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Product Review

Electric stimulation for treatment of chronic wounds

by *Keith Moore*

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Electric stimulation for treatment of chronic wounds

Electric stimulation (E-Stim) to initiate healing of recalcitrant wounds has been discussed in the literature for many years and many publications indicate its efficacy. This review by Keith Moore considers the clinical and laboratory evidence underpinning the use of E-Stim for treatment of chronic wounds.

Key words:
Chronic wound
Current of injury
Electric stimulation (E-Stim)
Galvanotaxis
Infection
Treatment

The diversity of management options available for chronic wounds (Schultz *et al*., 2005) gives some insight into the complexity of the defects that have to be reversed in order for healing to be initiated and wound closure achieved. Non-viable tissue requires debridement, appropriate treatment needed to lower bacterial numbers to levels that will not retard healing, moisture balance has to be achieved to encourage moist wound healing and stimulation of epithelial migration. Even when underlying factors, such as diabetes, vascular insufficiency, or pressure to the wound site, that contribute to non-healing have been managed, it is often found that multiple wound treatment interventions may be required. This suggests that no single treatment addresses the central cause of non-healing in the chronic wound environment.

Over the last decade our knowledge of normal and chronic wound physiology has grown so that a number of biologically active treatments have been developed for targets in the chronic wound. In addition to a deluge of anti-bacterial dressings (Graham, 2005) there are growth factors (Robson *et al*., 2001), tissue engineered dermal replacements (Marston *et al*., 2003) bioactive wound dressings (Cullen, *et al*., 2002) and specific agents such as protease inhibitors (Fray, 2003). These interventions tend to be specifically targeted and multiple interventions are often required. Whilst these may be useful in stimulating healing of some recalcitrant wounds there are obvious advantages to alternative interventions that would have wider applicability by treating core defects that inhibit healing.

Treatment modalities that reverse core defects are less well established although knowledge of at least one potentially modifiable central regulatory process has been known for many years. This is the current of injury which has been well documented in experimental studies (Borgens *et al*., 1977) and clinical practice (Ojingwa & Isseroff, 2003). The concept of a current of injury has underpinned the development of a device, the POSiFECT®RD bio-electric wound care dressing, which is currently available for treatment of chronic wounds. This review will explore the evidence describing how electric stimulation (E-stim) of chronic wounds induces healing and the data available to support the use of POSiFECT®RD for treatment of chronic wounds.

What is the current of injury?

Possibly the most well known generation of electric currents by cells is in the neuron where thermal, mechanical or chemical stimuli trigger electrical signals that can result in a sensation of pain. However, all cells within the body generate ionic currents across their membranes and this is where the current of injury originates.

Cell membranes possess a membrane potential which is the electrical potential difference or voltage across the membrane. Cells within intact skin are negatively charged on the inside whereas the exterior of the cell, the extracellular space, is positively charged. The difference in charge arises because cell membranes possess '*pumps*' that move sodium ions out of the cell in exchange for potassium ions which are pumped into the cell. For the skin this results in the epidermis being negatively charged relative to the deeper tissues that carry a positive charge (Kloth & McCulloch, 1996). The transcutaneous potential of intact skin can be measured at 40-80mV but as soon as a full thickness incision is made this disappears so that a voltage gradient forms between the wound and surrounding intact skin (Jaffe & Vanable, 1984). A micro-current will then flow from the area of higher potential, the intact skin, into the wound so that a current of injury is generated (*Figure 1*). The voltage peaks immediately after injury and gradually decreases as the wound heals (McGinnis & Vanable, 1986) leading to the concept that current flows may be defective in chronic wounds and that applying electrical currents to wounds may stimulate healing (Kloth, 1995).

It is well established that wounds heal optimally under a moist environment (Winter, 1962) and it has been suggested (Cutting, 2006) that, at least in part, this may be a consequence of allowing an optimum wound current flow. If wounds

