

Study to evaluate the effect of low-intensity pulsed electrical currents on levels of oedema in chronic non-healing wounds

- **Objective:** To evaluate the efficacy of a medical device, Accel-Heal, which generates a low-intensity pulsed direct current, on the management of oedema in chronic leg ulcers, using high-frequency diagnostic ultrasound.
- **Method:** High-frequency diagnostic ultrasound (20MHz) with an axial resolution of 60µm was used to assess the effect of an electrical stimulation device delivering a low-intensity pulsed current on levels of oedema in chronic non-healing venous and mixed aetiology leg ulcers for a period of 10 days. Thirty patients' wounds were monitored over a 3-month period, during which time changes in levels of oedema in the wound bed and surrounding tissues were imaged and measured.
- **Results:** A significant fall in the, previously high level, of periwound oedema was noted in the patient population after 10 days of device application. By 20 days after the first application of the device the level of periwound oedema had decreased by approximately 60% of the original level, which was maintained up to the 90-day follow-up. Occurring in parallel with this, scans of the wound bed showed a rapid decrease in the levels of oedema as the new wound matrix was laid down.
- **Conclusion:** The electrical stimulation device appeared to be effective in reducing oedema levels in a range of chronic wounds and their surrounding tissues.
- **Conflict of interest:** The study was funded by a grant from Synapse micro-current Ltd.

high-frequency diagnostic ultrasound; electrical stimulation; oedema; dehydration

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Electrical stimulation therapy involves the transfer of electrical current across wound tissues, usually via two electrodes. The net effect of this current is to induce a flow of ions through the wound bed. This type of therapy has been around for many years in one form or another, with beneficial effects in promoting wound healing reported in numerous studies.¹⁻⁴

The devices can be placed conveniently into the following three groups:⁵

- Direct current (DC)
- Pulsed direct current (pulsed DC), which are further divided into high and low intensity
- Alternating current (AC).

At present, DC, pulsed DC and AC stimulation modes all appear to have a measurable effect on tissues. Numerous effects have been identified, including galvanotaxic effects, whereby different cell types are attracted to different electrodes depending on their relative charge,^{6,7} and direct stimulatory effects, in terms of increased cell number and collagen synthesis, on cells such as fibroblasts.⁸⁻¹⁰ In addition to stimulating wounds directly, there is evidence that electrical stimulation also has an anti-bacterial effect,¹¹ and can increase blood flow in wounds.¹²⁻¹⁴ This is particularly important, as an adequate oxygen supply is a prerequisite for wound

healing, helping to promote cell proliferation and synthesis.

However, these effects cannot be attributed to a single mechanism of action. Several possible explanations exist, including cell-membrane effects and stimulation of chemical mediator production and/or release.⁵ As many of the studies investigating the mechanism for this therapy have been conducted on animals, care needs to be taken when extrapolating directly from this source of evidence.

Oedema plays a major role in causing peripheral circulation and tissue oxygenation problems in patients with venous leg ulcers (VLUs). Healing can be delayed by its presence, with maceration of peri-wound tissue also being a problem, which can enlarge the wound substantially.

The aim of this study was to assess the effect of delivering a pulsed DC electrical current, previously shown to reduce oedema in animal studies,^{15,16} into non-healing VLUs. We investigated its effect on oedema levels in the wound and surrounding tissues through the use of diagnostic ultrasound.

Method

In 2009, patients eligible for entry into the trial were identified, over a 3-month period, from those attending the TVCS Wound Healing Centre in Eastbourne,

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UK. The clinic is a specialist wound care centre, staffed by tissue viability nurse specialists. All patients attending this clinic are referred by local general practitioners (GPs) and nursing homes in the East Sussex area that have general concerns about wounds, which have stagnated and are failing to heal.

Participants

Patients were considered eligible for inclusion if they were mobile with full-thickness, non-healing leg ulcers. Non-healing was defined as no change in wound dimensions over a minimum period of 2 months. Further inclusion criteria were:

- Patient/carer able to maintain the electrical stimulation device in working order (equipment continually assessed over study period by clinician)
 - Any underlying medical condition, such as diabetes, under control and currently receiving the appropriate medical attention. This was monitored by a GP who was fully informed as to the patients’ involvement in trial.
- The exclusion criteria comprised:
- Currently undergoing corticosteroid therapy, radiation therapy or chemotherapy
 - Presence of ventricular arrhythmia
 - Atrial fibrillation or cardiac pacemaker
 - Metal implants near the area of treatment.

All participants were assigned to a specific clinician (MT) for the duration of the investigation. Wounds in this study comprised VLU and mixed aetiology ulcers.

