Electrotherapy and wound healing

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This review article presents a general summary of the application of various forms of electricity to the healing of dermal wounds. Mechanisms of action are briefly described followed by a summary of the conclusions of meta-analyses and reviews of clinical trials carried out in the period 1999 to the present. In recognition of its status as a respected independent review body, the recent and current work of the Cochrane Collaboration in this field is highlighted. Some tentative conclusions are drawn both from individual clinical studies and also from the corresponding reviews and meta-analyses, and the sources of these conclusions are highlighted in the text. Broadly, these are that high voltage pulsed current seems to be emerging as the most effective form of electrotherapy for treating dermal wounds. Secondly, that most forms of electrical stimulation have a positive effect on healing. Thirdly, that wound healing timescales when compared with conventional wound care can very often be halved. Fourthly, that electrotherapy has multiple mechanisms of action and is safe, well tolerated, and with very few adverse incidents recorded in the literature.

In wound healing, applications several different forms of electricity have been described, including direct current (DC), alternating current (AC), high-voltage pulsed current (HVPC) and low-intensity direct current (LIDC). Clinicians are probably most familiar with pulsed electromagnetic field (PEMF) for repair of fracture non-unions and transcutaneous electrical nerve stimulation (TENS) for pain control. Even though the electrical stimulation and wound healing literature uses several different types of electrical stimulation, they all appear to have positive results. (Gradner et al, 1999).

Ulcer aetiology

Probably due to its general incidence and prevalence, pressure ulceration is the form of ulceration most frequently investigated in clinical trials and many meta-analyses of trials covering the use of adjunct therapies in treating chronic ulceration contain patient cohorts predominantly with pressure ulceration often grouped together with those with chronic lower-limb and foot ulceration of arterial, venous and diabetic aetiology.

It is recognised that wounds of different aetiologies may respond differently to adjunct therapies and that the results recorded for one class of ulcer may not be consistently obtained with others. Clinical trials that include ulcers of mixed aetiology do not, therefore, lend themselves conveniently to meta analysis since on stratification into ulcer type sample numbers per type tend to be small.

This section of this review considers the role of electrotherapy as an adjunct therapy in healing chronic ulcers of all aetiology and presents the results of independent clinical trials, review articles and meta analyses.

Clinical trials

Clinical trials vary considerably in their technical design and in outcomes measured. In trials related to wound-healing interventions this diversity is apparent but most trials measure the rate of reduction of the surface area of the wound over time in both the intervention and control groups. This is often expressed as percentage area reduction (PAR) or as an absolute measurement of surface area in square centimetres. Often, however

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the differences in outcomes are described as 'significant'.

One further limitation is that few trials have focused on complete healing as an outcome measure and, while accelerating the reduction in size of the wound is very worthwhile in terms of both treatment cost reduction and patient benefit, the real value of an adjunct treatment must lie in its contribution to the achievement of complete healing.

It is also worth noting that in most clinical trials, the dosage of electrical stimulation therapy applied is typically one 30 or 45 minute session three to five times per week in each week of the period chosen for the trial. The author's experience at Neurocare is that complex wounds (particularly diabetic) benefit greatly from much more intensive treatment, ideally one/two episodes per day, and to be efficiently delivered, such treatment is administered on an in-patient basis or administered in the home.

It is also noted that the type of electrical stimulation used in clinical trials has varied considerably and this variety of device types has impeded the development of conclusions regarding the efficacy of the different forms of electrical signal delivered in relation to the aetiology of different ulcer types.

Wounds and wound healing

In the literature, a wound is generally considered to heal in four distinct, continuous, but partially overlapping phases (Velnar et al, 2009), which are described as the haemostasis, inflammatory, proliferative and re-modelling phases. This is a complex and elegant sequence of cellular and bio-chemical events, which research suggests may be partially or wholly electrically powered (Nuccitelli, 2003: Zhao, 2009; Li et al, 2012). Readers may be familiar with the concept of 'the current of injury', which is considered to be established by dermal trauma and which diminishes and finally ceases to flow when wound healing is completed (Zhao, 2009).

