Received: 3 October 2022 | Revised: 17 November 2022 | Accepted: 22 November 2022

DOI: 10.1111/iwj.14071

ORIGINAL ARTICLE

IWJ WILEY

Activation of healing and reduction of pain by single-use automated microcurrent electrical stimulation therapy in patients with hard-to-heal wounds

Peter Kurz[1] | **Gabriele Danner**[1] | **Jean-Paul Lembelembe**[2] | **HariKrishna K. R. Nair**[3] | **Robin Martin**[4]

[1]WPM Wund Pflege Management GmbH, Bad Pirawarth, Austria

[2]Department, Geriatrics & Wound Day Hospital, Clinique des Augustines, Malestroit, France

[3]Wound Care Unit, Kuala Lumpur Hospital, Kuala Lumpur, Malaysia

[4]Robin Martin PhD Scientific Consulting, Foggathorpe, UK

Correspondence
Robin Martin, Robin Martin PhD Scientific Consulting, Foggathorpe, UK.
Email: robin@robinmartinphd.com

Abstract

Evidence shows that Electrical Stimulation Therapy (EST) accelerates healing and reduces pain, but EST has yet to become widely used. One reason is the historical use of complex, clinic-based EST devices. This evaluation assessed the early response of different hard-to-heal wounds to a simple, wearable, single-use, automated microcurrent EST device (Accel-Heal, Accel-Heal Technologies Limited - Hever, UK). Forty wounds (39 patients: 18 female - 21 male), mean age 68.9 ± 14.0 years comprised of: seven post-surgical, three trauma, 12 diabetic foot (DFU), 10 venous (VLU), four pressure injuries (PI), four mixed venous or arterial ulcers (VLU/arterial) received automated microcurrent EST for 12 days. Early clinical responses were scored on a 0–5 scale (5-excellent—0-no response). Pain was assessed at 48 h, seven days, and 14 days on a 0–10 visual analogue scale (VAS). Overall, 78% of wounds showed a marked positive clinical response (scores of 5 and 4). Sixty eight percent of wounds were painful with a mean VAS score of 5.5. Almost every patient (96%) with pain experienced reduction within 48 h. All patients with painful wounds experienced pain reduction after seven days: 2.50 VAS (45% reduction) and further pain reduction after 14 days: 1.83 VAS (33%).

KEYWORDS

electrical stimulation, hard-to-heal wounds, pain reduction, single-use medical device, wound healing

Key Messages

- this evaluation assessed the early response of 40 hard-to-heal wounds to a simple, patient-friendly, single-use automated microcurrent EST device used for 12 days in clinic or home settings. Sixty eight percent of patients had painful wounds (mean VAS score 5.5)
- seventy eight percent of wounds showed a marked positive clinical response to EST. Almost every patient (96%) experienced some pain reduction within

48 h. All patients benefited from a mean pain reduction of 45% after seven days: (mean VAS score 2.50)
- simple single use EST devices have the potential to allow patients with a wide range of hard-to-heal wounds to benefit from activation of healing and rapid reduction of pain

1 | INTRODUCTION

The notion of using electrical stimulation therapy (EST) to accelerate wound healing is not a new idea. Studies of bioelectricity in developmental biology and wound healing go back at least 60 years.[1-3] Subsequent work with in vitro and ex vivo models has shown that endogenous bioelectrical signals play an important role in the mechanism of normal wound healing. Endogenous bioelectricity activates epithelial cell proliferation and migration through known pathways by phosphorylation and dephosphorylation of proteins: PI3 kinases/Pten,[4-6] ERK1/2 and p38 MAP kinases;[7] bioelectricity activates endothelial cells in preparation for angiogenesis[8] and promotes fibroblast migration and growth factor secretion.[6,9] Collectively, the evidence supports a coherent scientific rationale for the application of exogenous EST to chronic hard-to-heal wounds.[10] Indeed, significant clinical evidence for the beneficial effects of EST on chronic wounds has now accumulated[11-13] across a range of different EST devices.

Moreover, it is frequently observed that during the application of many EST devices, there is a reduction in wound pain.[14-16] Reduction in pain by EST has been shown to allow reductions in the quantity and strength of analgesics and increased compliance with therapies which can be painful such as compression bandaging for venous leg ulcers. Clinicians often reduce the level of compression they apply to venous ulcers to avoid causing pain, but there is strong evidence that full strength compression is the most beneficial treatment.[17] It follows, therefore, that devices that reduce pain may allow better application of full-strength compression. Controlling constant pain from chronic wounds is also important to minimise sleep disruption and maximise the sense of well-being and positivity.[18,19]

Yet despite the scientific rationale and abundant clinical evidence for acceleration of wound healing and reduction of pain, EST has not become a first-line wound therapy. There are three main reasons why this might be the case. First, as several different regimens of electrical signal can be efficacious, this has led to a perceived lack of appropriate intellectual property rights which may have inhibited investment from major manufacturers. Second, there has been a poor communication of the scientific basis for endogenous bioelectric signals as part of the mechanisms of normal wound healing. Unscientific descriptions of the effects of EST in the past may have dissuaded clinicians, academics, and industry from adopting the technology. Thirdly, clinical evidence has largely been collected with complex, clinic-based EST instruments, which require skilled operators, are inconvenient for patients, might themselves give unpleasant sensations and be costly for health care systems and unprofitable for wound care manufacturers. A similar situation has been noted in the use of EST for orthopaedic fracture non-unions. Although many ortho-surgeons are aware of the positive results from the technology, few use it because of the high costs and inconvenience of the available devices.[20] In other wound therapies, such as the use of Negative Pressure Wound Therapy (NPWT), the initial clinical success with large, complex, clinic-based devices, has been greatly expanded by the development of small single-use NPWT devices.[21,22]

This international, multi-site observational evaluation, which included clinicians with significant expertise of using both mobile and clinic-based EST devices, was established to assess the proportion of different hard-to-heal wound types that show positive early responses to healing and pain reduction following use of a simple, easy-to-use EST device that automatically delivers a low voltage microcurrent therapy round the clock every two–four hours.