Written informed consent to participate in the study was provided by all patients prior to the start. The product, Synapse Accel-Heal (Synapse micro-current Ltd.), was CE-marked and thus no ethics committee approval was sought.

Interventions

The intervention used was the Synapse Accel-Heal, which delivers a pulsed direct current and is officially certified as a class IIA device, under the medical directive 93/42/EEC. The unit contains a constant current generator, able to automatically adjust output in response to resistance changes in the skin. This ensures that a stable current is delivered, regardless of variations in skin resistance. The working current is 40µA, with a rectified ramp waveform.

The device consists of two electrode pads containing a moist conductive medium. These are placed either side of the wound on the intact skin, approximately 2cm from the wound edge. The pads are connected to the self-contained, pre-programmed device that is attached to either the patient’s waistband or externally to compression bandages. It is easy to apply and use, with only one off/on button to press. Each patient/carer was trained how to apply the device and maintain it correctly. None of the patients reported any problems with the use of the device dur-



Fig 1. Wound area indicating regions scanned

ing the study. Other, similar devices are available but they tend to emit high current levels (up to 1mA).⁵

Measures

High-frequency diagnostic ultrasound is a non-invasive method, allowing the clinician to obtain a high-resolution image of the wound bed.^{17–23} This is a simple procedure that gives the opportunity to see changes occurring within the wound before they become evident at the tissue surface, thereby giving early warning as to whether the wound is deteriorating or improving.²⁴

The scanner used in this investigation (EPISCAN, Longport) operates at a frequency of 20MHz, giving an axial resolution of 65µm.

Scans were acquired from three regions on each patient, as shown in Fig 1. Region 1 was the centre of the wound, region 2 the peri-wound tissue and region 3 the uninjured adjacent skin, as close to the wound site as possible without suffering from the effects of the wound. To allow for any variability in each region, a minimum of six scans were taken of each area to ensure a representative value for the tissue (Fig 2).

All patients received an initial scan at the start of the study to establish the baseline profile for their tissue. A scan of the patient’s uninjured skin adjacent to the wound site (region 3) was used as a comparator to represent the patients’ normal skin condition.

Patients received their first ultrasound scan of the wound and surrounding tissue following the recruitment period. The patients were then instructed to continue, uninterrupted, with their usual wound care protocol for a further 28 days. For the various wound types, this involved:

- VLUs — Two layer compression with a secondary absorbent dressing if the wound was highly exuding
- Mixed aetiology — Reduced compression depending on the degree of arterial involvement.

At the end of this period, the patients were scanned again to establish that the wound was still non-healing (no improvement in wound dimensions). This visit was classed as time 0.

Once it was established that the wound was non-healing, the patients started a 10-day course of electrical stimulation therapy. The device was worn and therapy applied continuously over the entire course, as described above. If the device was removed, for example for dressing changes, it was immediately reapplied by either the patient themselves or the same carer to ensure consistency. The clinic was in regular contact with the patients throughout this period to check that there were no problems with the device.

At the end of the 10 days, the electrical stimulation therapy ended and the patients were scanned again. Two further ultrasound assessments were done: one 10 days later and a final 3-month follow-up. No further electrical stimulation therapy was prescribed. Throughout the study, patients continued with their usual wound care treatment strategy (compression) in tandem with the electrical stimulation therapy.

Data analysis

Two aspects of the ultrasound scans were analysed:

- **Pixel distribution in the wound bed** Each scan of the wound bed was analysed using a form of pixel distribution analysis, whereby pixels below a certain intensity are classed as low echogenic pixels (LEP). The ratio of LEPs to total pixel count (TP) has been shown to reflect changes in dermal water content,^{25,26} with a high ratio representing high water content. Using this technique it was possible to get a quantitative assessment of the level of oedema present in the wound.

- **Peri wound skin oedema** Using ultrasound, it was possible to image and measure the width of the zone of oedema collecting beneath the epidermis of the intact peri wound skin. The zone width was then expressed as a percentage of the initial width at time 0, tending towards 0% for normal, uninjured skin.

Statistical analysis

A one-way analysis of variance (ANOVA) was used to investigate the significance of the effect of the therapy on wound and peri wound oedema. The significance level was taken as 0.001. All calculations were done using the Excel analysis toolpak.

To aid interpretation of these images, it is helpful to think of all areas that are dark red/black as high in fluid, whereas blue/white areas tend to be occupied by more fibrous and less hydrated structures, such as collagen fibre bundles. Normal uninjured skin would have lower fluid content and, therefore, a greater proportion of the blue reflections to the red/black, as shown in Fig 2.