Mechanisms of action of electrotherapy in wound healing

It has been noted in the literature that electrotherapy may have multiple modes of action in wound healing (Wounds International, 2013). Two possible mechanisms of action of electrotherapy in wound healing are described here. Firstly, the effect of introducing an exogenous electrical signal into the complex cellular and biochemical events within the wound itself. Secondly, the effect of increasing blood circulation through the wound site by stimulating the operation of the peripheral arterial and vascular systems by means of an electrical signal applied to muscle motor nerves.

Although many devices have been designed specifically for wound healing, others that have been designed for different therapeutic purposes, have been used in clinical trials (e.g. TENS) with the objective of expediting the healing of difficult to heal wounds. Research has mainly concentrated on the application of electrical signals to enhance the cellular and bio-chemical aspects of wound healing, rather than the augmentation of blood circulation through the wound. Where this is the chosen mechanism of action, one (usually of two) electrodes is placed either directly over the wound and the second close to the wound.

Since the majority of devices used are of direct current (DC) design (i.e. with a positive and negative contact) researchers often periodically change the polarity of the position of the electrode placed over the wound since *in vitro* research has shown that the cellular response and biochemical activity differ according to polarity. When the device used is chosen to enhance blood circulation by muscle activation, the position of muscle motor nerves tends to determine electrode location. However, the electrical signal produced will normally still pass through the wound site and it is, therefore, probable that wound healing benefits from multiple mechanisms of action as noted in many clinical studies.

In a normal healthy human, a dermal wound caused by impact or other trauma will, with cleansing and any necessary suturing, heal naturally in the sequence described above primarily by the normal functioning of the arterial and vascular systems in delivering nutrient-rich freshly oxygenated blood through the wound site, while at the same time removing waste accumulated in the lymph system (Williams et al, 2017). In those wounds particularly in the lower leg, which do not readily heal, the aetiology of the wound will usually be a deficiency(ies) in the peripheral arterial and/or vascular systems (Spentzouris and Labropoulos, 2009). This is true of ischaemic (arterial) ulcers, venous stasis and diabetic ulcers, but usually not of decubitus (pressure) ulcers.

If deficiencies in circulation are one of the most significant causes of these complex ulcers (and one of the factors undermining healing), it follows that an ideal therapy should address the underlying causes of the ulcer. A durable cure is much more likely if underlying causal factors are treated and many of the clinical studies cited here have successfully used HVPC devices, some of which are designed for muscle stimulation and usually described as neuromuscular electronic stimulation (NMES) devices. Such devices cause muscle contractions and, in so doing, enhance the efficiency of the peripheral arterial and vascular systems (Spentzouris and Labropoulos, 2009) in improving perfusion and removing waste through the lymph system. Measurements taken during treatment have shown significant increases in blood circulation (Tucker et al, 2010). The relationship between oxygen, blood circulation and wound healing is well understood and described in the literature (Gottrup, 2004; Sen, 2009; Schreml et al, 2010). At the tissue level, electrical current improves arterial blood flow, reduces tissue oedema and micro-vascular leakage (Reed, 1998) and promotes angiogenesis (Ud-Din et al, 2015). The improvement in circulation (Tucker et al, 2010) is known to increase tissue oxygenation (Gottrup, 2004; Sen, 2009; Schreml, 2010).

The mechanism of action in the wound healing application of NMES is supported by two of the six Food and Drug Administration (FDA) indications for muscle stimulators: "Immediate post surgical stimulation of calf muscles to prevent venous thrombosis" and "improve local circulation" where research has shown (Browse and Negus, 1970; Fahri et al, 1997; Czyrny et al, 2010) that stimulation of calf muscles is an extremely effective way of minimising stasis in immobilised patients both during and in the post-operation phase. The FDA indication for this NMES effect is currently the subject of a Cochrane Review (Hajibandeh et al, 2017).

Endogenous electrical activity alone will usually not heal complex ulcers and blood thinning pharmaceuticals (eg Heparin, Warfarin) when added to the treatment protocol may be ineffective, since reducing viscosity may not enhance flow when the pumping mechanism is defective. Such pharmaceuticals may also bring undesirable side effects (National Patient Safety Agency, 2005), which will add to the treatment risk profile and increase treatment costs.