2 | MATERIALS AND METHODS

2.1 | Recruitment of patients

This was an observational study that recruited patients in early 2021 with a total of 40 hard-to-heal wounds that were not responding to standard care and other advanced therapies. The studies took place at three different international locations: Austria, France, and Malaysia. Many of the wounds were causing significant pain. The EST device was regulatory approved for use in each location and all patients were treated according to the instructions for use. Patients were able to wear EST in the home or hospital setting as appropriate.

2.2 | Single-use EST device

The device used in this study was the Accel-Heal single-use EST device (Accel-Heal Technologies Limited, Hever, UK). The device consists of a small light weight power unit (7.5 cm × 4.5 cm) with a single on–off button and connections to two adhesive electrodes. This form of the device delivers an automatic program of low voltage biphasic and monophasic pulsed current (LVBMPC) for 48 h, starting when the device is switched on. Until now, use of the device has predominantly focussed on venous leg ulcers.[23,24] The EST is subsensory, does not trigger muscle contraction and is pain free and rarely detectable in conditions of adequate patient hydration. The program of LVBMPC therapy, which lasts for approximately 30 minutes, is automatically applied every two hours in the first 24 h and every four hours during the next 24 h. The current is applied in a fixed pattern with biphasic components changing from 50 to 500 microamps (μA) at pulse frequencies of between 50 and 900 Hz and a monophasic component operating at 40 μA. The program has the aim of maximising tissue response by reducing the chance of habituation by constantly stepping between different current settings and delivers an escalating pattern of higher frequency pulses which are associated with penetration into deeper tissues. The polarity of the electrode pairs switches from +ve to −ve 10 times a second. The device is current controlled with a feedback function that continually adjusts the voltage between the electrodes so that the specified current is always applied. This ensures the same therapy is delivered, even if the electrodes are situated different distances apart, or the tissues vary in the degree of hydration between patients. At the end of 48 h, a new power unit is attached and the same pattern of continuous LVBMPC therapy is delivered. Electrodes are placed on healthy skin either side of the wound enabling the clinician to use their preferred dressing for managing exudate and protecting the wound. The device incorporates a green light emitting diode (LED) indicator that signals correct current delivery (one flash every two seconds) or a failure to deliver current between the electrodes (two flashes every second). The devices are supplied six in-a-box, so the overall therapy lasts 12 days. In this observational study, several patients received further blocks of 12-day ES therapy. At the end of 48 h, the devices are discarded. In the UK, 12 days of single-use ES therapy is currently reimbursed at £240. The manufacturer has recently launched a newer model: Accel-Heal Solo which delivers the same ES program from a single device which lasts 12 days, but this wasn't available for the present evaluation.

2.3 | Wound and pain assessment

Wounds were monitored through clinical signs, pain, area, and depth assessments according to standard local practices. Patients reported their assessment of pain on a 0–10 visual analogue scale (VAS) were 0 is no pain and 10 is worst imaginable pain. Pain assessment was carried out at day 0, after 48 h and at days 7 and 14. Overall clinical responses at the end of the second week, which includes the 12-day application of EST, were scored on a 0–5 scale.

2.4 | Clinical response scale

Observations suggested that responses to EST were generally defined by changes in five criteria: Reductions in (i) pain (if present) (ii) peri-wound oedema (change from firm to soft tissue), (iii) peri-wound inflammation (less exudate, less erythema), (iv) dimension (depth and or area) and increases in (v) granulation and or epithelial tissue. An approach was adopted whereby the most positive responses to EST displayed marked changes in all, or most, of the five criteria, whereas less responsive wounds failed to show marked changes in most or any of the five criteria. Although we did not keep a detailed record of each criterion in each wound, a simple scoring system was used to summarise the aggregate responses to the standardised EST across the range of wounds.

Score	Criteria
5–Excellent	Marked changes in all criteria
4–Good	Marked changes in most criteria
3–Modest	Some changes in most criteria
2–Limited	Detectable changes in one or two criteria
1–Minor	Barely detectable changes in one or two criteria
0–No response	No changes in any criteria

3 | RESULTS

3.1 | Patient demographics

Table 1 summarises the patients recruited into the study. A total of 40 static hard-to heal wounds from 39 patients, (18 female 21 male), with a mean age 68.9 ± 14.0 years were evaluated. There were seven post-surgical, three trauma wounds, 12 diabetic foot ulcers (DFU), 10 venous

TABLE 1 Wound and patient demographics

Wounds	Number	Mean patient ages (years)	Wound duration (months)	Wound area (cm^2)
Post-surgical	7	63.3	18.2	4.0
Trauma	3	63.0	20.3	3.6
DFU	12	65.3	16.7	56.0
VLU	10	76.0	38.2	32.2
PI	4	72.0	44.3	14.0
VLU/Arterial	4	73.5	34.3	25.8
All wounds	40	68.9 ± 14.0	30.1 ± 34.0	26.2 ± 37.6