Results

Thirty consecutive patients with non-healing leg ulcers were entered into the trial: 13 male and 17 female. The participants were aged 46–95 years, with a median age of 74 years (mean 72.7). Wound

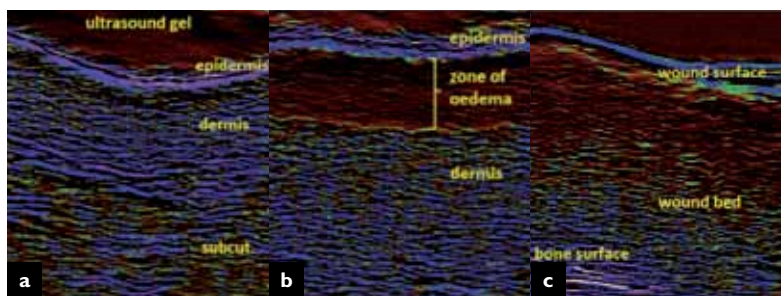
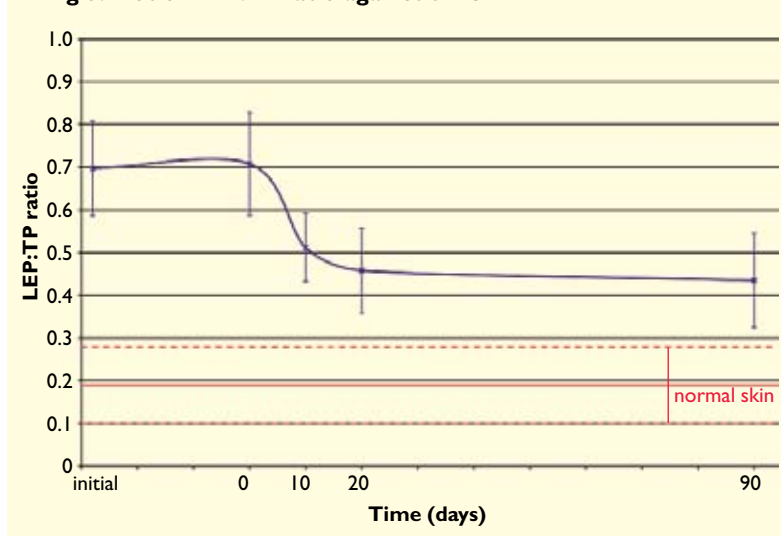


Fig 2. Typical ultrasound scans through a patient's normal uninjured skin (a), periwound skin (b) and venous leg ulcer (c)

Fig 3. Plot of LEP:TP ratio against time



durations were 2–96 months, with a median of 17 months (mean 21.9 months). Five participants were lost to follow-up and did not attend the final evaluation at 90 days.

Pixel distribution

As Fig 3 demonstrates, the LEP:TP ratio remains constant, within the uncertainty, between the initial assessment (0.70±0.09) and the time 0 assessment (0.71±0.12). This indicates there was no significant worsening over the 28 days and, more importantly, the ratio did not improve, confirming that they were non-healing wounds and qualifying the patient for inclusion in the trial.

After treatment started, the mean LEP:TP ratio noticeably decreased towards the normal level. By 10 days after the start of treatment, the ratio had fallen by approximately 38% (0.51±0.08) and after 20 days it was 55% lower (0.46±0.10). By 3 months, the mean ratio in the tissues was 63% below that seen at time 0 (0.44±0.11), tending toward levels seen in normal, uninjured tissue (0.19±0.09). This slow in the rate of decrease is to be expected since, as tissues heal, the highest rate