When ulcers have become infected, the infection must be treated before healing can resume. Where circulation is compromised the antibiotics used to treat infection may not reach the wound site. These ulcers can then become a primary cause of future amputation. The Introduction of an exogenous electrical signal designed to mimic the endogenous may have little effect if the aetiology is defective circulation.

There is reason to conclude, therefore, that enhancing blood flow by HVPC NMES may be the decisive primary mechanism of action of this form of electrotherapy in wound healing (Velnar et al, 2009) and may also assist the delivery of antibiotics to the infected wound site. Enhanced circulation will also contribute toward the maintenance of a moist wound bed. There are numerous randomised controlled trials (RCTs) in applications such as muscle rehabilitation post TKA which demonstrate that muscle condition will improve with NMES stimulation (Stevens et al, 2004; Avramids et al, 2011; Stevens-Lapsley et al, 2012).

Clinical trials

Clinical trials vary considerably in their technical design and in outcomes measured. In trials of wound healing interventions, this diversity is apparent but most trials measure the rate of reduction of the surface area of the wound over time in both the intervention and control groups. This is often expressed as percentage area reduction (PAR) or as an absolute measurement of surface area in square centimetres. Often, however, the differences in outcomes are described as 'significant'.

One further limitation is that few trials have used time to complete healing as an outcome measure and whilst accelerating the reduction in size of the wound is very worthwhile in terms of both treatment cost reduction and patient benefit the real value of an adjunct treatment must lie in its contribution to the achievement of complete healing.

It is also worth noting that in most clinical trials the dosage of electrical stimulation therapy applied is typically one 30 or 45 minute session three to five times per week in each week of the period chosen for the trial. The author's own experience at Neurocare is that complex wounds (particularly diabetic) benefit greatly from much more intensive treatment, ideally one/two episodes per day and to be efficiently delivered such treatment is administered on an in-patient basis or administered in the home.

It is also noted that the type of electrical stimulation used in clinical trials has varied considerably and this variety of device types has impeded the development of conclusions regarding the efficacy of the different forms of electrical signal delivered in relation to the aetiology of different ulcer types.

Cochrane collaboration

Cochrane have had a protocol open in this subject area for several years. Originally, it was entitled 'Electrical Stimulation for Chronic Wounds' and following previous changes in the personnel undertaking the work, in 2011, Gerard Koel and Pamela Houghton started work on the protocol. They completed the analysis of the selected clinical trials and presented their work at several conferences before publishing in 2014 (Koel and

Houghton, 2014). This is summarised below. Their work was not then and has not subsequently been published in the form of a Cochrane Review.

In 2016, Cochrane published a revised protocol entitled 'Electrical Stimulation for Treating Pressure Ulcers''' Work on this revised protocol is now being undertaken by a group of academics and clinicians in Australia.

Summary of Cochrane author conclusions

Koel G, Houghton PE (2014) Electrostimulation: current status, strength of evidence guidelines, and meta-analysis. *Adv Wound Care (New Rochelle)* 3(2): 118–26

This article summarises the results of effect studies with the application of electrostimulation (ES) as additional treatment to standard wound care (SWC). Therefore, five published narrative reviews are discussed. In addition, 15 studies with a clear RCT design are analysed systematically and the results are presented in four forest plots. The healing rate is expressed in the outcome measure percentage area reduction in 4 weeks of treatment (PAR4). This leads to a continuous measure with mean differences between the percentage healing in the experimental group (SWC plus ES) and in the control group (SWC alone or SWC plus placebo ES). Adding ES to SWC in all wound types increases PAR4 by an extra 26.7% (95% confidence interval [CI] 15.6, 37.8); adding unidirectional ES to SWC increases PAR4 by 30.8% (95% CI 20.9, 40.6) and adding unidirectional ES to the treatment of pressure ulcers increases PAR4 by 42.7% (95% CI 32.0, 53.3).