Note: A total of 40 hard-to-heal wounds from 39 patients, (18 female 21 male), were recruited. Mean patient ages, wound duration, and wound area are shown ± standard deviation.

leg ulcers (VLU), four pressure injuries (PI), and four arterial or mixed venous arterial ulcers (VLU/arterial). The wounds had been present for a mean duration of 30.1 ± 34.0 months (n = 37) and had been static non-healing within the study institution prior to the commencement of EST for a mean of 2.6 ± 1.1 weeks (n = 28), despite a range of interventions. The mean wound area was 26.2 ± 37.6 cm^2 (n = 35). The breakdown of patient demographics for each wound indication is also shown in Table 1. In general, post-surgical and trauma wounds were of less duration (19.26 versus 33.4 months) in slightly younger patients (63.1 versus 71.7 years) and of much smaller surface area (3.8 versus 32) cm^2 than DFU, VLU, PI, and VLU/Arterial non-healing wounds.

3.2 | Clinical response to EST

Each patient received one 12-day application of EST with wound assessment at days 7 and 14. The overall pattern of clinical response as assessed on the 0–5 scale is shown in Figure 1A. The response of 18 wounds was graded 5 (excellent) with 10 wounds being scored 4 (good) giving a total of 28/36 (78%) of the wounds that were scored, showing a significantly positive clinical response. In these wounds, reductions in pain, peri-wound oedema, exudate, inflammation, wound depth, area, and increases in granulation tissue growth and re-epithelialisation were typically observed. Changes were often seen within four–six days. The proportion of wounds showing significantly positive responses (scoring 5 or 4), is broken down within individual wound types in Figure 1B: Post-surgical: (86%); Trauma: (100%) and DFU: (90%); showed a high proportion of excellent (5) or good (4) clinical responses. VLU: (67%); PI: (50%); Arterial Ulcer and mixed Venous/Arterial: (67%) had a lower number of cases rated excellent or good.

3.3 | Clinical signs of changes in wound and peri-wound tissues

A frequently observed early sign (48 h) that EST is influencing a non-healing wound was the softening of peri-wound skin. The transition from hard to soft peri-wound may indicate the reduction of oedema and this is likely to improve peri-wound perfusion. In a previous study, the reduction in oedema following application of the same single-use EST device was quantified in venous and mixed aetiology leg ulcers using high frequency ultrasound imaging after 10 days of EST.[25] One patient within the current series suffered from a long-term post-operative non-healing abscess following a lipoma removal 30 years ago. The peri-wound tissue had become insensate. However, following application of automated microcurrent EST with a clinical response rating of excellent (score 5), the patient was able to subtly feel the EST application and experienced a reduction in exudate and stimulation of granulation tissue growth. This suggests that the EST application was somehow able to improve neural function.

3.4 | Characteristics of non-responsive wounds

A total of 8/36 wounds had a modest or poor response to EST: 0, 1, 2, or 3. Poor responses, that is, scoring 0, 1 or 2 on the 0–5 scale were seen in each of the different wound types recruited in this study. In one patient (PI), it was not initially possible to obtain any electrical connection between the two adhesive electrodes as indicated by the LED lights on the ES device. Normal conduction (indicated by the LED indicator on the device) was restored following assessment of a blood sample and correction with nutritional supplementation for iron deficiency. Ultimately, however, there was still an absence of

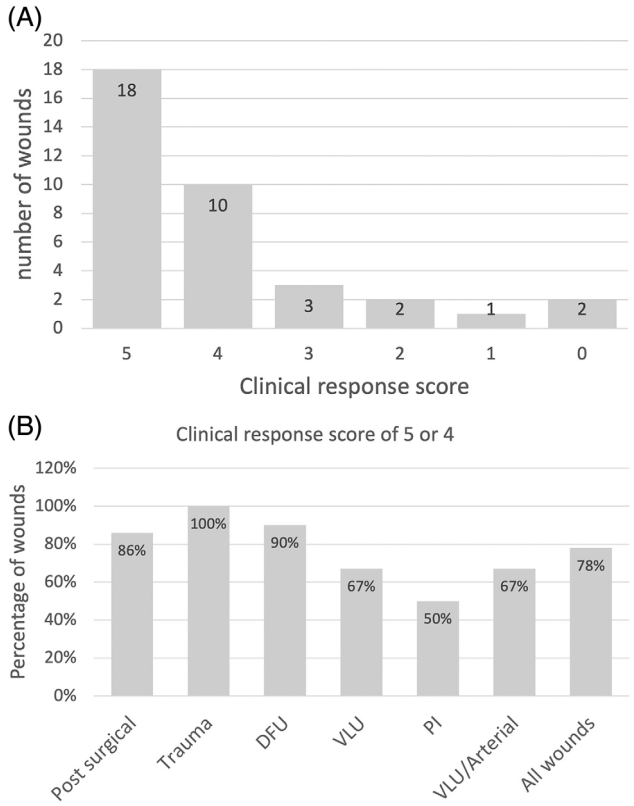

FIGURE 1 Clinical response to EST in each wound type. (A) Overall clinical responses at the end of the second week, including the 12-day application of EST, were scored on a 0–5 scale: 5–Excellent; 4–Good; 3–Modest; 2–Limited; 1–Minor; 0–No response. Evaluated wounds n = 36. (B) Proportion of each wound type with clinical response scores of 5 or 4. Overall clinical responses were captured at the end of the second week which includes the 12-day application of EST. (Scored on a 0–5 scale: 5–Excellent; 4–Good; 3–Modest; 2–Limited; 1–Minor; 0–No response. Evaluated wounds n = 36)

a favourable clinical response (score 0). In other patients, there were no obvious parameters that divided the wounds into positive responders or non-responders. Completing Wound Bed Preparation (WBP)[26,27] is a pre-requisite. At 1 site (M), six wounds were exposed to EST before WBP was completed and these seemed to respond less convincingly than four comparable wounds where WBP was complete (described elsewhere).[28]