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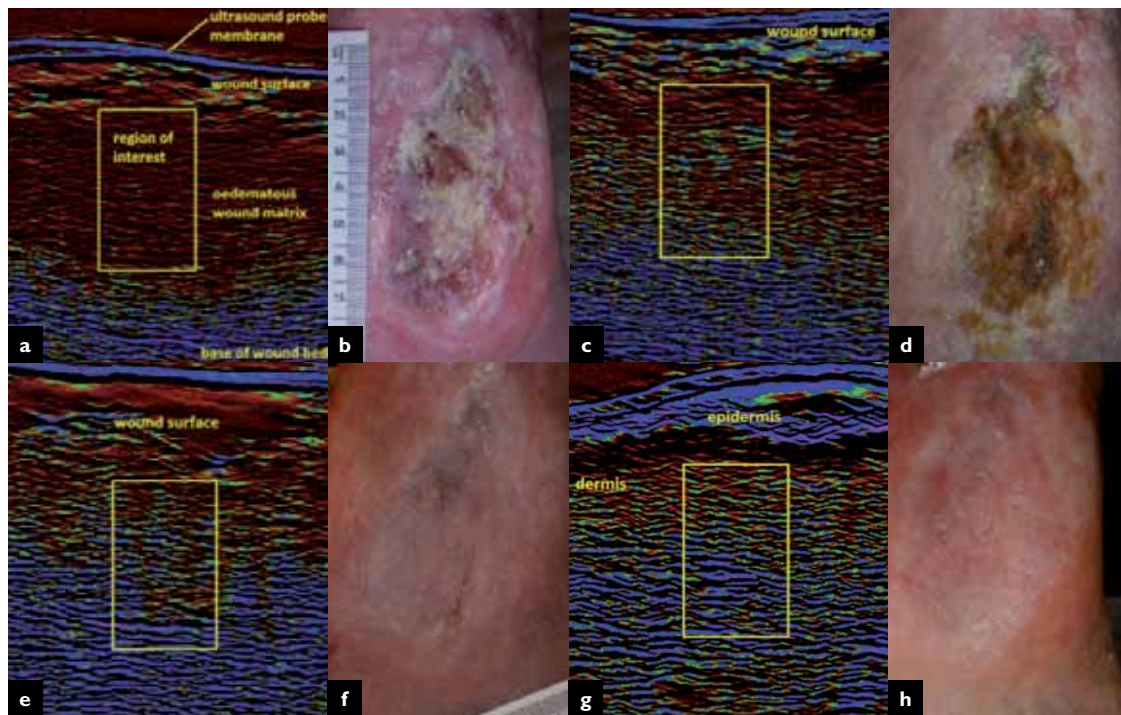


Fig 4. Sample ultrasound scans and wound photographs for time 0 (a)(b), day 10 (c)(d), day 20 (e)(f) and day 90 (g)(h)

of change is usually early and then slows as healing moves to completion.

Fig 4 shows a sample of ultrasound scans of a VLU at various time points after treatment started. On each scan the region of interest (8mm²), where the pixel analysis was carried out, is indicated. The region of interest was placed in the same location on each scan (centre of the scan, just below the wound surface or epidermis). For clinical reference, each associated wound photograph is also shown alongside the ultrasound scan in Fig 4.

As the scans show, the wound area at time 0 was saturated with oedema, recognised by the red/black colour. The accompanying photograph also shows this, with the surrounding periwound tissue also inflamed (periwound data is dealt with in the following section). After 10 days of treatment, we can see that the nature of the tissue within the wound cavity is changing dramatically, losing a high degree of the oedema present at time 0. After 20 days, the fluid has decreased even more and this level was maintained up to the 90-day time point. Note the tissue at 90 days has a predominance of blue pixels, which are indicative of fibrous tissue, comparable to that seen in normal skin (Fig 2). The reduction in oedema over the test period was highly significant ($p < 0.0001$).

Periwound skin oedema

The results for the periwound skin oedema analysis are shown in Table 1 and expressed graphically in Fig 5. This shows that the oedema actually increased

from the initial assessment to time 0, 28 days later. By 10 days after the start of treatment, the zone has decreased to approximately 60% ($63 \pm 24\%$). After 20 days the zone has decreased to approximately 40% ($40 \pm 19\%$) of that seen at time 0. This lower level of oedema was maintained up to the 90-day time point.

Fig 6 shows a sample of ultrasound scans of the periwound area at various time points after treatment commenced. From these scans, the decrease in the depth of the zone of oedema can be seen clearly. From time 0 to 10 days after the start of treatment, a marked decrease in this zone can be noted. A further decrease is then seen from 10 to 20 days. This decrease is maintained up to the 90-day time point. The reduction in periwound oedema over the test period was highly significant ($p < 0.0001$)

Discussion

The results of the analysis showed that the high levels of oedema seen initially in the wound and surrounding tissues decreased rapidly after the application of the therapy (Fig 3). This decrease was maintained for 3 months, even after the 10-day electrical stimulation therapy period had finished.

As stated in the introduction, there are numerous studies reporting positive effects in both clinical and animal models, however, the precise mechanism of action of this therapy is still not clear, with a number of potential mechanisms theorised.

It may be that electrical stimulation has a direct effect on vasodilation, either via neuronal or chemi-

cally mediated pathways.²⁷ There is also some evidence that the central nervous system may play a role in the response, as it has been shown that patients with spinal injuries do not respond as well to electrical stimulation.²⁸

Electrical stimulation has been shown to have an effect on capillary filling in tissue with venous stasis, leading to a significant reduction in oedema.²⁹ Removal of excess fluid from wound and periwound area is vitally important, as healing can otherwise be impeded.³⁰ Dormant fluid in the wound area can contain many inhibitory substances, such as pro-inflammatory mediators and bacteria; therefore, its removal will benefit wound healing.

