Electrical Stimulation of Wound Healing

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INTRODUCTION
We generally do not think of skin as an electrically - responsive tissue. Yet, the skin generates an electric current upon wounding, and increasing evidence implicates endogenous electric fields as important mediators of the repair process. For decades, investigators have attempted to enhance skin wound healing by applying various forms of electrical stimulation (ES). This concept of therapeutic ES is not new and is in current use for other clinical indications including neuromuscular rehabilitation, pain control, and bone healing. This review will take an evidence-based approach to evaluating both the clinical and basic research that provides strength of evidence for the use of ES to accelerate or improve cutaneous wound healing.

ELECTRICAL STIMULATION FOR WOUND HEALING
ES, or electrotherapy, is defined as the application of electric current from electrodes placed directly within a wound or on skin in close proximity to it. Its use in skin wound healing is not new; the use of electrosysiatically charged gold leaf to enhance the healing of small pox lesions is noted about 300 years ago, and rediscovered more recently in the 1960’s. The use of ES for the treatment of diseases in general was abandoned early in the last century because of concerns regarding the efficacy of this therapy. ES faded from the medical practice after the Flexner Commission report in 1910 suggested that ES was not scientifically based. It was not until the past three decades that renewed interest in this technique has emerged. As the number of successful studies being published increases, the use of ES for the treatment of soft tissue injuries is slowly becoming more widely accepted. ES has very recently been approved for Medicare coverage by the Centers for Medicare and Medicaid Services (CMS) for the treatment of stasis, arterial, pressure and diabetic ulcers that have not responded to standard wound therapy. Thus, the use of this modality by dermatologists may increase, and understanding the underpinnings of its efficacy is important to its effective therapeutic use.

Electrical Stimulation Modalities
Three basic treatment regimens are commonly used today, direct current (DC), pulsed current (PC), and alternating current (AC) (Figure 1). The advantages and disadvantages of each are briefly described to facilitate comparison of the reported results using these modalities.

Direct Current (DC)
Electric current that is continuous and unidirectional in flow (from cathode to anode) is defined as direct current. This form of current is also sometimes referred to as galvanic current. The duration of the current may vary from 1 second to longer times. If the flow of current is unidirectional but less than 1 second, it is no longer a DC current but referred to as pulsed current. Continuous DC is pulseless, thus has no waveform (Figure 1A) and no reversal of polarity unless it is reversed manually.

The passage of electric current through tissue produces electrothermal, electrochemical or electrophysical effects. The electrothermal effect is described by Joule’s Law which states that heat production is proportional to the square of the total current, the resistance, and the time for which the current flows. Normal skin presents high resistance, thus thermal damage may ensue from continuous DC stimulation. When using DC to treat wounds, to avoid thermal damage both the amplitude and treatment time must be minimized.
Pulsed Current (PC)

A mechanism to reduce the electrothermal and electrochemical hazards of DC current application is to utilize pulsed current (PC), defined as a unidirectional or bidirectional flow of charged particles for a short duration of time. In the successful protocols, each pulse tends to last for a milli or microsecond followed by a relatively long interpulse interval at which current amplitude is zero. Most PC protocols do not exceed 20 mA of total current and are thus very safe to use.

Numerous, and sometimes confusing, names have been assigned to PC (e.g. interrupted square, trapezoidal, triangular, sawtooth, spike) because of the different shapes the waveforms exhibit. One of the ways of eliminating the confusion is to describe the pulses according to three basic parameters of the waveforms: amplitude, duration, and frequency. This can be further simplified by grouping in two common delivery configurations: either monophasic or biphasic.

A monophasic pulse is a brief duration of unidirectional flow of charged particles. An example of a monophasic PC is the commonly used high voltage pulsed current (HVPC). The waveform of HVPC is a monophasic spike delivered in pairs (twin peaked, Figure 1B). Because each peak or spike has very short pulse duration (2 to 50 msec), a high voltage (100 to 500V) is needed in order to produce currents in the mA range. The amplitude and pulse rate often selected for wound healing is usually between 80 to 200V and 50 to 120 pulses per second (pps) respectively, minimizing the electrochemical changes under the delivering electrodes in skin.

Biphasic pulse is one that deviates from baseline (zeroline) first in one direction and then in the opposite direction. The biphasic waveform can be delivered in a number of protocols, and an example is demonstrated in Figure 1C. One biphasic protocol that has been used successfully in some clinical trials is the low voltage pulsed current (LVPC).

