monophasic waveforms, have the ability to attract opposite (positive) charged particles when applied to wounded tissue. This mechanism is known as galvanotaxis, which is a directional migration of various types of cells such as endothelial cells and keratinocytes, which enhances re-epithelialisation.[18-21]

Other electrical currents, such as alternating current (AC), have been reported to activate cutaneous sensory nerves, which mediate increased blood flow and the sensation of the injured tissue around wounds.[22-24]

Stochastic resonance

There is accumulating evidence that sensory nerves may play an important role in tissue repair.[25-28] However, most are animal studies, and the effect of sensory nerve activation in human wound healing remains mostly unexplored.[29,30]

Physicists are discovering evidence that adding random noise in the right way to certain electronic devices and biological systems can increase the detectability of signals and the transmission efficiency of information. Intuitively, noise (such as sound or light) should impede the detection of weak signals, but a wide range of studies (from computer models to human experiments) has demonstrated that low-level mechanical or electrical noise presented directly to sensory neurons can significantly

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Table 1. Wound characteristics at baseline

Patient no.	Age	Male/female	Wound duration (months)	Wound type	Wound location	Comoribidty?
1	88	Female	45	Pressure ulcer, articular fistula	Malleolar	No
2a	85	Female	27	Pressure ulcer	Right heel	No
2b		Female	27	Pressure ulcer	Left heel	No
3a	74	Male	19	Pressure ulcer	Left trochanter	No
3b		Male	23	Pressure ulcer	Right trochanter	No
4	91	Female	38	Pressure ulcer with osteomyelitis and bone exposure	Medial malleolus	No
5	46	Male	28	Pressure ulcer	Lateral malleolus	Paraplegia
6	85	Female	240	Post-actinic with osteomyelitis and bone exposure	Sacral	Diabetes
7	68	Female	30	Vasculitic	Lateral shin	No
8	63	Male	46	Ischaemic	Lateral heel	Diabetes
9	85	Female	18	Amputation stump	Tarsal	No

enhance their ability to detect weak stimuli. This phenomenon of noise improving sensory performance is termed stochastic resonance.[31-34]

Localised electrical stimulation of noise to the lower extremities of older adults may improve postural control and tactile sensitivity through the stimulation of sensory nerves.[35-37] Stochastic resonance enhances sensation in patients with diabetic neuropathy,[38-40] and may affect tissue repair at the molecular and cellular level.[41,42]

BST (Bioelectrical Signal Therapy) is a computerised electrical stimulation of electrical noise combined with a pulse train (Figs 1 and 2). This specific mode of electrical stimulation activates sensory nerves in humans via stochastic resonance.[34,43,44]

The safety and efficacy of BST therapy were evaluated in a multicentre controlled randomised study on grade III PUs.[45] Following the study treatment period of 57 days, 50% of patients in the BST group who had ulcers above the knee achieved complete closure compared with 9% in the placebo group (p=0.035). No adverse effects were reported in the BST study group.

Recently, BST has been approved as a non-invasive electrical stimulation device for hospital, nursing home, and homecare treatment of chronic wounds in Europe – CE-0473 (2004); Canada - MDR-36 (2007); Australia – ARTG, No. 143941 (2007).

While BST therapy has been validated for the treatment of PUs, it has not been tested in difficult to-treat, long-standing (1.5–20 years' duration), intractable chronic wounds where other standard treatment methods have failed. This study, therefore, sought to explore its effectiveness on recalcitrant ulcers of various aetiologies.

Method

Setting and design

This was an open-label, observational, case series undertaken to evaluate the effect of BST treatment on recalcitrant wounds. The study was conducted at the Difficult Wounds Unit, San Luca Hospital, Turin, Italy. The inclusion criteria were:

- Patients with chronic, non-healing wounds, who had previously undergone treatments such as debridement, tissue engineering or topical negative pressure, and whose wounds had neither reduced in size nor demonstrated signs of healing such as epithelialisation, granulation or scar formation
- Patients aged >18 years
- Patients with the ability to give informed consent
- Patients with clean wounds.[46]

The exclusion criteria followed the contraindications for BST as outlined by the manufacturer:

- Patients with infected or necrotic wounds[47,48]