Critical issues

There is a discrepancy between the proven effectiveness of ES as additional treatment to SWC and the application of ES in real practice. Possible drawbacks are the lack of clinical expertise concerning the proper application of ES and the extra time effort and necessary equipment that are needed.

Future directions

Clinicians concerned about the optimal treatment of patients with delayed wound healing should improve their practical competency to be able to apply ES.

Gardner SE, Frantz RA, Schmidt FL (1999) Effect of electrical stimulation on chronic wound healing: a meta analysis. *Wound Repair Regen* 7(6): 495–503

The purpose of this meta-analysis was to quantify the effect of electrical stimulation on chronic wound healing. Fifteen studies that included 24 electrical stimulation samples and 15 control samples were analysed. The average rate of healing per week was calculated for the electrical stimulation and the control samples. Ninety-five percentage confidence intervals were also calculated. The samples were then grouped by type of electrical stimulation device and chronic wound and reanalysed. Rate of healing per week was 22% for electrical stimulation samples and 9% for control samples. The net effect of electrical stimulation was 13% per week an increase of 144% over the control rate. The 95% CIs of the electrical stimulation(18–26%) and control samples (3.8–14%) did not overlap. Electrical stimulation was most effective on pressure ulcers (net effect = 13%). Findings regarding the relative effectiveness of different types of electrical device were inconclusive. Although electrical stimulation produces a substantial improvement in the healing of chronic wounds, further research is needed to identify which electrical stimulation devices are most effective and which wounds respond best to the treatment.

Barnes R, Shahin Y, Gohil R, Chetter I (2014) Electrical stimulation vs. standard care for chronic ulcer healing: a systematic review and meta-analysis of randomised controlled trials. *Eur J Clin Invest* 44(4): 429–40

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to October 2013 on RCTs, in English and on human subjects, which assessed the effect of electrical stimulation on ulcer size as compared to standard care and/or sham stimulation. Data from included RCTs were pooled with use of fixed and random effects meta-analysis of the weighted mean change differences between the comparator groups. Heterogeneity across studies was assessed with the I2 statistic.

Results

Twenty-one studies were eligible for inclusion in the meta-analysis. In six trials ($n = 210$), electrical stimulation improved mean percentage change in ulcer size over total studies periods by 24.62%, 95% confidence interval (CI) 19.98–29.27, $P<0.00001$ with no heterogeneity. In three trials ($n=176$), electrical stimulation insignificantly improved mean weekly change in ulcer size by 1.64%, 95% (CI) -3.81 to 7.09, $P=0.56$ with significant heterogeneity ($I^2 = 96\%$, $P<0.00001$). In six trials (n = 266), electrical stimulation decreased ulcer size by 2.42 cm^2, 95% (CI) 1.66–3.17, $P<0.0000$, with significant heterogeneity. In one trial ($n=16$), electrical stimulation also insignificantly improved the mean daily percentage change in ulcer size by 0.63%, 95% (CI) -0.12 to 1.37, $P=0.10$, with significant heterogeneity.

Conclusion

Electrical stimulation appears to increase the rate of ulcer healing and may be superior to standard care for ulcer treatment.

Thakral G, Lafontaine J, Najafi B et al (2013) Electrical stimulation to accelerate wound healing. *Diabet Foot Ankle* 4. doi: 10.3402/dfa.v4i0.22081

A total of 21 RCTs were initially identified that used electrical stimulation to treat wounds. A literature review was planned and performed in Medline. The following search strategy was used in the PubMed database: 'electrical stimulation' [Mesh] and 'wound healing' [Mesh]. Titles and abstracts were screened and full texts were analysed for meeting the inclusion criteria. Only RCTs in humans were included. Case studies and clinical trials focused on children and the congenital disability were excluded. Out of these studies, five were excluded because they had less than eight subjects in the treatment groups . Sixteen RCTs that used a variety of different applications of electrical stimulation to treat wounds were evaluated.

Conclusion

There are many opportunities to improve clinical outcomes with electrical stimulation. In many ways, electrical stimulation appears to be a perfect adjunctive therapy.