3.5 | Reduction in pain

The percentage of wounds causing pain is shown in Figure 2A. Across all wound types, there was a total of 27/40 (68%) wounds which were painful (any VAS score greater than 0). The proportion of painful wounds was broadly similar in the different indications, although only 50% of PI were painful, the number of PI recruited was low (4). In contrast, all the VLU/arterial wounds were painful, although once again only four such wounds were included in the evaluation.

Figure 2B shows the mean VAS pain score for those wounds that were painful at the start of therapy was 5.5. In each of the wound indications, all the painful wounds scored a mean of between 4.3 and 6.6. Figure 2B also shows the pain scores at the 7-day and 14-day assessments which includes the 12-day period of automated microcurrent EST. In each case, the mean pain score drops markedly by day 7 and generally this effect is maintained by day 14. Of particular significance were VLU and VLU/Arterial cases where dermatological conditions such as: Milian's White Atrophy, Lipodermatosclerosis and Arteriosis, which are known to be very painful,[29] were observed to experience significant reductions in pain. Figure 2C illustrates that the effects of EST on pain reduction were frequently detectable by 48 h, with almost every wound type recording a VAS score reduction in the first 2 days. Reductions in the need for analgesics such as Tramadol, Gabapentin, or morphine for patients with some of the most painful wounds were recorded, with pain subsequently managed with just paracetamol or without analgesics altogether. Assessments of the types of pain amongst the 40 wounds suggest that both nociceptive and neuropathic pain can be reduced by single-use microcurrent EST.

3.6 | Extended EST therapy

Some patients received an additional 1, 2, or 3 blocks of 12-day EST therapy, with the goal of bringing their wounds to complete closure. Typically, where the first application showed excellent or good clinical responses, a follow-on device was offered, if available, often after a break of a week to 14 days. Examples of responses to a single 12-day EST used on a non-healing post-surgical wound following a toe amputation on a diabetic foot and a non-healing trauma wound treated sequentially with successive blocks of 12-day therapy are shown in Figures 3 and 4, respectively.

4 | DISCUSSION

The purpose of this investigation was to assess the clinical capabilities of a single-use automated microcurrent EST device to see if it could elicit positive clinical responses across a wide range of hard-to heal indications. Amongst 40 hard-to-heal wounds recruited from three international sites, 78% of wounds displayed marked reductions in peri-wound oedema, inflammation, wound

