The efficacy of electrical stimulation in lower extremity cutaneous wound healing: a systematic review

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Abstract

Current gold standard lower extremity cutaneous wound management is not always effective. Cutaneous wounds generate a “current of injury” which is directly involved in wound healing processes. Application of exogenous electrical stimulation has been hypothesised to imitate the natural electric current that occurs in cutaneous wounds. The aim of this extensive review is to provide a detailed update on the variety of electrical stimulation modalities used in the management of lower extremity wounds. Several different waveforms and delivery methods of electrical stimulation have been used. Pulsed current appears superior to other electrical modalities available. The majority of studies support the beneficial effects of pulsed current over conservative management of lower extremity cutaneous wounds. Although it appears to have no benefit over causal surgical intervention, it is a treatment option which could be utilised in those patients unsuitable for surgery. Other waveforms and modalities appear promising; however, they still lack large trial data to recommend a firm conclusion with regards to their use. Current studies also vary in quantity, quality and protocol across the different modalities. The ideal electrical stimulation device needs to be non-invasive, portable, cost effective and provide minimal interference with patients’ daily life. Further studies are necessary to establish the ideal electrical stimulation modality, parameters, method of delivery and duration of treatment. The development and implementation of newer devices in the management of acute and chronic wounds provides an exciting direction in the field of electrotherapy.
**Introduction**

Chronic wounds, defined as the presence of a wound for greater than 30 days, occur as a result of deficiencies in wound healing processes (1, 2). Chronic wounds are divided aetiologicallly into arterial insufficiency, venous insufficiency, diabetes and pressure related wounds (3). Chronic lower extremity wounds represent a significant burden on patients quality of life and the healthcare system (4, 5). Although there are standard treatment modalities available for the management of lower extremity wounds based on aetiology including revascularisation (6), compression therapy (7), off-loading (8-11) and pressure relief (12), they are not always effective. Adjuvant therapies are also available but their optimal use is unknown (13-15).

Human skin is electrically charged, termed the “skin battery” (16). Cutaneous wounds generate large and persistent endogenous electric currents and fields named the “current of injury” (16, 17) (figure 1A) which is involved in numerous processes of wound healing (4). These observations have led to the hypothesis that applied electrical stimulation (ES) may promote chronic wound healing by imitating the natural electrical current that occurs in cutaneous wounds (18).

ES affects all the stages of wound healing and its mechanism of action is multifactorial as identified by pre-clinical studies which have led to its implementation in the management of human wounds (figure 1B and supplementary text) (18-27).

Several different waveforms and delivery methods of ES have been used in chronic lower extremity wound healing (figure 2). The wide variations in ES protocols used
has left uncertainty as to which ES waveform is superior in the management of cutaneous wounds. The aim of this comprehensive review is to provide a detailed update on the different ES modalities used in the management of chronic lower extremity wounds.

**Search strategy**

Please refer to supplementary text and figure 3 (28).

**Pulsed current**

Pulsed Current is the unidirectional or bidirectional flow of charged particles for less than one second in which each pulse is separated by a longer off period of no current flow (29). It is usually delivered with both polarity electrodes placed on the wound or proximally on the skin. Pulsed current can have a monophasic or biphasic waveform. Monophasic pulsed current can be described as high voltage pulsed current (HVPC) or low voltage pulsed current (LVPC) with the treatment electrode usually placed on the wound surface (30). The biphasic pulsed current waveform can be asymmetric or symmetric with both electrodes usually being placed on the wound edge (31). There are multiple methods of assessing pulsed current studies. We have separated studies based on wound type treated (table S1), however, other beneficial techniques include separating monophasic and biphasic pulsed current as undertaken in a meta-analysis by Koel and Houghton (32).