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Table 2. Summary of results

Patient no	Grade/ wound depth (baseline)	Grade/ wound depth (study end)	Wound surface area (cm²) (baseline)	Wound surface area (cm²) (study end)	Wound closure(%)	Wound appearance (study end)	Time (days)
1	IV	Healed	4.4	0	100	Scar	90
2a	IV	Healed	4.1	0	100	Scar	60
2b	IV	Healed	2.1	0	100	Scar	54
3a	IV	II	3.7	2.5	32	Epithelialisation	90
3b	IV	II	4.4	0.6	86	Epithelialisation	90
4	IV	IV	3.5	1.7	51	Bone exposure	90
5	III	III	0.9	1.7	None	Granulation	60
6	Muscle and bone	Muscle and bone	5.7	1.4	75	Granulation	90
7	Dermal	Dermal	8.8	8.9	Dropped out	Dropped out (due to skin Irritation)	15 stopped (due to Irritation)
8	Muscle fascia	Heal	3.7	0	100	Scar	90
9	Bone	Heal	0.4	0	100	Scar	45

- Patients with arrhythmia, an active pacemaker or defibrillator, pregnancy, or who were breastfeeding
- Patients with wounds at chest level or above due to possible effect of electrical current on cardiovascular activity
- Malignant tumour in close proximity to the wound.

The study group comprised nine patients (three males and six females) with a total of 11 non-healing ulcers whose duration ranged from 1.5 years to 20 years. All patients gave informed consent.

The wounds were divided into four categories:
- Pressure ulcers: grade IV (n=6) and grade III (n=1)
- Vasculitic ulcer: one
- Post–actinic (due to radiotherapy) ulcer: one
- Ischaemic lesion: one
- Post-surgical lesion: one

Patient demographic and baseline wound details are presented in Table 1.

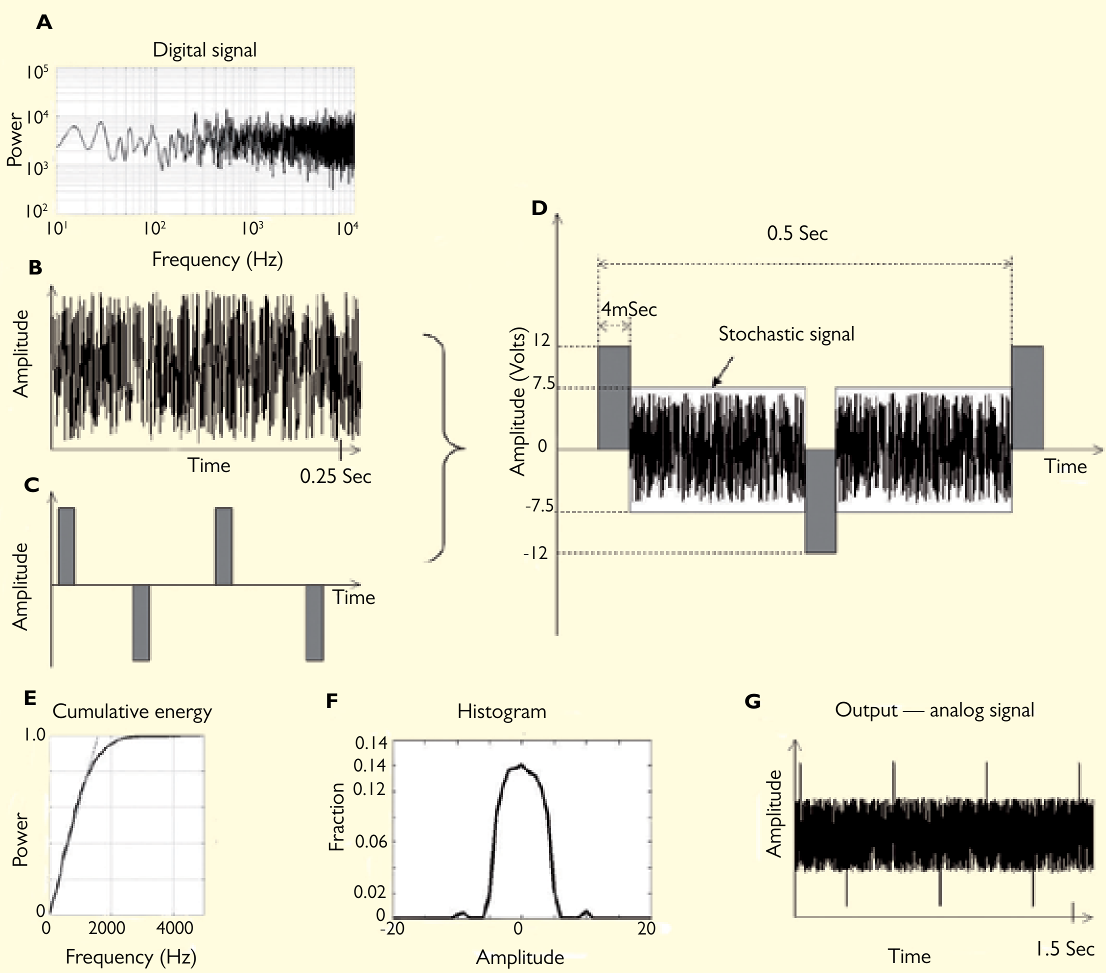
At the initial examination, the patient's demographic data, age, sex, general health state, comorbidities, wound duration, wound size, previous local and systemic treatments and medications were documented.