DC causes an electrochemical reaction in tissue as well. Positively charged sodium ions migrate toward the negatively charged pole (cathode), combining with water to yield the base sodium hydroxide. At the anode (positive pole), there is formation of hydrochloric acid due to the redistribution of chlorine. These resultant changes in pH may induce chemical burns or blisters. Shortening treatment time, polarity reversal, or decreasing current amplitude can minimize this hazard.

Figure 2. Generation of skin wound electric fields.

Unbroken skin maintains a "skin battery", derived by apical-basal transport of Na⁺, and generation of a transepithelial potential (2a). When wounded, the potential drives current flow through the newly formed low resistance pathway (2b), generating an electric field whose negative vector points toward the wound center at the lower portion of the epidermis.
Alternating Current (AC)

AC is defined as a current that changes the direction of flow with reference to the zero baseline at least once every second. The typical AC is symmetrical (although asymmetric waveforms have also been used) and can be delivered in various waveforms (Figure 1D & E). The transcutaneous electrical nerve stimulation (TENS) devices currently available use a type of AC. Current is usually delivered at 15 to 20 mA with a pulse duration of 150 μsec. Some successful studies using AC for wound healing have been reported in the literature (see Table 4).

THEORETICAL AND SCIENTIFIC BASIS FOR USE OF ES

Evidence for electric fields in wounds

The existence of ionic currents exiting injured tissues has been known for some time: it was first demonstrated by Matteucci in 1830, Dubois-Reymond, founder of the science of bioelectricity, was the first to experimentally demonstrate in 1843 the existence of wound currents. He measured approximately 1 μA of current from a wound in human skin. Other, more recent studies have confirmed this finding; for example, currents of up to 10 μA/cm² have been measured with the vibrating probe technique exiting amputated finger tips in children. Trans epithelial potentials between 20-50 mV, inside positive, have been recorded in human skin, maintained by a "skin battery", presumably generated by inward transport of sodium ions through the membrane Na⁺K⁺ ATPase pumps. In intact human skin, current flow is limited by very high resistance stratum corneum. When a wound disturbs the epidermal integrity, there is a net flow of current through the low resistance wound pathway and the resultant generation of a lateral electric field within or beneath the adjacent epidermis. The negative pole of this field vector therefore points toward the wound from all neighboring regions (Figure 2).

Numerous studies have shown that there is a "current of injury" when amphibian skin is wounded, and have provided other compelling evidence for a role of endogenous electric fields in wound healing in the next. When wound electric fields are nullified either pharmacologically or electrically, the rate of wound re-epithelialization is significantly reduced. Jaffe and Vanable have suggested that since a moist environment is required for current flow, this may account for the more rapid healing noted in wounds that are occluded with film dressings. Together, there is a significant scientific literature to support the notion that endogenous electric fields form immediately upon wounding of skin and play a role in the wound healing process.

Galvanotaxis

One mechanism by which the electric fields may participate in wound healing is by directing cell migration and, as such, enhancing wound healing. The concept of directional migration in an electric field, or galvanotaxis, is not a new one. Many cell types have been noted to exhibit this response (reviewed by Nuccitelli and Robinson). Of importance in skin wound healing is the recent work demonstrating that the migration of human skin-derived keratinocytes is also guided by electric fields, notably fields of the same magnitude as those found in mammalian wounds. Application of an electric field across a wound made in vitro to a confluent sheet of cultured keratinocytes enhances the migration of the cathodally facing cells (Figure 3). Thus, wound-generated electric fields may contribute to wound healing by guiding keratinocyte migration and enhancing re-epithelialization. Endothelial cells also respond to electric field with a directional migratory response, and the wound-generated electric field may, likewise, direct dermal angiogenesis required for wound repair.

The mechanism by which cells respond to an electric field with directional migration is the subject of ongoing investigations. Electric field-induced lateral electrophoresis and redistribution of proteins within the plasma membrane is one proposed mechanism. For example, the EGF receptor rapidly localizes on the cathodal side of keratinocytes exposed to dc electric fields. Other possible targets include membrane channels and regulators.
tant changes in ion fluxes\(^{20}\), changes in the organization of the actin cytoskeleton\(^{21-23}\) in the distribution of adhesive structures, such as integrins\(^{24}\), or local activation of protein kinases\(^{25-28}\). Intensive investigation in this area continues.