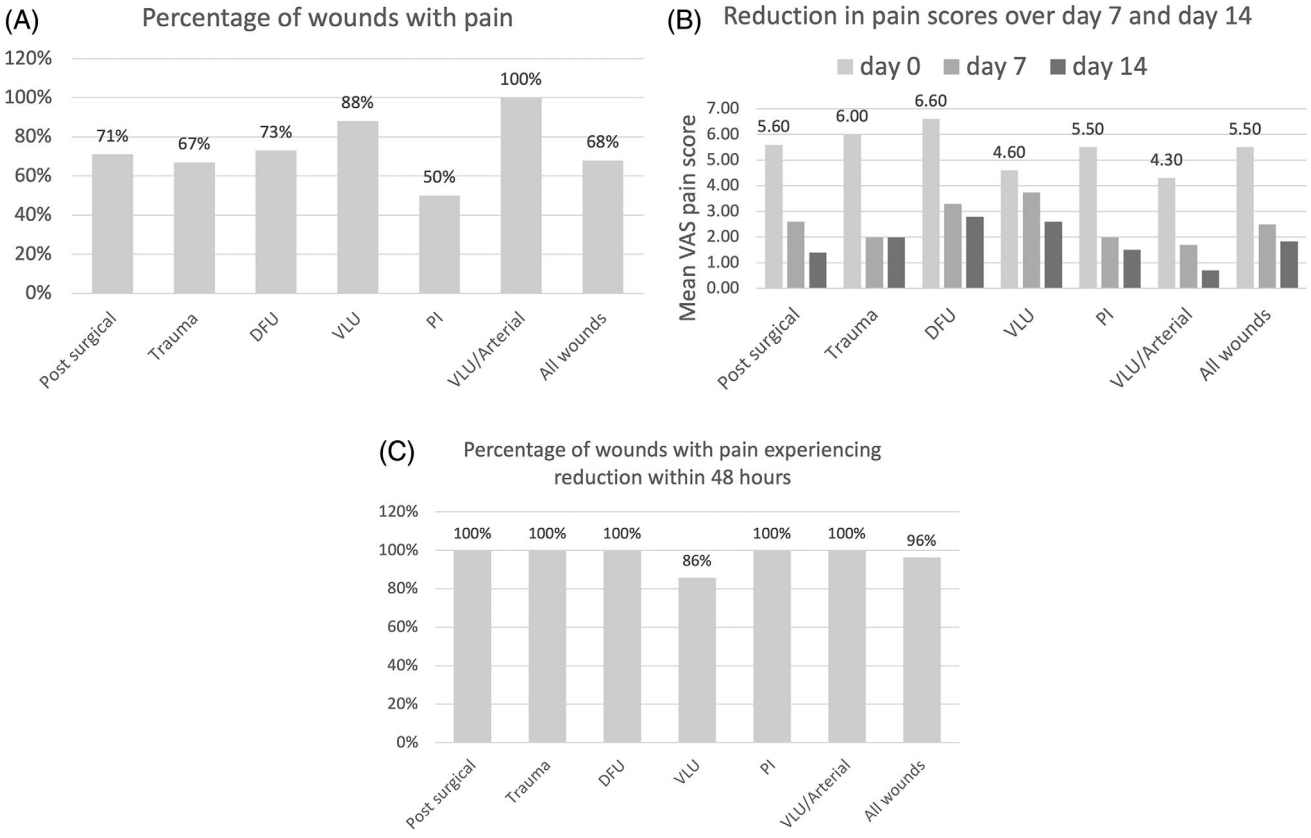

FIGURE 2 Percentage of wounds with pain and the response to EST. (A) Across all wound types, there was a total of 27/40 (68%) wounds which were painful (any VAS score greater than 0). (B) Mean VAS pain scores from day 0, day 7, and day 14 evaluation points (n = 27). Values shown are means for the day 0 evaluation. Patients where the VAS score was 0 were not included in day 0 means. (C) Response to pain within 48 h. Percentage of wounds with pain at Day 0 experiencing a reduction in VAS pain score within 48 h of commencing EST. (VAS pain scores were whole numbers between 0 and 10)

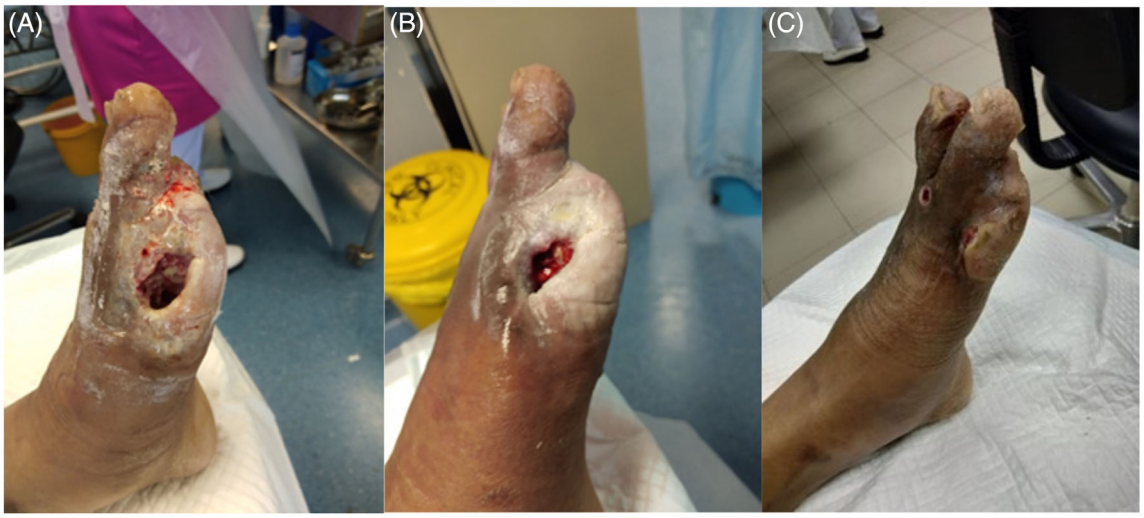

FIGURE 3 Single application EST-Case study-post-surgical amputation wound on diabetic foot. A 38-year-old male with diabetes had ray amputation of left big toe (two months ago) and the wound became infected. Patient complained of wound pain score 7. (A) Day 1–3.5 × 2.5 cm area × 5.5 cm deep; patient experienced significant pain relief after EST (pain score from 7 to 5 in 48 h) (B) Day 13 after 12-day ES therapy 2.5 × 2 cm area × 5 cm deep; (C) Day 71–1 × 1 cm area × 0.5 cm deep