The results suggest that the device used in this study could, in part, be responsible for stimulating the removal of excess oedema from the wound and surrounding tissues but at the same time maintaining a moist environment, which is critical for optimal wound healing.

Conclusion

Statistically significant improvements were noted in the wounds and periwound skin of patients treated with the electrical stimulation device. It must be noted that, in the absence of a control group, it could be argued that there is no definitive link between these improvements and the device, however, it should be stated that these wounds were non-healing when entered in the trial with the only change in their treatment being the inclusion of the electrical stimulation device.

The exact mechanism of action for how this effect on oedema is achieved remains unclear, with further research required. However, any device able to reduce oedema will generally have a positive impact on patient comfort and convenience, not to mention the cost benefit of the reduced dressing changes. ■

Table 1. Summary of results for periwound oedema analysis

Assessment	Mean zone of oedema thickness (mm)	Mean zone of oedema thickness (%)*	±SD	No. of observations
Initial	1.60	100	0	30
Time 0	1.67	107	16	30
10-day	0.93	63	24	30
20-day	0.64	40	19	30
90-day	0.66	40	21	25

*Mean zone of oedema thickness expressed as a percentage of the initial thickness.

Fig 5. Plot of mean zone of oedema thickness expressed as percentage of initial thickness against time

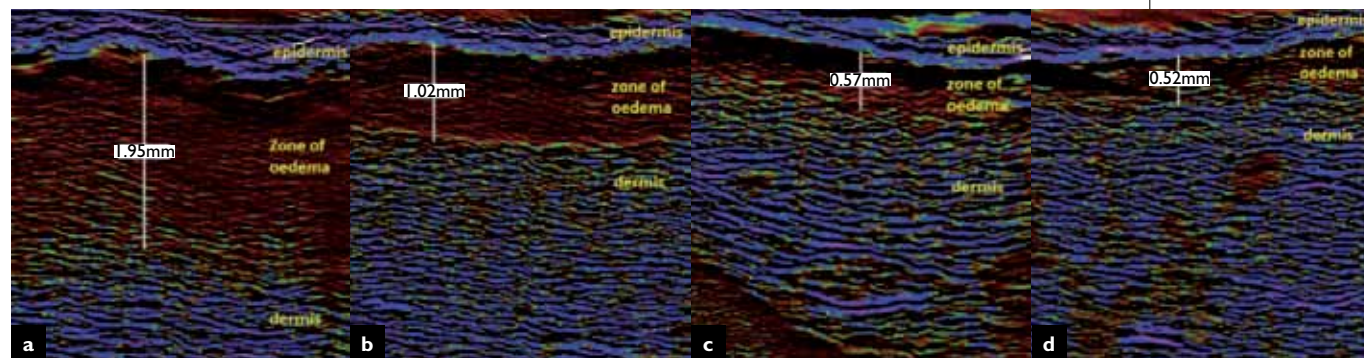
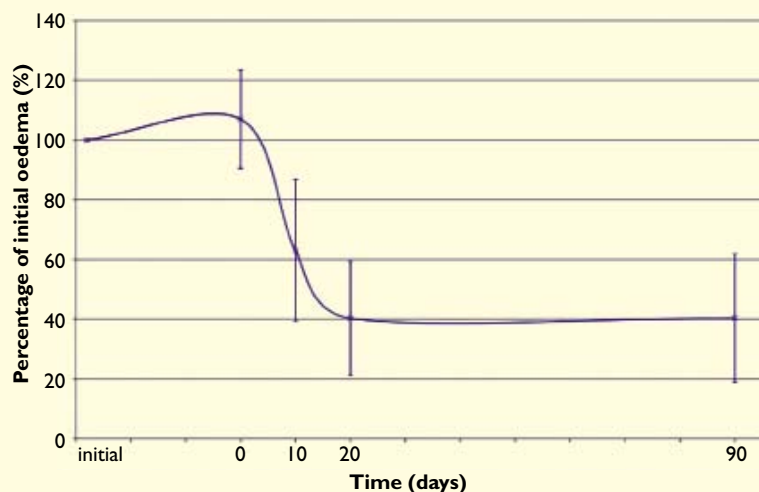


Fig 6. Sample ultrasound scans showing changes in the periwound skin over time for time 0 (a), day 10 (b), day 20 (c) and day 90 (d)

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