Two studies have assessed the effect of HVPC on arterial insufficiency lower extremity wound healing. A retrospective observational study showed peri-wound
truncutaneous oxygen (TcPo2) increased during electrotherapy and at one year 90% of electrically stimulated wounds had healed in comparison to only 29% with standard care (33). However, numbers recruited over the 4 year period were relatively low at 11 patients in each group. These results were further corroborated with a randomised controlled trial (RCT) comparing active HVPC against the application of sham HVPC over 14 weeks in 8 patients with ischaemic lower extremity wounds (34). The use of active HVPC led to smaller wounds and improved peri-wound microcirculation as assessed by TcPo2 measurements. Although treatment duration was long as with the first study, participant numbers were small increasing the likelihood of possible false-positive results. Debreceni et al showed an 83% improvement in a prospective study of 24 patients with chronic lower extremity ischaemic wounds, 75% of whom had tissue loss prior to commencing biphasic pulsed current. They noted wound healing and cessation of gangrenous processes following ES. They also found a significant improvement in pain free walking distance and increases in distal tissue oxygen saturations (35).

Eight studies, including 6 RCTs, have assessed the effect of pulsed current on venous insufficiency lower extremity wounds. Polak et al showed application of HVPC through the active electrode placed on the wound (polarity alternated at 3 weeks) for a mean of 7 weeks led to the significant acceleration of wound surface area and volume reduction in 22 patients in comparison to controls (36). There was approximately a 25% further reduction in wound surface area and volume compared to those receiving traditional management. However, there was no blinding to intervention and no information on whether the two groups were comparable at baseline was available. Franek et al evaluated the effect of double-peak monophasic...
impulses using a similar arrangement to Polak et al (36) on lower extremity wound healing in comparison to age and sex matched controls receiving either topical medicinal treatment or Unna’s boot (37). Although all three treatment modalities led to a significant reduction in wound size; the rate of healing, wound granulation and cleansing was significantly higher in those receiving ES. In a follow on randomised controlled clinical trial they combined ES parameters described previously with either conservative management or causal surgical intervention in the management of 110 patients with lower extremity venous wounds. They split the patients into four arms of equal size; 2 groups were treated conservatively and 2 groups with surgical intervention, with one group in each category managed with concomitant ES for 7 weeks (38). Complete wound healing was significantly higher in all three groups receiving active treatment in comparison to the conservative treatment group which comprised compression and drug therapy. However, there was no difference noted in active inter-group analysis. This is in keeping with an earlier RCT which found similar wound healing rates in patients who were managed with ES or standard treatment post-surgery (39). The findings from the two studies suggest that HVPC does not enhance wound healing in comparison to successful surgery, however is superior to conservative management. Unfortunately, although the 3 studies by Franek et al (37-39) included large numbers of patients with a relatively long duration of treatment, they all lacked blinding. In contrast, a large RCT of 305 subjects divided into 9 different treatment groups found compression therapy as an adjunctive treatment to causal surgical intervention was superior to ES in terms of wound healing and that ES was no more effective than compression therapy in those managed conservatively (40). Although randomised, there was no blinding to intervention and the initial decision of grouping was based on patient choice as to
whether they agreed to surgical intervention or not and the groups were not equally
distributed. A double-blinded RCT showed no significant difference in venous lower
extremity wound area, capillary density and TcPo2 between subjects receiving LVPC
or standard compression therapy (41). Although in the ES group wound area
reduced from a median of 550mm$^2$ to 80 mm$^2$; a more than two fold decrease in
comparison to the placebo group. This lack of significance was also found in a
prospective study with small subject numbers which found no significant reduction in
wound surface area with ES, even though 2 out of the 8 wounds had healed
completely (42). This is most likely as a result of the studies being under powered.
On the contrary, a further prospective study showed accelerated healing of venous
leg wounds in 15 patients receiving LVPC for 38 days with 2 wounds healed
completely and 13 showed a mean size reduction of 63%. Capillary density
increased by 43.5%, while TcPo2 partial pressure increased by 82.4% (43).
However, the study lacked appropriate controls, randomisation and blinding.