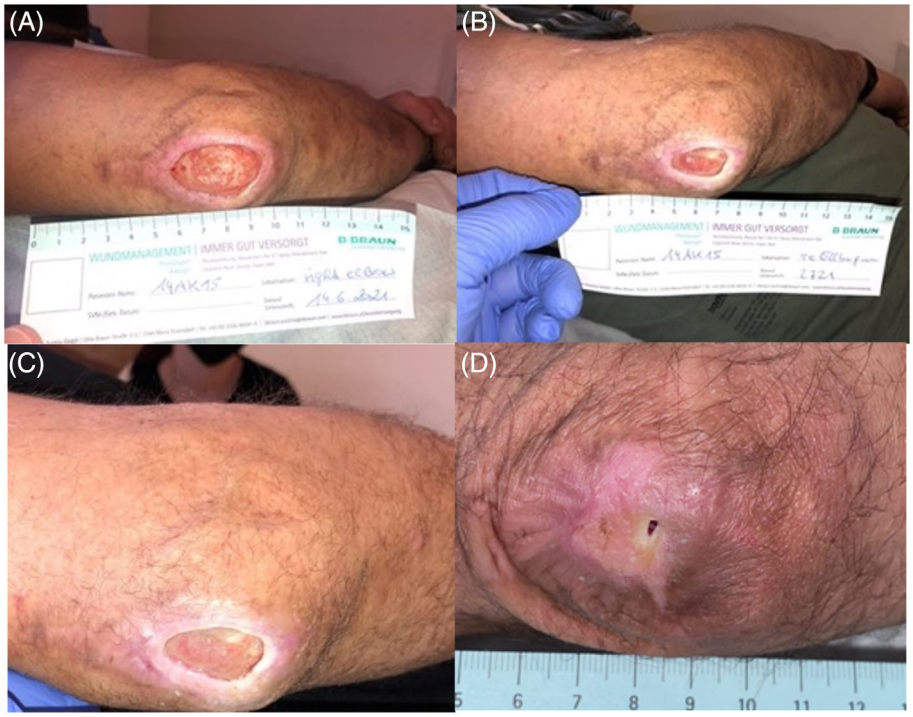

FIGURE 4 Extended EST-case study of hard-to-heal trauma wound (A). Day 1–32-year-old male. Farming accident five months ago. Recurrent massive local infections with surgical interventions and NPWT. Problems with excess alcohol consumption. Wound has remained painful and hard-to-heal since the accident. No healing for one week under institutional standard care prior to commencement of microcurrent EST. Wound area 7.4 cm^2, Pain score 5. (B) Day 24–After first and second 12-day EST. Patient reported pain reduction in 48 h—pain score 4. Early clinical response score 5 (Excellent). Wound area 2.3 cm^2 Pain score 4. (C) Day 62: after third 12-day EST. (D) Day 148: After fourth 12-day EST—nearly closed

depth and area, that had not been seen during the preceding weeks of care in the same institutions. In these wounds, the clinical signs suggest the physiology of the wound had changed and that reparative process were in motion. Every patient with a painful wound recorded a reduction in pain by the end of the second week which included the 12-days of EST. Although it is to be expected that when wounds begin to heal, inflammation reduces and pain levels fall naturally,[30] a majority of the patients in the present study experienced reductions in pain after only 48 h, which were in some cases variously described as 'surprising' or 'same day effect.' Several patients were able to move from opioid to non-opioid analgesics. In one patient, the reactivation of feeling following a long experience of insensate peri-wound tissue, echo's previous findings that EST can have neurogenic activity.[31]

There have not been any direct mechanistic studies on the mechanism of pain reduction caused by the microcurrent device used in the present study. However, experiments where gene expression in the skin of healthy volunteers was compared between placebo and 48 h of automated microcurrent EST showed reduced expression of approximately 105 genes, including those involved in inflammatory pathways such as SERPINB4, S100A7, S100A8, and S100A9.[32] Interestingly, in a study of VLU patients, high levels of S100A8/9 in wound exudate were directly correlated with high VAS pain scores.[33]

Two of the present authors have several years of experience with alternative EST devices which show efficacy in wound healing and pain reduction. These include the WoundEL® device (WoundEL Healthcare, Saint-Etienne France)[14] and the BEST, Biofeedback Electro-Stimulation Technology, (Avazzia, Inc., US).[15] Whilst direct head-to-head comparison in powered and randomised studies would be required before numerical comparisons could be made, it is our assessment that the single-use microcurrent device used in the present study (Accel-Heal) appeared to be of at least equivalent efficacy in healing and pain reduction and probably gives a faster response. This may be because of the continuous nature of the automated microcurrent Accel-Heal EST program operating 'round-the-clock' over 12-days.

One issue that remains unresolved in the design of EST devices is whether it is necessary to deliver a fixed polarity between the wound edge (+ve) and the centre of the wound (−ve) in order to mimic the endogenous current of injury and provide directionality for cell migration.[5,34,35] The present study uses pulsed microcurrent delivered from electrodes that switch polarity ten times a second. Previous in vitro experiments have shown enhanced migration and phosphorylation of ERK1/2 with both direct current and pulsed current EST, so it is likely cells in wounds do respond to electrical pulses.[36] As to the necessity for a constant polarity to direct migration? Perhaps, the activation of multiple wound healing functionalities such as increased growth factor expression,[5,37] increased growth factor receptor expression, phosphorylation of regulators of cell proliferation as well as increased speed of migration[6,7] are together sufficient to switch-on healing and that a fixed polarity

in the centre of the wound is a redundant feature. Recent in vitro work has demonstrated that the Accel-Heal device accelerates keratinocyte migration and increases the proportion of cells positive for the proliferation marker p63 across wounds in a Human Skin Equivalent model.[38]

We acknowledge there are some limitations to this study. The present evaluation has focussed on the visible activation and reduction in pain in the first few days of EST. For a complete assessment of the potential of this technology, further studies are needed where EST is continued for several weeks to confirm, as we suspect from a few cases, that extended EST drives a high proportion of wounds to closure. Future investigations should adopt a more formal approach using the scoring criteria summarised by the 0–5 clinical response scale developed in this study, which should be compared with previously published and validated evaluation systems. The lack of comparative groups of patients randomised to standard care also means it is formally difficult to be completely sure that wounds which shift their physiology during EST therapy, might not have performed so spontaneously. Nevertheless, the patients had been in institutions where expert wound care was being delivered without any observable effect. Application of automated microcurrent EST resulted in a high proportion of wounds experiencing marked shifts in physiology, activation of healing and rapid reduction of pain. Other investigations have also demonstrated positive responses with other simple EST devices.[39]