**In vitro cellular effects of ES**

DC effects on cell migration, i.e., galvanotaxis, have been well documented, as noted above. Pulsed DC protocols, which limit the potential for cellular damage, have also demonstrated potentially beneficial cellular effects. An increase in protein synthesis and thymidine incorporation into DNA has been observed by Bourguignon and Bourguignon\(^{29}\) in cultured human fibroblasts treated with high voltage pulsed current (HVPC) in the range of 50-200V and pulse rates of 60-125 pps. Voltages intensities greater than 250V inhibited both protein and DNA synthesis. This same treatment protocol upregulates insulin receptors on fibroblast membranes\(^{30}\). The rationale for low voltage pulsed current (LVPC) protocol in clinical wound healing studies may also derive from work by Petty and colleagues\(^{31}\) who have demonstrated that electric fields with periods of 20-s match endogenous cellular metabolic oscillations in NADP, and thus may contribute to a metabolic effect. Using AC (10 pps, approximately 40 mVrms) Cheng and Goldman\(^{32}\) noted that fibroblasts exposed to the field demonstrated increases in \(4\)-H-thymine incorporation. Of particular significance in this study, is the experimental protocol, in which fibroblasts were incorporated into a 3-dimensional collagen matrix prior to electric field exposure, thus, providing a better model of the dermal wound environment. Oscillating electric fields of very low periodicity (1pps, 2V/cm) can also affect cell function. Cho et al.\(^{33}\) documented numerous morphologic changes accompanied by alterations in migratory speed and directness of migration in macrophages exposed to these fields. Evidence cited from the above studies demonstrate that electric fields, delivered to cells in multiple varieties of waveforms, have numerous biologic cellular effects and thus may contribute to the wound healing process.

**Animal studies**

Animal studies using a variety of wound models and ES protocols have, with few exceptions, reported an enhancement in some aspects of wound healing (Table 1). Notable is the improvement in tensile strength observed in wounds treated with DC, usually with the negative electrode placed over or within the wound site\(^{34-40}\). Other studies demonstrate concomitant increases in the number of fibroblasts within the wound, and an increase in collagen production\(^{41-45}\). As other ES protocols have become popular, they too have been assessed in animal models. The pulsed HVPC and LVPC protocols, have also demonstrated a positive effect on wound healing, primarily increasing the rate of wound closure. Overall, the studies using continuous DC demonstrated increased wound tensile strength while those with HVPC did not. Certain cautions should be used when extrapolating animal studies to humans. For example, pig dermis is considerably thicker than human dermis and as such the difference could create a different skin resistance thus interfering with current flow. The studies are not directly comparable to one another, given the variety in animal models, wounds, ES protocols and electrodes used. In addition, most of the animal wound studies are not models for chronic non-healing wounds. These caveats aside, one can nevertheless conclude that the animal studies provide evidence to support the efficacy of ES in wound healing, although it is not quite clear which ES protocol is superior.

**Antibacterial Effects of ES**

When a wound is infected, its healing is delayed. There is evidence from both in vitro and in vivo studies suggesting that ES have bactericidal and bacteriostatic effects on microorganisms known to colonize dermal wounds. The growth of Escherichia coli B in culture medium is inhibited with treatment of DC 1.0 - 140 mA, but not AC protocols\(^{46}\). The effect is most notable at the cathode. Likewise, DC treatment has been noted to decrease the growth rate of Staphylococcus aureus\(^{47}\) in vitro. Since the magnitude of the effect varies with the type of electrodes used, toxicity from electrolytic products cannot be ruled out in these studies. In full thickness rabbit skin wounds experimentally infected with Pseudomonas aeruginosa, cathodal DC stimulation with 1mA significantly decreased bacterial count\(^{48}\), providing in vivo confirmation of the in vitro results. HPVC has also been examined for its ability to curtail bacterial growth. Growth of the common wound bacteria Staphylococcus aureus, E. coli, and Pseudomonas aeruginosa is inhibited by HPVC, with a linear relationship between inhibition and duration of exposure of HVPC and the voltage (150-300V)\(^{49}\). In an attempt to identify the mechanism by which HVPC kills bacterial in vitro, Szuminski and colleagues\(^{50}\) delivered HVPC at 500V into culture media containing 4 different species of bacteria that commonly colonize wounds, S. aureus, E. coli, Klebsiella and P. aeruginosa. Both direct and indirect (production of antimicrobial factor in the medium exposed to ES) bactericidal effects were observed, both at the positive and negative poles. Although there was no local increase in temperature during the application of the current, the investigators were unable to determine whether the inhibitory effect was due to direct action of the current on the organism, or the pH changes observed. It should be noted that voltages used in this study are higher than those used in clinical settings. Thus further investigation is needed to clarify the role of ES in infection control in wound healing.