The wounds were photographed and measured at baseline (day 0) then on treatment days 15, 30, 45, 60 days and at 90 days' follow-up.

Fig 1. The BST system applied on a wound

Treatment with BST was given for 60 days and a follow-up observation continued for a further 30 days (patients were observed during the follow-up period each week for recurrence and/or progression of wound healing). This time period was selected based on the manufacturer's recommendations[45] and other reports on electrical stimulation in chronic wound healing.[49] It should be noted that, where the treatment was given in the home settings, the patients operated the device themselves (briefly, by connecting the electrodes wire to the device).

Fig 2. The output waveforms of the BST stimulator, their digital generation and conversion to analog signals, as a frequency distribution of the signal, the time plot of the signal, the histogram and power density.



(a) The digital precursor (of the output stochastic signal); the signal exhibits the same range of power (V^2) over its frequency spectrum (0–10,000Hz) — a spectral presentation of the 'white noise'
(b) A paradigm of the digital precursor (amplitude over time from 0 to 0.25 Sec) — a temporal presentation of the 'white noise'
(c) The digital rectangular pulse train; the pulse has symmetrical biphasic (charge-balanced) waveform, with constant time intervals between pulses — a schematic presentation
(d) The analog output; the two waveforms (rectangular pulse train intergrated with the stochastic signal); low pass filtered at 2500Hz. The periodic output has a low frequency of 2Hz — a schematic presentation
(e) The power distribution (from 0 to 1 [100%]) of the output stochastic signal (generated from the low pass filtered white noise precursor); 0.8 (80%) of energy concentrated within the frequency spectrum from 0 to 1300Hz
(f) The analog output signal exhibits a bell shaped stochastic 'white' signal
(g) A paradigm of the analog output signal (amplitude over time 0 to 1.4 Sec) — the stimulation/treatment mode

At each assessment, the following parameters were observed and recorded:
- Surface area, measured using Visitrak (Smith & Nephew) and digital photography
- Any adverse reactions
- Percentage of decrease in wound surface area
- Wound appearance at treatment end: percentage of epithelialisation, granulation, exudate and scar formation.

Treatment

Subjects (regardless of the setting) were treated with BST for 30 minutes, three times a day. Standard wound care, including pressure relief, debridement and/or antibiotics, and compression therapy were administered as appropriate. Dressings used during the study period included hydrocolloids, hydrogels, foams or alginates. These were changed routinely in accordance with the manufacturer's recommenda-