In this article, we show that a high proportion of wounds respond to single-use microcurrent EST which makes the case for the wider introduction of microcurrent EST for wound healing and pain relief. Future prospective, comparative studies are recommended to explore the full potential of automated microcurrent EST devices in painful and hard-to-heal wounds.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Robin Martin https://orcid.org/0000-0002-9314-0437

REFERENCES

1. Carey LC, Lepley D. Effect of continuous direct electric current on healing wounds. *Surg Forum*. 1962;13:33-35. http://www.ncbi.nlm.nih.gov/pubmed/14018634
2. Foulds IS, Barker AT. Human skin battery potentials and their possible role in wound healing. *Br J Dermatol*. 1983;109(5):515-522. doi:10.1111/j.1365-2133.1983.tb07673.x
3. Borgens RB, Vanable JW, Jaffe LF. Bioelectricity and regeneration. I. Initiation of frog limb regeneration by minute currents. *J Exp Zool*. 1977;200(3):403-416. doi:10.1002/jez.1402000310
4. Zhao M, Song B, Pu J, et al. Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-γ and PTEN. *Nature*. 2006;442(7101):457-460. doi:10.1038/nature04925
5. Zhao M. Electrical fields in wound healing—an overriding signal that directs cell migration. *Semin Cell Dev Biol*. 2009;20(6):674-682. doi:10.1016/j.semcdb.2008.12.009
6. Li L, Gu W, Du J, et al. Electric fields guide migration of epidermal stem cells and promote skin wound healing. *Wound Repair Regen*. 2012;20(6):840-851. doi:10.1111/j.1524-475X.2012.00829.x
7. Rouabhia M, Park HJ, Abedin-Do A, Douville Y, Méthot M, Zhang Z. Electrical stimulation promotes the proliferation of human keratinocytes, increases the production of keratin 5 and 14, and increases the phosphorylation of ERK1/2 and p38 MAP kinases. *J Tissue Eng Regen Med*. 2020;14(7):909-919. doi:10.1002/term.3040
8. Zhao M, Bai H, Wang E, Forrester JV, McCaig CD. Electrical stimulation directly induces pre-angiogenic responses in vascular endothelial cells by signaling through VEGF receptors. *J Cell Sci*. 2004;117(Pt 3):397-405. doi:10.1242/jcs.00868
9. Rouabhia M, Park H, Meng S, Derbali H, Zhang Z. Electrical stimulation promotes wound healing by enhancing dermal fibroblast activity and promoting Myofibroblast Transdifferentiation. Eddington DT, ed. *PLoS One*. 2013;8(8):e71660. doi:10.1371/journal.pone.0071660
10. Martin-Granados C, McCaig CD. Harnessing the electric spark of life to cure skin wounds. *Adv Wound Care*. 2014;3(2):127-138. doi:10.1089/wound.2013.0451
11. Koel G, Houghton PE. Electrostimulation: current status, strength of evidence guidelines, and meta-analysis. *Adv Wound Care*. 2014;3(2):118-126. doi:10.1089/wound.2013.0448
12. Lala D, Spaulding SSJ, Burke SSM, Houghton PEP. Electrical stimulation therapy for the treatment of pressure ulcers in individuals with spinal cord injury: a systematic review and meta-analysis. *Int Wound J*. 2016;13(6):1214-1226. doi:10.1111/iwj.12446
13. Avendaño-Coy J, López-Muñoz P, Serrano-Muñoz D, Comino-Suárez N, Avendaño-López C, Martin-Espinosa N. Electrical microcurrent stimulation therapy for wound healing: a meta-analysis of randomized clinical trials. *J Tissue Viability*. 2021;31:268-277. doi:10.1016/j.jtv.2021.12.002
14. Leloup P, Toussaint P, Lembelembe J, Célérier P, Maillard H. The analgesic effect of electrostimulation (WoundEL®) in the treatment of leg ulcers. *Int Wound J*. 2015;12(6):706-709. doi:10.1111/iwj.12211
15. Nair HKRR. Microcurrent as an adjunct therapy to accelerate chronic wound healing and reduce patient pain. *J Wound Care*. 2018;27(5):296-306. doi:10.12968/jowc.2018.27.5.296
16. Milne J, Swift A, Smith J, Martin R. Electrical stimulation for pain reduction in hard-to-heal wound healing. *J Wound Care*. 2021;30(7):568-580. doi:10.12968/jowc.2021.30.7.568
17. Atkin L, Martin R. An audience survey of practice relating to pain in the management of chronic venous leg ulcers. *Br J Community Nurs*. 2020;25(Sup12):S20-S24. doi:10.12968/bjcn.2020.25.Sup12.S20