In summary, the research literature provides evidence that ES has inhibitory effects on common pathogens that colonize dermal wounds. In vitro studies have shown that antibacterial effects are more likely to occur with non-noxious \(\mu\)A DC applied to wound pathogens via the cathode whereas the voltage required for antibacterial effect with HVPC would be intolerable for patients (250 to 500V). Antibacterial effects of other ES protocols are lacking. The mechanisms by which ES inhibit these organisms are unknown and remain controversial.

**CLINICAL SCIENCE RESEARCH**

Forty years after the first reported clinical use, ES is still not a first line clinical modality for treating skin wounds. The lack of knowledge regarding the mechanism as well as lack of carefully controlled studies seems to be major arguments to dissuade its use. In spite of the evidence showing beneficial effects of ES, lack of standardization across treatment protocols has made it
Low Voltage PC studies

Since 1991, 4 randomized, double blind, multi-center studies evaluating LVPC treatment for chronic wounds have been published. These studies enrolled larger numbers of patients, ranging from 47 to 74, primarily with decubitus ulcers of stage II, III, or IV. In each protocol the control group received sham ES with an inactive device, and documented standard care. Three studies, Feeder et al., Mulder,39, and Gentzkow et al.40 used similar treatment protocols of approximately 30 mA, 64-128pps applied 30 minutes twice daily to the wounds. The fourth study by Wood et al.41 applied much lower currents (300-600 µA at 0.88 pps) three times a week for unreported treatment periods. The outcome measured in each study was the change in the percentage of the initial ulcer area, defined by the product of the width X length of the wound. All four studies demonstrate statistically significant reductions in the areas of the ES treated wounds.

Despite the rigor of the studies, these too have come under recent criticism. For example, Shefet et al.42 have pointed out assignment bias and resultant differences between the control and treatment groups in Gentzkow’s study. Margolis43 noted that the reported 9% healing rate for the control decubitus ulcers in Wood’s study was lower than expected using standard moist saline dressings. These shortcomings notwithstanding, the preponderance of the evidence does support a role for this ES protocol in enhancing chronic wound closure, at least in stage II-IV decubitus ulcers.

High Voltage PC

Fewer randomized controlled trials of HVPC have been performed, and these have evaluated limited numbers of patients, with mixed ulcer diagnoses, which weaken the study design and outcome analysis. One, by Kloth and Feeder44, evaluated 16 patients with chronic ulcers of various etiologies treated with 45 minutes of HVPC, 100 to 175V at 105 pps, 5 days per week. The polarity of the stimulating electrodes was reversed when the rate of ulcer healing plateaued. Ulcers of both treatment and control (sham treated) groups received standard wound care. The ulcers of the treatment group healed over a mean period of 7.3 weeks at a rate of 45% per week. A concern of this study is that the patients in the control group had a mean increase in wound size on average of 11% per week, varying significantly from the reported healing rates for ulcers with standard care.45 A subsequent study by Griffin et al.,46 in a single-blind randomized controlled trial, demonstrated similar acceleration of healing when they assessed the efficacy of HVPC on 17 spinal cord injured men with stage II, III and IV decubitus ulcers. The treatment protocol in this study was HVPC of 200V intensity at 100 pps with the cathodal electrode applied directly to the wound for 1 hour a day for 20 days. The control group was sham treated, and both groups received standard wound care in addition to the HVPC or sham HVPC. Despite this relatively short treatment protocol, the HVPC-treated patients with stage IV ulcers showed a 67% decrease in wound surface area by the 20th day of treatment compared to 15% decrease for the control group. Given the small sample size, these findings have not achieved statistical significance. The third randomized controlled study of patients with chronic dermal ulcers treated with HVPC was performed by Gogia et al.47 Twelve patients with
stage III ulcers of mixed etiologies on the leg or foot received either standard wound care or standard wound care in addition to HVPC of 250V at 100 pps with the cathodal electrode placed directly over the wound daily for 20 minutes a day, 5 days a week for 4 weeks. Treatments began with the negative electrode placed over the wound for 4 days; then polarity reversed for the final 16 treatments, citing some of the earlier animal work to support the choice of these reversal parameters. Although the study reports a 37.4% of HVPC-treated lesions had healed compared to 27.2% for control lesion, these findings did not reach statistical significance given the small number of subjects.