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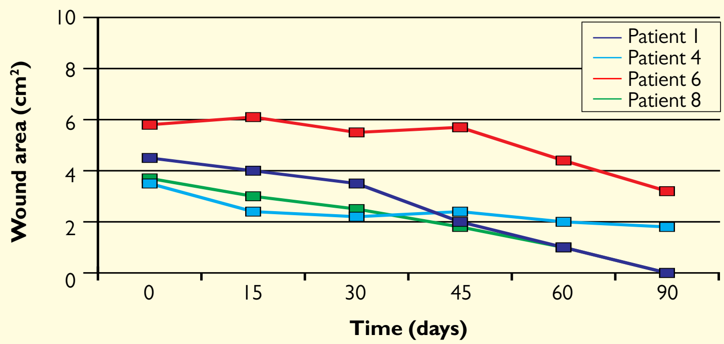
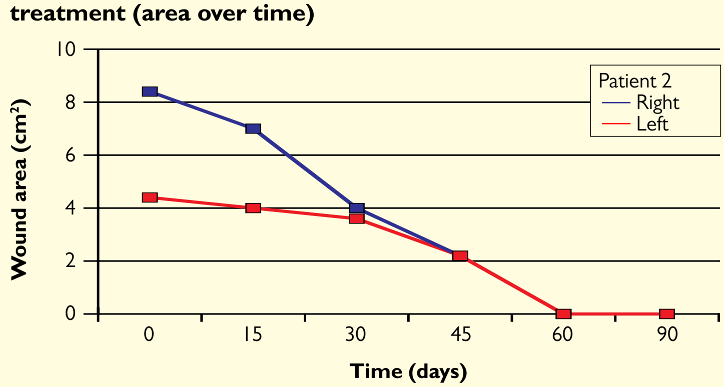
Fig 3. Wound area measurements of patients 1, 4, 6 and 8 throughout BST treatment (area over time)



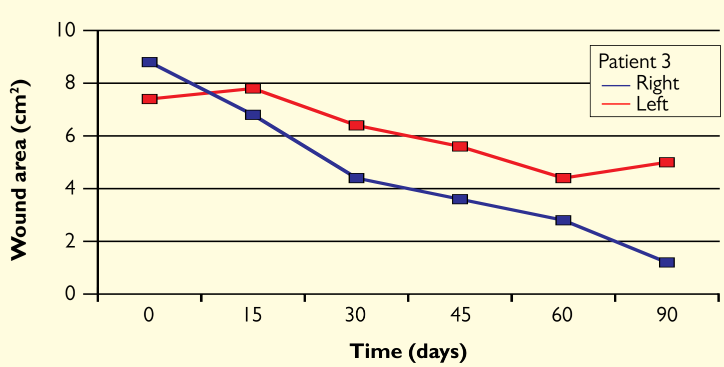
Patient 1: Malleolar pressure ulcer with articular fistula, grade IV (duration: 45 months)
Patient 4: Malleolar pressure ulcer with exposed bone and osteomyelitis, grade IV (38 months)
Patient 6: Sacral pressure ulcer in the post-actinic area, grade IV (240 months)
Patient 8: Ischaemic lateral heel (46 months)

Fig 4. Wound area measurements of patient 2 throughout BST treatment (area over time)



Patient 2: bilateral heel pressure ulcers, grade IV grade (duration of both ulcers: 27 months)

Fig 5. Wound area measurements of patient 3 throughout BST treatment (area over time)



Patient 3: Trochanter bilateral pressure ulcers, IV grade (19 months, 23 months)

tions. Dressings that included metallic wound treating products, such as silver dressings, were excluded as it is possible that they could interact with the electrical field generated by electrical stimulation. The treatments applied during the study were the same as those applied to the patients before entry, when there had been no signs of improvement.

Device

The electrical stimulation was administered through the BST device (Lifewave, Israel), which is equipped with a single channel electrical stimulator and a pair of soft surface electrodes which are placed 2–5cm on the healthy skin surrounding the wound. Since the BST stimulation is based on alternating current rather than DC, there is no need to place the electrodes on the wound. If the peri-wound was macerated, the electrodes were placed 5cm away from the wound.