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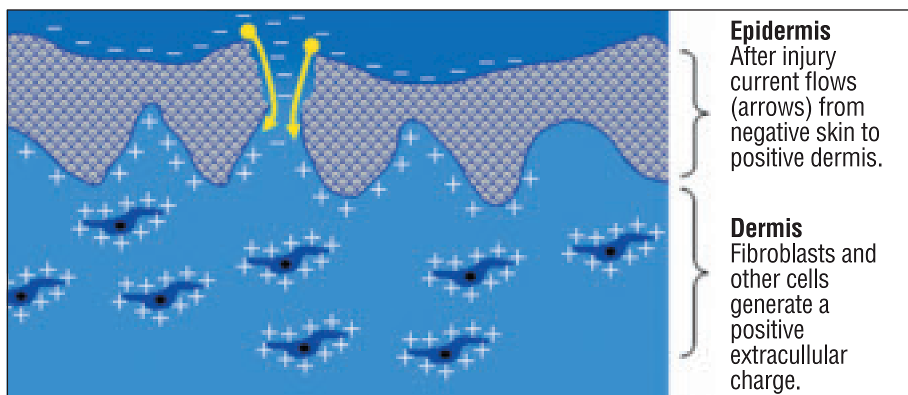

Figure 1: The current of injury.

are allowed to dry the wound current decreases, whereas there is a current flow in moist wounds (Jaffe & Vanable, 1984).

Delivery of E-Stim to the wound

At its most basic E-stim of a wound requires applied current to be passed from the periphery of a wound to the wound bed in the same way that the current of injury flows as shown in *Figure 1*. The most common way of achieving this is to place one electrode in contact with the peri-wound skin and one contacting the wound bed. Both electrodes are connected to a battery driven power source with control circuitry that applies the desired stimulating electrical current. The E-stim applied can either be of a high or low voltage and is usually delivered as one of three types of current:

Direct Current (DC): The electric current flows in one direction only from positive to negative electrode. This type of current is usually intended to mimic naturally occurring wound currents and is of low intensity.

Alternating Current (AC): The flow of current is rapidly reversed many times per second.

Pulsed: Pulsed E-stim may be either DC or AC but is delivered in pulses so that there is an off cycle where no electricity is delivered to the wound between pulses. Pulses may be in micro or milliseconds.

With so many variables in terms of delivery there are obviously a number of different approaches possible for electrical stimulation of chronic wounds. This makes it difficult to compare individual studies. There is, however, a large body of clinical evidence (Ojingwa, 2003) to indicate that healing is improved by E-stim regardless of the type of current applied and experimental evidence to identify possible mechanisms of healing stimulation.

Clinical evidence for efficacy

Pressure ulcers: Pulsed low voltage DC treatment of stage II and III pressure ulcers evaluated in a double blind multicentre study resulted in 25 of 43 ulcers healing in the active treatment group within eight weeks compared to one in the placebo group where the majority of ulcers increased in size (Wood *et al.*, 1993). Higher pulsed voltages of 100-175v for 45 minutes/day, five days a week appeared equal or greater in effectiveness in a smaller study (Kloth, & Feedar, 1988). All the ulcers in the treatment group of nine patients healed with a mean time to healing of 7.3 weeks and a mean healing rate of 44.8 per cent. In contrast the sham treated placebo group of seven patient's ulcers increased in size by 29 per cent.

Leg Ulcers: Low voltage DC E-stim is also effective in accelerating healing of leg ulcers where a 2.5 times faster healing rate was observed compared to standard wet-to-dry dressings and whirlpool therapy (Carley & Wainapel, 1985). The E-stim treated ulcers also required less debridement, no infections occurred and the patients reported less pain at the wound site. As with pressure ulcers, leg ulcers will also respond to higher voltage pulsed currents. In a double blind prospective study of 27 subjects 42 ulcers of venous, arterial or diabetic origin (Houghton *et al.*, 2003) were randomised to two groups that received E-stim or sham treatment for 45 minutes three times a week for four weeks. The investigators concluded that '*E-stim should be used to accelerate healing for chronic vascular ulcers*' as ulcers in the active treatment group reduced in area by approximately 50 per cent over the four week treatment period.

E-stim with POSiFECT®RD

The POSiFECT®RD bio-electric wound dressing (Biofisica, Hampshire, UK) has recently been launched in the UK for the treatment of chronic wounds. This device incorporates an E-stim system into a single use wound dressing. The dressing has a circular anode that contacts the peri-wound skin and a central cathode that is placed in contact with the wound bed.A DC microcurrent generated by an integral miniature circuit and battery passes between the electrodes to replicate the natural current of injury and stimulate healing.

Four pilot studies have demonstrated that POSiFECT®RD treatment exerted a positive effect on healing of pressure ulcers and venous leg ulcers. One of these (Feldman *et al.*, 2005) indicated that pressure ulcer healing was initiated during weeks 1-3 of E-stim treatment and this observation has led to a treatment protocol where cycles of three weeks active treatment are separated by one week of standard treatment.