Thus, the HVPC studies each seem to have some shortcomings in study design, which limit the interpretation of the findings. Although the currently reported work is certainly intriguing, more studies with larger sample sizes and rigorous study design are needed, to be able to reach a firm conclusion regarding the utility of HVPC in wound healing.

**Alternating Current (AC) Studies**

AC has been applied to chronic wounds in two types of protocols: symmetric square-wave, most commonly delivered using a portable TENS device, or asymmetric biphasic pulsed wave. As opposed to DC or PC stimulators, AC stimulation is generally delivered by electrodes adjacent to the wound rather than directly overlying it.

**TENS**

Initial case report and uncontrolled case reports treating patients with TENS applied to nerves in the vicinity of the wounds suggested this approach might be beneficial. The etiologies of the treated ulcers were varied, but included neuropathic lesions, with the rationale that the neural stimulation provided by TENS would enhance healing. One interesting study by Kaada and Emms used TENS therapy to treat 32 patients with longstanding lower leg ulcers secondary to ischiosomy. Patients received trains of 5 pulses (25 mA at 100 pps, 0.1 to 0.2 millisecond duration) for 30 minutes sessions, twice daily for 5 to 6 days per week. Twelve weeks post-treatment, 59% of the patients healed completely. All those who completed therapy healed completely with a mean healing time of 5.2 weeks. All the above TENS studies were uncontrolled studies, and all used different treatment regimens, making conclusions difficult to draw.

Thus far there has been only one randomized controlled study of the effect of TENS on wound healing. Lundberg et al. 1986 studied 64 diabetic patients with stasis ulcers. The patients received either TENS therapy (treatment parameters not given) for 20 minutes, twice daily for 12 weeks or sham treatment. The polarity was changed after each session. All patients received standard wound care, which was a compression dressing, After 12 weeks, 42% of the treated group healed compared to 15% of the control, with statistical significance. This study does support a role of TENS stimulation in the treatment of ulcers in diabetic patients.

**Biphasic Pulsed**

Asymmetrical biphasic pulsed waveforms have been used in some wound healing studies, presumably because the asymmetry of the waveform allows the polarity of one pole to predominate. One case series and one non-randomized control trial have suggested that this modality may be useful in enhancing healing in a wide array of chronic ulcers. However, only one randomized controlled trial has evaluated the efficacy of this modality.

Baker et al. evaluated the effects of two stimulation waveforms on healing rates in patients with diabetic ulcers. Patients received stimulation with either an asymmetric biphasic or symmetric biphasic square-wave pulse both at 50 pps, at unreported amplitudes. A third group received a sham ES. All patients in the study received standard wound care. In this study, treatment with asymmetric biphasic ES showed a statistically significant 80% increase in the healing rate, as compared to controls. This study suggests that the asymmetric biphasic waveform may be more advantageous in ulcers in diabetic patients. The rationale for this is not entirely clear.

It appears that most of the studies on the efficacy of AC stimulation for wound healing evaluated patients with decubitus ulcers. No inferences may be comfortably extended to other types of non-healing wounds. The double-blind randomized controlled study by Lundberg et al. 1986 is particularly strong, and its results do support a role for AC therapy in decubitus ulcers. Its efficacy in other chronic wounds remains to be evaluated.

**STRENGTH OF EVIDENCE RATING FOR ES**

In 1994, the Agency for Healthcare Research and Quality (AHRQ) convened a panel of experts who subsequently published a guideline for the treatment of pressure ulcers. The panel recommended that clinicians "consider a course of treatment with electrotherapy for stage III and IV pressure ulcers that have proved unresponsive to conventional therapy. In the 1994 AHRQ document, the strength of evidence rating assigned to ES was "B" based on the following rating scale:

A : Results of two or more randomized controlled clinical trials (RCT) on chronic wounds in humans provide support.

B : Results of two or more controlled clinical trials on chronic wounds in humans or when appropriate results of two or more controlled trials in an animal model provide indirect support.

C : This rating require one or more of the following: 1) results of one controlled trial; 2) results of at least two case series/descriptive studies on chronic wounds in humans; or 3) expert opinion.