The electrical stimulator had an embedded computer (ATmega128, 16MHz, 8-bit microcontroller, Atmel Corp. San Jose, CA, USA), stimulation circuits, and user controls. The electrical output was a low-intensity current (maximal current density of 0.3mA r.m.s/cm^2), which is used in wound care to avoid damaging healthy tissue.[13,49]

Electrical stimulation waveform

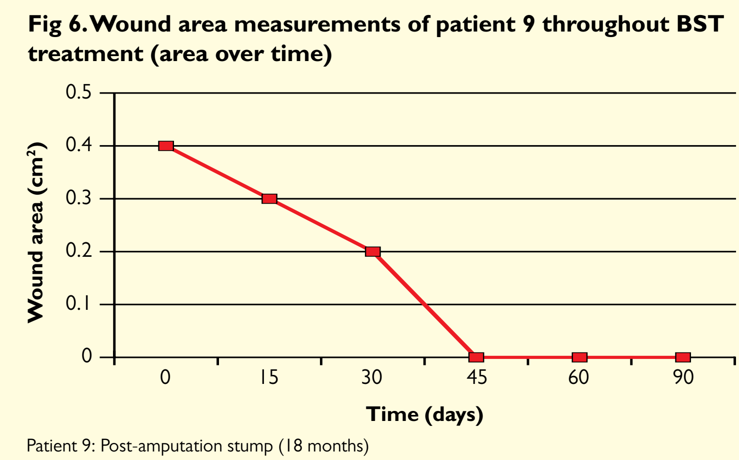
The stimulation mode is a low-frequency (2Hz) periodic pulse sequence composed of two integrated waveforms; a rectangular pulse train and a stochastic (random) signal (Fig 2). Following the digital synthesis and integration of the two signals (and their conversion to analogue signals), the integrated waveforms are filtered by a low pass filter at 2500Hz.

The stochastic waveform component originates from a digital precursor that is a white signal (ie, the same intensity range exists along the frequency spectrum). The output of the stochastic signal has maximum amplitude of 7.5 ± 0.5 volts (on 2 kiloohms), duration of 0.246 seconds with 80% of energy on the bandwidth of 0 to 1300Hz, along this bandwidth the signal exhibits a stochastic white waveform. The output of the rectangular pulse train is a periodic biphasic pulse which has maximum amplitude of 12 ± 1 volts (on 2 kiloohms) and pulse duration of 4 mSec (milliseconds). This combination of stochastic signal with the rectangular pulses enables the stimulation of sensory nerves.[31-43] The increased sensory activity has been shown to accelerate epithelial and vascular growth and cell proliferation on the border of the wounds.[22-24,50]

Data analysis

The study results were summarised with descriptive statistics. Variables that include subjects whose wounds closed completely are presented as a number and percentage with 95% exact binomial confidence

Fig 7. Patient no 2 (right heel) whose baseline wound duration was 27 months: before treatment (a) and on day 60 (b)



interval (CI). For each subject, the overall percentage area of the wound healed (between 0% and 100%, the mean and standard deviation) were calculated.

Results

Of the nine patients observed (Tables 1 and 2), four (no. 1, 2, 8, 9) experienced complete closure of five ulcers, giving a mean closure rate of 55.5% (95% CI: 22.2%–86.3%); the overall mean closure rate was 82.5% (SD=25.2%). In three of these five ulcers, complete closure was observed between 45 to 60 days of treatment. The remaining two ulcers healed at 90 days (30 days after the end of treatment).

Three patients (no. 3, 4, 6) made good progress, with the ulcers reducing in size and showing increased epithelialisation. Treatment was stopped in patient 7 due to an allergic skin reaction around the electrode contact site. The PU area of patient 5, who was paraplegic, increased during the study.

Figs 3–6 illustrate the reduction in wound area recorded for individual patients during the 90 day treatment period. Photographs showing the progression towards healing are shown in Figs 7–9.

Discussion

This open-label, observational, case series was designed to provide preliminary indications of the possible role of stochastic resonance in wound healing. We demonstrated that stochastic white noise applied to hard-to-heal ulcers for 60 consecutive days reduced the wound surface area to less than half its original size in eight out of the nine subjects. A poor response to treatment was observed in the remaining subject, who has paraplegia.

Although this was a small case series (eight subjects with 10 wounds completed it), it should be borne in mind that the patient population represents a 'worst-case scenario', where wounds had been present for many months or years and had not responded to standard or advanced (tissue bioengineering) treatments.