Four RCTs have assessed the effect of pulsed current on diabetic lower extremity
wounds. Peters et al showed a 30% higher rate of complete wound healing in
diabetic patients receiving HVPC through Micro-Z™ (a small ES device that delivers
current via a microcomputer to a Dacron-mesh silver nylon stocking) for 8 hours
nightly in comparison to wound care consisting of weekly debridement, topical
hydrogel, and off-loading with removable cast walkers (44). Lundeberg et al
assessed the effect of biphasic asymmetric pulsed current on wound healing. Sixty
four patients with chronic diabetic lower extremity wounds were randomised to
receive either active or sham ES. The ES was applied twice daily just outside the
wound surface area and polarity was alternated every treatment. At 12 weeks there
was a significant difference in both wound area and wounds completely healed in the ES group compared to controls (42% of wounds healed completely in active group compared to 15% in the control group) (45). Baker et al found asymmetric biphasic pulsed current was superior to symmetric biphasic pulsed current (46). They compared these two ES waveforms to a control group and found asymmetric biphasic pulsed current significantly enhanced diabetic lower extremity wound healing by 60%. However, their control group consisted of a combination of those who received low level microcurrent stimulation and those receiving no ES. Petrofsky et al showed symmetric biphasic pulsed current in combination with local dry heat of 37°C enhanced diabetic wound healing significantly (47) compared to isolated local wound heating. However, they did not compare the combined effect of ES and heat with ES alone. Again, the latter 3 studies (45-47) lacked any form of blinding. In a prospective study, Alon et al reported 80% of 15 neuropathic diabetic foot wounds healed completely following treatment with HVPC for 1 hour, 3 days a week (48). In a retrospective study, Burdge et al showed the benefits of HVPC in 30 diabetic patients with lower extremity wounds. They showed 78% of wounds healed completely at a mean of 14 weeks (49). However, these results were confounded by the additional combination therapy of revascularisation, surgical wound debridement and antibiotic therapy in certain cases. In a case series of 6 patients with diabetic inframalleolar cutaneous wounds, Goldman et al utilised HVPC to improve wound healing (50). They measured the wound surface area as well as TcPo2 levels at the edge of the wound as a marker of tissue microcirculation. They showed 4 out of the 6 wounds healed completely and mean TcPo2 increased from 2 to 33 mmHg. Two case reports have shown positive effects of HVPC in diabetic lower extremity wound
healing (51, 52), however, in the latter despite full wound closure the patient regressed and underwent a major amputation (52).

A single un-blinded RCT by Franek et al using the same parameters and electrode setup as previously described (39) confirmed the benefits of HVPC in the accelerated healing of recalcitrant stage 3 and 4 pressure induced lower extremity wounds leading to almost double the rate of change in wound surface area and a significant increase in granulation tissue formation compared to standard supportive care and topical treatments (53).

Six studies assessed the effect of pulsed current on a combination of lower extremity wounds of various aetiologies. Houghton et al showed application of HVPC with no polarity switch during treatment, for a short duration of only four weeks at 100 µs, at a frequency of 100 Hz and 150 V for 45 minutes, 3 times weekly, reduced the wound size of arterial, venous and diabetic lower extremity wounds by almost 50% which was more than twice the amount compared to sham treatment (54). This was supported by a case series of three patients with mixed aetiology lower extremity wounds (55). A further case series of 10 patients with conventional treatment resistant leg wounds of various aetiologies responded to complete healing within an average time of 17.6 weeks (56). However, HVPC treatment was given in conjunction with acoustic pressure wound therapy and also the concomitant wound dressings and therapies given varied between patients. A RCT assessing pulsed current in lower extremity wound healing found accelerated healing of amputation stumps in patients who had undergone a major lower extremity amputation.
secondary to arterial or diabetic causes (57). The author’s however declare the randomisation process was not perfect and indeed ES did not affect re-amputation rates. In two prospective studies, Kaada first showed a 90% healing rate in 10 patients who underwent high frequency pulsed current ES for lower extremity wounds of various aetiologies (58) and in a second study found low frequency pulsed current accelerated healing in patients with chronic lower extremity leprous wounds via a proposed mechanism of micro-circulation improvements secondary to ES treatment (59).