Three further case studies have reported using this treatment regime. One (Hampton & Collins, 2006) documents the successful treatment of a large, necrotic, intractable grade III heel pressure ulcer which measured 4.5 × 6cm. After seven days POSiFECT®RD treatment much of the fibrous slough had debrided and the ulcer reduced in size to 3 × 4cm. Only a small quantity of slough remained by week four, size reduction continued and the wound margin was surrounded by healthy epithelial tissue. Healing continued so that by week seven the ulcer measured 1.5 × 1.5cm and was completely closed by 13 weeks after initiation of E-stim.

The remaining studies suggest that E-stim with POSiFECT®RD may stimulate healing, at least in part, by exerting an anti-bacterial effect. Treatment of a painful ulcer with a green malodorous discharge indicating colonisation with *.P aeruginosa* eliminated evidence of *Pseudomonas* infection after four weeks with an accompanying decrease in rate of exudation (Hampton & King, 2005). By week eight, after another cycle of 'three weeks on/one week off' the wound was granulating with islands of epithelial tissue and POSiFECT™RD was discontinued. By week 18 the ulcer was healed. Another non-healing venous leg ulcer of two years duration in which bacterial biofilm was judged to be delaying healing was also induced to initiate healing (White *et al.*, 2006). The patient could not tolerate compression therapy

but after six days of treatment with POSiFECT®RD the wound had reduced in size and slough reduced by 50 per cent. After a further 17 days the wound exhibited 100 per cent granulation tissue.

A prospective, descriptive, evaluative, non-blinded clinical trial with a sample size of 18 patients with 21 recalcitrant wounds (nine pressure ulcers, 11 venous leg ulcers, one traumatic wound) has recently been completed (Hampton *et al*., 2005; Biofisica UK Ltd, 2006, Data on file). All the wounds were previously non-healing for greater than six months. The wounds were treated with two cycles of three weeks with POSiFECT®RD bio-electric therapy followed by one week of standard care. Patient's wounds were assessed at eight weeks and again at 16 weeks. The total mean surface area of the wounds was 18cm^2 at commencement of the study and 10.3 cm^2 at the end of eight weeks. This was an average healing of 7.65 cm^2 wound area decrease demonstrated in previously non-healing wounds over an eight week period. At 16 weeks, six wounds had healed completely, and a further six were almost healed. All the other wounds showed some improvement – even in patients who discontinued/dropped out part way through the programme. The authors concluded that the results of this study were significant and demonstrated the clinical effectiveness of POSiFECT®RD and its potential for initiating wound healing. Also noted was that POSiFECT®RD did not cause any pain or discomfort in any wounds. The observation was made that treatment possibly decreased pain in painful wounds although this requires further investigation. At one year follow up 10 wounds had healed, and none of the previously healed wounds had recurred.

How E-stim aids healing

The interaction of E-stim with the chronic wound to initiate the healing effects described earlier has recently been reviewed in detail (Cutting, 2006) and only key aspects will be described here. Many functional cellular defects are known to be associated with the non-healing state of chronic wounds such as bacterial bio-burden, chronic inflammation, defective granulation tissue and defective re-epithelialisation that causes a slowing or cessation of healing (Moore, 2004). E-stim has been demonstrated in experimental systems to regulate cell functions that are potentially important to reverse these defects and stimulate healing.

The presence of bacteria in chronic wound tissue often acts as a major factor in delaying healing (Bowler, *et al*., 2001) and stimulating chronic inflammation in wound tissue. E-stim has been shown to inhibit bacterial growth *in vitro* (Kincaid & Lavoie, 1989) and on intact human skin (Bolton *et al*., 1980). Anti-bacterial effects have been demonstrated in *P. aeruginosa* infected experimental incisional wounds (Rowley *et al*., 1974) and similarly bacterial proliferation within human pressure ulcers has been demonstrated to be inhibited after three days of E-stim treatment (Wheeler *et al*., 1971). However, bacteria can grow as free organisms or as a biofilm on the wound surface. Biofilms are formed by bacteria producing a carbohydrate film (glycocalyx) that protects them from antimicrobial therapy. Bacteria are released from the biofilm to produce localised infections and wound breakdown (Sibbald, 2003). E-stim is known to disrupt biofilms (Costerton *et al*., 1994) and the recent successful treatment of a leg ulcer where healing was delayed by biofilm suggests that this E-stim delivery by POSiFECT®RD acts to disrupt bacterial biofilms.