Firstly, no device-related complications or adverse effects have been reported in the existing literature. The therapy is safe and easy to use. Second, as electrical stimulation decreases bacterial infection, increases local perfusion, and accelerates wound healing, it addresses these three pivotal factors in surgical wound complications.

Electrical stimulation offers a unique treatment option to heal complicated and recalcitrant wounds, improve flap, replantation and graft survival, and even improve surgery results. This is an approach that can be applied in the operating room and used throughout the recovery process. Electrical stimulation is a simple, inexpensive intervention to improve surgical wound healing. Rigorous clinical trials are needed to help understand the dosing, timing, and type of electrical stimulation to be used.

Summary of clinical data and appraisal

The four meta-analyses and systematic reviews above between them summarise the results of most of the individual clinical studies that have been carried out on electrotherapy and wound healing in the period 1985–2010. The selection criteria used in each of these papers is similar; where possible favouring RCTs over other forms of clinical investigation.

The Cochrane authors concluded that "ES stimulates faster wound size reduction in all types of chronic wounds and that "the report provides the highest level of evidence to support the clinical use of ES for the treatment of chronic wounds".

Gardner et al (1999) concluded that although electrical stimulation produces a substantial improvement (i.e. 2.5 times faster) in the healing of chronic wounds, further research is needed to identify which electrical stimulation devices are most effective and which wounds respond best to the treatment

Barnes et al (2014) conclude that electrical stimulation appears to increase the rate of ulcer healing and may be superior to standard care for ulcer treatment.

And finally, Thakral et al (2013) conclude that there are many opportunities to improve clinical outcomes with electrical stimulation. In many ways, electrical stimulation appears to be a perfect adjunctive therapy. They also note that "first, no device-related complications or adverse effects have been reported in the existing literature. The therapy is safe and easy to use."

The point made above concerning safety is important since even occasionally reported adverse incidents would serve to undermine the widespread adoption of electrotherapy in wound healing.

However, it must also be acknowledged that each of these papers observe that further research is needed to establish ideal treatment parameters for each type of wound; which of the great variety of different forms of electrotherapy are the most effective and how can optimum dosage be established.

Further meta-analyses/review articles with broad conclusions

Ud-Din S, Bayat A (2014) Electrical stimulation and cutaneous wound healing: a review of clinical evidence. *Healthcare (Basel)* 2(4): 445–67

All types of ES demonstrated positive effects on cutaneous wound healing in the majority of studies. However, the reported studies demonstrate contrasting differences in the parameters and types of ES application, leading to an inability to generate sufficient evidence to support any one standard therapeutic approach. Despite variations in the type of current, duration, and dosing of ES, wound healing the majority of studies showed a significant improvement in wound area reduction or accelerated compared to the standard of care or sham therapy, as well as improved local perfusion.

Clark M (2013) Electrical stimulation and wound healing. *Wounds International* 4(eSupplement): 4–7

ES increases fibroblast production, promotes cell migration, increased wound angiogenesis and tissue oxygenation, and decreases bacterial burden. The strength of evidence based on clinical trials for the healing of wounds using ES is substantial. Some key questions remain to be answered before ES becomes a common intervention in wound care, including whether specific wound types respond better to ES than others.

Conclusion
Although questions remain, reports from basic research in bioelectrochemistry, and the first analysis of clinical effects of ES in wound healing, show that ES has the potential to become a mainstream intervention in the treatment of chronic wounds.

Ashrafi M, Alonso-Rasgado T, Baguneid M, Bayat A (2017) The efficacy of electrical stimulation in lower extremity cutaneous wound healing: a systematic review. *Exp Dermatol* 26(2): 171–8

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.

Kawasaki L, Mushahwar VK, Ho C et al (2014) The mechanisms and evidence of efficacy of electrical stimulation for healing of pressure ulcer: a systematic review. *Wound Repair Regen* 22(2): 161–73

A total of seven RCTs and two observational studies met the inclusion criteria. Moderate level of evidence of efficacy with low risk of bias was shown in all seven RCTs. Although some studies have used continuous direct current, most other investigators opted to use high-voltage pulsed current to minimise the risk of skin burn and to achieve greater current penetration. Overall, the incidence of adverse effects was very low. Two studies that assessed the economic impacts of electrical stimulation revealed substantial healthcare cost savings. The mechanisms through which electrical stimulation exerts a positive effect on pressure ulcer healing are reasonably well established.