18. Hellström A, Nilsson C, Nilsson A, Fagerström C. Leg ulcers in older people: a national study addressing variation in diagnosis, pain and sleep disturbance. *BMC Geriatr*. 2016;16(1):25. doi:10.1186/s12877-016-0198-1
19. Leren L, Eide H, Johansen EA, Jelnes R, Ljoså TM. Background pain in persons with chronic leg ulcers: an exploratory study of symptom characteristics and management. *Int Wound J*. 2021;19:1357-1369. doi:10.1111/iwj.13730
20. Bhavsar MB, Han Z, DeCoster T, Leppik L, Costa Oliveira KM, Barker JH. Electrical stimulation-based bone fracture treatment, if it works so well why do not more surgeons use it? *Eur J Trauma Emerg Surg*. 2020;46(2):245-264. doi:10.1007/s00068-019-01127-z
21. Malmsjö M, Huddleston E, Martin R. Biological effects of a disposable, canisterless negative pressure wound therapy system. *Eplasty*. 2014;14:e15. http://www.ncbi.nlm.nih.gov/pubmed/24741386
22. Cuomo R, Grimaldi L, Nisi G, Zerini I, Giardino FR, Brandi C. Ultraportable devices for negative pressure wound therapy: first comparative analysis. *J Invest Surg*. 2021;34(3):335-343. doi:10.1080/08941939.2019.1616009
23. Ovens L. Electrical stimulation therapy and electroceutical treatment for the management of venous leg ulcers. *Br J Community Nurs*. 2017;22(Suppl 3):S28-S36. doi:10.12968/bjcn.2017.22.Sup3.S28
24. Guest JF, Singh H, Rana K, Vowden P. Cost-effectiveness of an electroceutical device in treating non-healing venous leg ulcers: results of an RCT. *J Wound Care*. 2018;27(4):230-243. doi:10.12968/jowc.2018.27.4.230
25. Young S, Hampton S, Tadej M. Study to evaluate the effect of low-intensity pulsed electrical currents on levels of oedema in chronic non-healing wounds. *J Wound Care*. 2011;20(8):368, 370–373. doi:10.12968/jowc.2011.20.8.368
26. Schultz GS, Barillo DJ, Mozingo DW, Chin GA. Wound bed advisory board members. Wound bed preparation and a brief history of TIME. *Int Wound J*. 2004;1(1):19-32. doi:10.1111/j.1742-481x.2004.00008.x
27. Leaper DJ, Schultz G, Carville K, Fletcher J, Swanson T, Drake R. Extending the TIME concept: what have we learned in the past 10 years?(*). *Int Wound J*. 2012;9(Suppl 2):1-19. doi:10.1111/j.1742-481X.2012.01097.x
28. Nair HKR. Powering the progression of hard- to-heal wounds with electrical stimulation: observational analysis of wounds treated with Accel-heal. *Wounds Asia*. 2022;5(2):38-47.
29. Barron GS, Jacob SE, Kirsner RS. Dermatologic complications of chronic venous disease: medical management and beyond. *Ann Vasc Surg*. 2007;21(5):652-662. doi:10.1016/j.avsg.2007.07.002
30. Charles H. Venous leg ulcer pain and its characteristics. *J Tissue Viability*. 2002;12(4):154-158. doi:10.1016/s0965-206x(02)80024-9
31. Sebastian A, Volk SW, Halai P, Colthurst J, Paus R, Bayat A. Enhanced neurogenic biomarker expression and Reinnervation in human acute skin wounds treated by electrical stimulation. *J Invest Dermatol*. 2017;137(3):737-747. doi:10.1016/j.jid.2016.09.038
32. Lallyett C, Yeung C-YC, Nielson RH, et al. Changes in S100 proteins identified in healthy skin following electrical stimulation: relevance for wound healing. *Adv Skin Wound Care*. 2018;31(7):322-327. doi:10.1097/01.ASW.0000533722.06780.03
33. Goto T, Tamai N, Nakagami G, et al. Can wound exudate from venous leg ulcers measure wound pain status?: a pilot study. *PLoS One*. 2016;11(12):e0167478. doi:10.1371/journal.pone.0167478
34. Jünger M, Arnold A, Zuder D, Stahl H-W, Heising S. Local therapy and treatment costs of chronic, venous leg ulcers with electrical stimulation (Dermapulse): a prospective, placebo controlled, double blind trial. *Wound Repair Regen*. 2008;16(4):480-487. doi:10.1111/j.1524-475X.2008.00393.x
35. Molsberger A, McCaig CD. Percutaneous direct current stimulation - a new electroceutical solution for severe neurological pain and soft tissue injuries. *Med Devices (Auckl)*. 2018;11:205-214. doi:10.2147/MDER.S163368
36. Ren X, Sun H, Liu J, et al. Keratinocyte electrotaxis induced by physiological pulsed direct current electric fields. *Bioelectrochemistry*. 2019;127:113-124. doi:10.1016/j.bioelechem.2019.02.001
37. Zhao M, Dick A, Forrester JV, McCaig CD. Electric field-directed cell motility involves up-regulated expression and asymmetric redistribution of the epidermal growth factor receptors and is enhanced by fibronectin and laminin. *Mol Biol Cell*. 1999;10(4):1259-1276. doi:10.1091/mbc.10.4.1259
38. Bonnard C. Microcurrent electrical stimulation therapy accelerates re-epithelialization in an in vitro human skin wound model. *Wounds Aust 2022 Sydney*. 2022.
39. Zulbaran-Rojas A, Park C, El-Refaei N, Lepow B, Najafi B. Home-based electrical stimulation to accelerate wound healing—a double-blinded randomized control trial. *J Diabetes Sci Technol*. 2021;111(6):193229682110351. doi:10.1177/19322968211035128

How to cite this article: Kurz P, Danner G, Lembelembe J-P, Nair HKR, Martin R. Activation of healing and reduction of pain by single-use automated microcurrent electrical stimulation therapy in patients with hard-to-heal wounds. *Int Wound J*. 2023;1-9. doi:10.1111/iwj.14071