Another comprehensive review of the modality has been recently undertaken in the UK by the National Coordinating Centre for Health Technology Assessment. Although sixteen randomized controlled trials were included in their review many were excluded because of the previously noted flaws in their design. Their conclusion, published in 2001, was that there may be some benefit associated with electrotherapy in the healing of chronic wounds, but that the evidence was generally insufficient to unequivocally conclude that ES is beneficial for the treatment of chronic wounds.
Of particular interest to practitioners in the United States, however, is the Centers for Medicare and Medicaid Services (CMS, formerly known as HCFA) July 2002 decision on coverage of ES for chronic wounds. The decision was based on a comprehensive review that began in 1995, with in-depth analysis of all published clinical trials, and input from the American Physical Therapy Association, an outside technology assessment firm (Emergency Care Research Institute, whose 313 page 1996 comprehensive report is available on-line), the Association for the Advancement of Wound Care, reports from the Agency for Health Care Policy and Research, and the Medical and Surgical Procedures panel of the Medicare Coverage Advisory Committee (MCAC). The panel concluded that there was adequate evidence to draw the conclusion that ES is an effective adjunctive therapy for chronic non-healing wounds. Their decision was to allow coverage for ES in chronic wounds that do not respond to standard care. Interestingly, the panel specifically did not single out any one type of ES delivery system, thus allowing this to the discretion of the practitioner. This decision has the potential to radically change our approach to wound care, by providing national coverage for ES as a second-line of treatment for a large group of patients with venous stasis, diabetic, arterial, or pressure ulcers. To be able to use this new therapeutic tool to the patient's full advantage, the dermatologic community will need to develop treatment protocols that allow for continued assessment of the efficacy of this novel modality.

PRECAUTIONS

Adverse effects of ES are rarely reported, and consist of anecdotal reports of skin irritation or tingling sensation that is perceived under the electrodes in occasional cases. Skin irritation is more likely to be reported when continuous DC or monochastic PC with long pulse duration is used. Pain may be experienced in patients with severe peripheral vascular occlusive disease.

Contraindications

The following conditions are considered to be contraindications for the use of ES to for wound healing.

Presence of Cancer

It has been recommended that ES not be used in patients who have concurrent malignancies. The concept expressed is that ES may cause mitogenic activity or proliferation of the malignant cells.

Osteomyelitis

Patients with active osteomyelitis have been precluded from the use of ES. Stimulation of tissue repair may facilitate premature closure of the wound leading to the covering of the area of osteomyelitis. This may also result in abscess formation.

Implanted electrical devices

Electrical implants and cardiac pacemaker functions may be disrupted by ES. Use of ES device (TENS) by Rasmussen and associates to patients with different cardiac pacemakers was found to be safe.

Topical substances with metallic ions

Topical substances containing metallic ions used for wound treatment (e.g., povidone-iodine, zinc, silver sulfadiazine etc.) should be cleaned thoroughly before application of ES. Heavy metal ions are known to be toxic when absorbed percutaneously. Direct current has the ability through the process of iontophoresis to transfer these heavy metal ions into the systemic circulation. Thorough cleaning is therefore mandatory before the use of ES.

Overlying Vital Organs and Nerves

ES is contraindicated in the upper chest and anterior neck. These areas of the body are very sensitive to any stimulation because of the presence of certain vital organs (carotid sinus, phrenic nerve, parasympathetic nerve and ganglia and the heart).

DEVICES

At present, not a single ES device has been approved or received premarket approval (PMA) by the Food and Drug Administration (FDA) for wound healing. PMA requires extensive clinical trials to show safety and effectiveness of the device. Therefore, use of any ES device at this time is considered "Off Label", for which there is sanction as part of the practice of medicine. Indeed, the CMS decision to allow use of ES for chronic wounds notes specifically that while currently no devices are approved by the FDA for delivering ES to cutaneous wounds, "lack of approval for this particular indication, does not preclude physicians and other health care providers from providing this therapy as an off-label use." Noting these caveats, Table 5 lists devices that have been used off-label for ES therapy. Some manufacturers were contacted, and those who provided data are presented in the table. Devices such as Neuro-muscular Electrical Stimulator (NMES) have specific FDA applications which include: (a) increase local blood circulation, (b) reducing edema, (c) preventing retardation of muscle atrophy and (d) strengthening muscle and preventing postoperative venous thrombosis. Pain Management Devices such as TENS have specific FDA-approved applications, which include (a) relief of both acute and chronic pain, (b) increase in local and distal blood circulation and (c) relief of postoperative pain.