Kloth LC (2014) Electrical stimulation technologies for wound healing. *Adv Wound Care (New Rochelle)* 3(2): 81–90

Conclusion
Numerous clinical trials described in subsequent sections of this article have demonstrated that ES used adjunctively with standard wound care (SWC), enhances wound healing rate faster than SWC alone.

Houghton PE (2014) Clinical trials Involving biphasic pulsed current, microCurrent, and/or low-intensity direct current. *Adv Wound Care (New Rochelle)* 3(2): 166–83

Critical issues
Reviewing a collection of published reports on this subject reveals that not all forms of ES produce beneficial results. Rather, only certain ES protocols such as monophasic pulsed current applied to the wound and biphasic pulsed current that is applied for 2 hours daily to peri-ulcer skin at intensities that produce motor responses have consistently demonstrated positive results.

Future directions
Optimal stimulus parameters and treatment schedule for ES used to treat chronic wounds need to be determined. Researchers publishing in this field should provide detailed information about their ES treatment protocol and use a similar terminology to describe the ES waveform and stimulus parameters.

Polak A, Franek A, Taradaj J (2014) High-voltage pulsed current electrical stimulation in wound treatment. *Adv Wound Care (New Rochelle)* 3(2): 104–17

A range of studies point to the efficacy of ES in wound treatment, but the methodology of its application has not been determined to date. This article provides a critical review of the results of clinical trials published by researchers using HVPC to treat chronic wounds. The efficacy of HVPC as one of several biophysical energies promoting venous leg ulcer (VLU) and PU healing has been confirmed. Additional studies are needed to investigate its effect on the healing of other types of soft tissue defects. Other areas that require more research include the identification of the therapeutic effect of HVPC on infected wounds, the determination of the efficacy of cathodal versus anodal stimulation, and the minimal daily/weekly duration of HVPC required to ensure optimal promotion of wound healing.

Summary of clinical evidence wound healing

In the first part of this review, the author has identified a considerable number of trials conducted in many locations around the world with many different forms of electrotherapy devices, which have shown that the introduction of electrical energy whether to change molecular and biochemical events within the wound or to cause muscle contractions to improve blood and lymph flow through the wound or in many cases to cause both these changes simultaneously will accelerate the healing of dermal wounds.

Many trials have shown that electrotherapy, when used as an adjunct to the conventional care pathway can at least halve healing timescales. To the author's knowledge, no other adjunct therapy used in wound healing has been clinically shown to achieve similar results. Trials have also commented that the therapy is inherently safe, cost effective and, most importantly, can be patient self-administered in the home.

Many clinicians/academics carrying out individual trials have observed that the lack of adoption of electrotherapy in wound healing partly reflects the way that those in the front line are trained(e.g. Koel/Houghton) in that physiotherapists who do receive some tuition in electrotherapy as part of undergraduate study do not (in the UK) become involved in dermal wound healing whereas general nursing training, including those who specialise in tissue viability and who subsequently occupy the front line in wound healing, are given no training in electrotherapy modalities.

It is also commonly mentioned in clinical trials that the sheer variety of device types and treatment protocols that have been deployed undermine the elucidation of which forms of electrical signal are most effective and on which aetiology of ulceration. However, against a backdrop of opinion that many forms of electrical signal will expedite the healing of most forms of ulcer/wound a consensus would seem to be emerging that HVPC is generally effective at the cellular and biochemical level and that an HVPC device which can be set at a level to produce muscle contraction brings additional benefits in aiding the throughput of oxygenated blood and evacuating lymph fluid.

No doubt these questions could occupy researchers for years but, in the meantime, there are devices currently available that can radically reduce wound treatment timescales, reduce treatment costs and improve the patient experience, which if not adopted would have the effect of allowing the perfect to become the enemy of the excellent. WME

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