The consensus from the above studies is the use of pulsed current is overall beneficial in the management of venous and diabetic lower extremity wounds. Pulsed current treatment is not superior to causal surgical intervention but is beneficial compared to standard wound care in the majority of cases. There is a lack of high quality studies available to judge confidently its effect on arterial and pressure wounds and further robust trials are necessary to identify the optimal pulsed current waveform.

**Direct current**

DC Is the continuous, unidirectional flow of charged particles for 1 second or longer (29). Application of DC can lead to wound irritation and damage (29). Therefore in wound studies application of low-intensity direct current (LIDC) is utilised (table S2). LIDC is a continuous monophasic waveform with current of an intensity less than or
equal to 1 mA. LIDC is often sub-divided into LIDC and microcurrent. The difference is the latter produces only sub-sensory level stimulation (60).

Only sub-analysis of a single prospective study has demonstrated the effect of DC on ischaemic lower extremity wounds (61). Wolcott et al applied LIDC directly on the wound at an intensity ranging between 200 to 800 $\mu$A three times daily lasting a total of 6 hours, with polarity reversal every 72 hours. They found in the 15 arterial insufficiency wounds treated an 82.2% reduction in wound volume over a mean of 6 week duration (61). This study lacked appropriate controls and the duration of treatment varied between participants.

Five studies, including 2 RCTs, have assessed the effect of DC on lower extremity wounds of venous aetiology. Katelaris et al showed no significant difference between venous wounds managed with povidone-iodine alone, normal saline alone or normal saline with ES. In fact, they noted a significant retarding effect on wound healing with the use of LIDC at 20 $\mu$A (62). However, this was when ES was used with local applications of povidone-iodine which may explain the unexpected findings. Also each of the four groups only consisted of 6 patients. A further single-blinded RCT by Korelo et al showed that although microcurrent ES significantly improved pain associated with venous leg wounds, it had no benefit on wound healing (63). However, they also had relatively small numbers and the treatment duration was only for 4 weeks. Assimacopoulos et al were the first to report a case series of the successful healing of 3 patients with chronic venous leg wounds with the application of negative polarity LIDC directly on the wound at 100 $\mu$A for 6 weeks (64). Wolcott
et al also assessed the effect of LIDC on 5 venous insufficiency leg wounds and found an 85% wound volume reduction over a mean of 6 weeks (61). Castana et al showed the successful healing of a chronic venous lower extremity wound in a 47 year old man using a novel wireless microcurrent stimulation (WMCS) device applied once or twice daily for 45 minutes over a 35 day period (65). The WMCS method uses the current-carrying capacity of charged air gas, based on the ability of nitrogen and oxygen to receive or donate electrons. The charged particles create a LIDC ranging between 1.5–4.0 μA which is delivered to the patient via the contactless device which is placed 10-15cm from the wound for a recommended time of 45-60 minutes per session.

A double-blinded RCT by Mohajeri-Tehrani et al showed no significant difference in wound surface area between 20 diabetic foot wounds treated either with 12 hourly sessions of cathodal LIDC over 4 weeks or those receiving sham ES (66). Ramadhinara and Poulas were the first to show the beneficial effect of WMCS in the treatment of diabetic wounds in 2 cases (67).

The 7 studies investigating the effects of DC on lower extremity wounds provide limited information. Overall the higher grade studies assessing the effect of DC on venous aetiology lower extremity wounds show no benefit, however the studies only include small number of participants or the active intervention is confounded by other concomitant treatments. As with venous wound, high grade studies show no benefit of DC on diabetic lower extremity wound healing, whereas lower grade studies show a positive effect. There is only a single low grade study showing the beneficial effects

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of DC on arterial insufficiency wounds and there are no studies available assessing the effect of DC on pressure induced lower extremity wounds. No firm conclusions can be drawn on the effect of DC on various lower extremity wound aetiologies and further robust research is needed to firmly establish any benefits.