Fig 8. Patient no 2 (left heel) whose baseline wound duration was 27 months: before treatment (a) and on day 54 (b)

The ability of BST to stimulate healing of hard-to-heal ulcers was particularly evident in that five patients achieved complete wound closure, 55.5% (95% CI: 22.2%–86.3%). These include grade IV pressure ulcers, post-actinic, ischaemic and post-surgical ulcers, whose duration ranged from 18 to 46 months. Patient number nine, who had an 18-month-old post-surgical lesion, achieved complete closure after 45 days and stayed healed.

Though less reduction in ulcer surface urea was observed in the other three patients, BST treatment resulted in substantial improvement in tissue viability. For example, considerable epithelialisation was

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observed in patient number 3, who had grade IV bilateral pressure ulcers (with durations of 19 and 23 months); the surface areas reduced by 32% and 86% respectively. The difference in healing between these two ulcers is inexplicable, although these finding correlate with the reported effect of BST on below-knee ulcers.[45]

Patient number 5, who has paraplegia and had a grade III PU on his lateral malleolus, was the only patient whose ulcer surface area did not reduce, showing only improved granulation. We cannot explain this. However, defective wound healing associated with paraplegia has been reported by others,[25] indicating the role of sensory nerves in the wound healing process. Hence, future studies on stochastic resonance, such as the BST, should consider paraplegia as a comorbidity that may affect this electrical stimulation mode of treatment.

Recently, the efficacy and safety of the BST prototype was investigated in a proof-of-concept multicentre double-blind RCT involving patients with grade III PUs (n=63) and a placebo group.[45] Both underwent surgical debridement as required, followed by a hydrocolloid or collagen dressing and pressure relief. The mean healing rate (complete ulcer closure) in the BST group was 27.3%, compared with 9.5% in the control group (p=0.04). Analysis of complete closure by ulcer location revealed that 50% of patients in the BST group who had ulcers above the knee achieved complete closure compared with 9% in the controls (p=0.035). A positive trend in complete closure was indicated for ulcers below the knee (18% for BST group and 10% in the placebo group), but this effect did not reach significance (p=0.22). The BST treatment was found to be safe and no adverse effects were reported.

Our observational study differs in several aspects. First, the patients enrolled into the RCT had ulcers with a maximum duration of 24 months, whereas we report on patients with ulcers whose duration ranged from 1.5 to 20 years. This was a limitation of the RCT prediction strength as ulcers with a long duration are usually harder to heal.

Second, all the patients enrolled into the RCT had grade III PUs, whereas most of our patients (5/6) had grade IV (only one was grade III). Thus, our study indicates the potential effectiveness of the BST on deep wounds.

In the RCT patients were treated during the first two weeks for 20 minute three times a day, followed by 30 minute three times a day until study end. We treated all patients with 30-minute sessions three times a day throughout the study period. Treating for 30 minutes (instead of 20) three times enabled us to observe a change in the wound bed after two weeks of treatment.

The results of our observations give a preliminary indication that BST therapy may be explored in controlled trials involving patients with higher grade ulcers of over 24 months' duration.

Fig 9. Patient no 1 (malleolar) whose baseline wound duration was 45 months: before treatment (a) and after day 60 (b)

No adverse effects were noted, even though one patient stopped the treatment due to a skin 'allergy' to the electrodes (a side-effect outlined by the manufacturer). We believe, therefore, that the use of this electrical current can be applied in a comfortable manner that is relatively painless and has minimal safety concerns.

Many studies have discussed the role of damaged sensory nerves in the pathophysiology of wound healing.[22-30] However, to the best of our knowledge no report on the direct effect of human sensory nerve stimulation in wound healing exists in the literature. Only recently, studies have started to explore the role of stochastic resonance in medicine[31-44] and have provided intriguing findings on the effects of stochastic noise stimulation on the increased sensitivity of sensory nerves. Consequently, they have pointed to the application of stochastic resonance as a potential treatment for patients with chronic ulcers and neurological comorbidities such as stroke or peripheral neuropathy.

The clinically approved BST device for chronic wounds, which transmits stochastic electrical noise, motivated us to explore the potential role of this electrical stimulation in wound healing. It should be acknowledged that while we did not measure nerve activity during the BST treatment, we applied the same electrical signal as reported by others on stochastic resonance. These results intrigued us to explore stochastic signalling around wounds as the basis for this mechanism of action.[51] ■

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