Decreasing the number of bacteria within chronic wound tissue will assist in conversion of chronic inflammation to a resolving inflammatory response. This is considered one of the key events in initiating healing of chronic wounds (Moore, 1999). The population of macrophages involved in chronic inflammation have to be replaced with fresh monocytes recruited from the blood and E-stim may play a role here by accelerating their migration towards the anode placed in the wound bed (Orida & Feldman, 1982; Cho *et al*., 2000).

Formation of healthy granulation tissue depends on the proliferation of fibroblasts and their ability to synthesise a functioning extracellular matrix. This is an energy consuming process and requires angiogenesis to produce new blood vessels to supply oxygen and nutrients. There is considerable experimental evidence that E-stim interacts in all aspects of granulation tissue synthesis. It increases fibroblast protein synthesis and proliferation (Bourguignon & Bourguignon, 1987), increases collagen production (Canseven & Atalay, 1996) and improves collagen fibre organisation (Brown *et al*., 1987) to give increased healed wound strength (Taskan *et al*., 1997).

Angiogenesis can be enhanced by E-stim improving dermal capillary formation in human ischaemic wounds (Goldman *et al*., 2004) possibly by stimulating angiogenic responses after interacting with endothelial cell growth factor receptors (Zhao *et al*., 2004).

Once a healthy and functional wound bed has formed keratinocytes have to migrate over it to close the wound and form new epidermis. In the same way that macrophages will migrate towards the cathode in electrotherapy systems keratinocyte migration is also enhanced and directed in the same way. The effect of enhanced directional migration in an electrical field is called galvanotaxis or electrotaxis and plays an important role in the healing process (Nishimura *et al*., 1996). A recent study (Zhao *et al*., 2006) has elegantly characterised the intra-cellular events that occur as cells migrate within an electrical field. It demonstrated that exposure to an electric field induced signals to be passed across the cell membrane on the side of the cell that migrated towards the anode. The same signals are generated by migrating keratinocytes during wound healing. The importance of electric currents during healing was demonstrated by the fact that healing could be inhibited by reversing the electric field.

The chronic wound exhibits many cellular defects and the fact that E-stim may address many of these simultaneously goes some way to explaining how the positive clinical effects demonstrated by POSiFECT®RD may be generated.

Conclusion

There is a long history of using E-stim to treat chronic wounds and many laboratory investigations that provide a rationale for its use. This large body of published data allows one to draw the conclusion that E-stim is of benefit as an aid to healing chronic wounds. Despite this the E-stim treatment modality is not widely understood. This may be because the majority of publications report on the use of experimental systems each using a delivery system favoured by the authors. The consequence is that each report is unique and the reader cannot easily draw on the evidence to allow selection of a readily available treatment option and evaluate it for themselves. Obviously this will act as a barrier to adoption of the technology and further investigations of efficacy. In addition the technology for delivering E-stim has not been readily available or usable outside a research setting.

The recent introduction of the POSiFECT®RD bio-electric wound care

dressing should change this situation. It provides an E-stim system in a single use dressing that is applied directly to the wound and may be used alone for pressure ulcers or in conjunction with compression bandaging for treatment of venous leg ulcers. The published POSiFECT®RD clinical studies demonstrate that it has proven efficacious in treating recalcitrant ulcers. In at least two case studies (Hampton & King, 2005; White *et al*., 2006) a clear anti-bacterial effect was observed prior to initiation of healing. This indicates one valuable facet of POSiFECT®RD in healing chronic wounds. Definition of a precise mode(s) of action awaits further studies.

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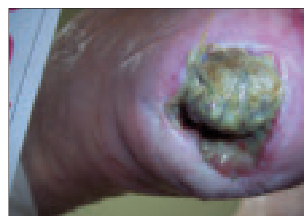
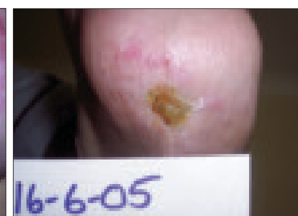


Grade 4 necrotic heel 14.3.05 non-healing for 18 months



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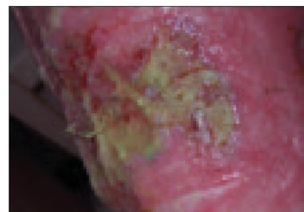

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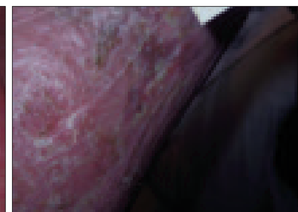

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