**Frequency rhythmic electrical modulation systems**

FREMS is a bio-compatible device that uses sequences of electrical stimuli that automatically vary in terms of duration, pulse, frequency and voltage amplitude which is led by the patient. This in turn produces improvement in skin micro-vascular circulation and is the basis for its use in wound healing (68) (table S3).

Three RCTs to date have assessed the effect of FREMS on lower extremity wound healing. All unfortunately did not clarify if either the participant or investigator were blinded. Santamato et al applied either antiseptic topical alone or in combination with FREMS to venous leg wounds for 3 weeks. They found FREMS led to a decrease in wound surface area by 90% at 30 days from treatment cessation which was significantly superior to that seen in the control arm (69). Jankovic and Binic used FREMS in a randomised control trial in 35 patients with chronic lower extremity wounds of various aetiologies. They found FREMS accelerated wound healing (82% reduction in leg wound surface in the treatment group compared to a 46% reduction in the control group) and significantly reduced pain (70). However, a standardised dressing protocol was not used in the study. A more recent randomised control trial using FREMS identified accelerated wound healing of lower extremity wounds in the
active treatment group; however by the end of the study, the percentage of wounds healed in the two groups were similar (90%) (71). A weaker case-control study in 30 patients with diabetic foot wounds found application of FREMS led to a significant improvement in wound healing at 30 and 45 days post commencement of treatment compared to traditional treatment (72).

The lack of clarification as to the standard wound therapy used in the studies to date and the absence of its effect on arterial and pressure related wounds makes the need for more robust clinical trials to be conducted to further clarify the effect of FREMS on lower extremity wound healing.

**Low frequency transcutaneous sensory nerve stimulation**

LF-SNS has been shown to improve wound healing in animals and induce vasodilatation through activation of sensory nerve terminals (73) (table S3). The LF-SNS is a battery operated device that delivers low frequency ES with intensity of 4 mA and frequency of 5Hz (74). The application of the device involves electrodes which are strapped over a proximal nerve innervating the wound (74). Please refer to supplementary text for further information regarding studies (74, 75).
Bioelectrical stimulation

The use of only two bioelectric dressings employed to deliver ES to lower extremity wounds have been reported (table S3). They are PosiFect RD® and Procellera® (figure 4). The studies are relatively weak and only consist of a small case series and two single case studies. PosiFect RD® is a battery operated dressing containing a dual mode electrode system that generates continuous DC flow to the wound site. Its application involves one electrode applied to the wound site and the second electrode encircling the first and applied to the surrounding skin. Hampton et al have shown in two case studies the complete healing of intractable lower extremity wounds with the use of PosiFect RD® within 12 weeks (76, 77). Procellera® is also a battery operated single layer dressing that is activated by wound moisture to deliver ES to the wound site (29). The use of Procellera® has shown faster healing, improved scarring and patient subjective outcomes in lower extremity acute cutaneous wounds (78). However, this was a relatively small case series of 13 patients and did not include chronic wounds. Well-designed RCTs are necessary including the effect of these bioelectric dressings on chronic lower extremity wounds before firm conclusions on the clinical benefits can be drawn.

Conclusions and future perspectives

The majority of studies support the beneficial effects of pulsed current over conservative management of lower extremity cutaneous wounds. Although it appears to have no benefit over causal surgical intervention, it is a treatment option which could be utilised in those patients unsuitable for surgery. DC seems inferior to pulsed current and although the other waveforms and modalities appear promising,
they still lack large trial data to recommend a firm conclusion with regards to their use in lower extremity cutaneous wound healing.

The ideal ES device needs to be non-invasive, portable, and cost effective and provide minimal interference with patients’ daily life. Recent ES technology available can be divided into wearable dressings, contactless delivery systems and portable devices. Bioelectric dressings such as PosiFect RD® and Procellera® are wearable technology that provides ES to the wound with minimal disruption to daily activities. Another portable and cost effective bioelectric dressing which has been investigated in a rat ischaemic wound model and is undergoing clinical experiments utilises an electrode bandage with two gel electrodes and a battery powered stimulator printed circuit board (79). These innovative wearable technologies satisfy many parameters however clinical evidence to date is limited to case studies and case series and further large scale trials are required to confirm their true benefits. Contactless devices such as WMCS are less labour intensive as the only patient contact to the device is through a single neutral electrode attached to the wrist and the device is positioned at a single location over the wound. Although findings to date seem promising, there was early termination of the treatment in some cases. Reasons for early termination included cutaneous reactions to ES, pain, patient withdrawal and non-compliance. Other reasons for withdrawal included severe cutaneous infection and death; however, these were unrelated to the ES treatment. Further robust evidence is needed to assess its clinical safety and validity. Evidence for the use of portable devices in lower extremity wound management is scarce. LF-SNS lacks large trial data and the single RCT to date provides conflicting findings compared to
earlier reports. A portable electro-biofeedback device which was first investigated on its successful effects on cutaneous scarring (80, 81) has shown accelerated healing of acute cutaneous wounds in the arm (22, 27, 82, 83). It produces a novel electrical waveform which degenerates with time termed the degenerate wave. It is a low intensity device with a concentric electrode, which applies impulses of short duration (a six-hundredth of a second) and of relatively high amplitude (20–80 V) with a frequency default at 60 Hz and detects changes in skin impedance (30). However to date the effects of this device have not been investigated in lower extremity cutaneous wounds.

On balance the majority of studies have shown accelerated wound healing with the use of ES compared to standard therapy and placebo. There are several ES modalities available and used successfully for lower extremity wound healing, however the number of studies range in quantity and quality across the different modalities. They also differ in their protocol of use. This leads to difficulty in firmly establishing the best ES device available for the management of lower extremity wounds. Further studies are necessary to establish the ideal ES modality, parameters, method of delivery and duration of treatment. The development and implementation of newer devices in the management of acute and chronic lower extremity cutaneous wounds provides an exciting direction in the field of electrotherapy.
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Conflict of interest

The authors have no conflicts of interest to declare.

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84. http://procellera.com/

Figure legend

**Figure 1.** A: Current of injury. Undamaged skin has an endogenous electrical potential and a transcutaneous current potential of 20–50 mV. Following an injury to the skin, a flow of current through the wound pathway generates a lateral electrical field termed the current of injury. B: Effect of electrical stimulation on wound healing; i) Inflammatory phase of wound healing - electrical stimulation enhances blood flow, inhibits bacterial growth, increases tissue oxygenation and decreases wound oedema; ii) Proliferative phase of wound healing - electrical stimulation increases wound contraction, keratinocyte and fibroblast proliferation, angiogenesis and collagen deposition; iii) Remodelling phase of wound healing - electrical stimulation enhances collagen maturation and remodelling.

**Figure 2.** A: Electrical stimulation modalities used in the treatment of lower extremity cutaneous wounds with their associated range of parameters. B: Waveforms of the different electrical stimulation modalities used in the management of lower extremity cutaneous wounds; i) High voltage pulsed current; ii) Symmetric biphasic pulsed current; iii) Asymmetric biphasic pulsed current. FREMS – frequency rhythmic electrical modulation systems; LF-SNS - low frequency transcutaneous sensory nerve stimulation; DC – direct current; LIDC – low intensity direct current; WMCS - Wireless Microcurrent Stimulation; V- volts; Hz – hertz; A – ampere; AC - alternating current.

**Figure 3.** Flow chart of search strategy and results.

**Figure 4.** Illustration of Procellera® bioelectric dressing (84).