Safety of Devices

Extensive safety studies on ES devices for wound healing have not been performed. To date, there have been no adverse reactions or complications reported in any DC studies of wound healing. In PC studies, there have been 7 cases of uncomfortable tingling, 1 case of skin irritation and 1 case of excessive bleeding at the ulcer site reported in 2 studies. AC studies of wound healing have reported no complications or any adverse reactions. More rigorous investigation for possible adverse effects, as required by FDA for approval, needs to be undertaken.

SUMMARY AND IMPLICATIONS FOR CLINICAL PRACTICE

The use of ES is currently attracting interest because of its potential to improve and accelerate wound healing. In vitro and in vivo studies have shown that ES can increase both DNA and collagen synthesis, direct epithe-
lial, fibroblast, and endothelial cell migration into wound sites, inhibit the growth of some wound pathogens and increase tensile strength of the wound scar. Animal studies of ES, with rare exception, demonstrate the beneficial effect of ES on various aspects of wound healing. Clinical reports are heavily dominated by case reports and case series, which are suggestive, but not definitive studies. A number of randomized controlled trials have demonstrated efficacy of ES for healing of chronic wounds, with the strongest evidence supporting its use for pressure ulcers, but inconsistencies in the protocols used by the different investigators make it difficult to choose one ES regimen over another. The recent decision of the Centers for Medicare and Medicaid

Table 1. Effects of ES on Wound Healing in Animal Studies

<table>
<thead>
<tr>
<th>Author (Reference #)</th>
<th>Animal</th>
<th>Wound Type</th>
<th>ES Type</th>
<th>ES Type</th>
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<tr>
<td>Arameshopo et al. 23</td>
<td>Rabbit</td>
<td>Incisional</td>
<td>DC, 50-100 µA</td>
<td>Increase tensile strength</td>
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<td>Kuroki et al. 36</td>
<td>Rabbit</td>
<td>Full-Thickness excisional</td>
<td>DC, 20 µA</td>
<td>Increase tensile strength</td>
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<td>Bylow et al. 40</td>
<td>Dog</td>
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<td>DC, 6-12 mA</td>
<td>Increase tensile strength</td>
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<td>Tawada et al. 47</td>
<td>Rat</td>
<td>Incisional</td>
<td>DC, 300 µA</td>
<td>Increase fibrinogen and wound tensile strength</td>
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<td>Smith et al. 48</td>
<td>Mouse</td>
<td>Incisional</td>
<td>DC, 10-20 mA</td>
<td>Increase matrix formation</td>
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<td>Druce et al. 49</td>
<td>Guinea pig</td>
<td>Full-Thickness excisional collagen sponge implant</td>
<td>DC, 20-100 µA</td>
<td>Increase fibrinogen and collagen alignment</td>
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<td>Cuche et al. 50</td>
<td>Pig</td>
<td>Burn</td>
<td>HVPSC, 175V, 40pps</td>
<td>Increase wound contraction and number of fibroblasts</td>
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<td>Camilleri et al. 51</td>
<td>Rats</td>
<td>Burn</td>
<td>Biphasic DC, 40 µA, 67</td>
<td>Increase collagen density</td>
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<td>Rabbit</td>
<td>Incisional</td>
<td>DC, 200-300 µA</td>
<td>Increase PMN and lymphocytes</td>
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<td>Rabbit</td>
<td>Incisional</td>
<td>DC, 40-600 µA</td>
<td>No increase in tensile strength over control</td>
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<td>Alonso et al. 54</td>
<td>Pig</td>
<td>Full-Thickness excisional</td>
<td>DC, 50-500 µA</td>
<td>Increase epidermalization of superficial skin</td>
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<td>Brown and Goggin 55</td>
<td>Rabbit</td>
<td>Incisional</td>
<td>HVPSC, 30-60V, 40 pps</td>
<td>No significant improvement in wound healing</td>
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<td>Brown et al. 56</td>
<td>Rabbit</td>
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<td>HVPSC, 30-60V, 40 pps</td>
<td>Increase rate of wound closure</td>
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<td>Brown et al. 57</td>
<td>Rabbit</td>
<td>Full-Thickness excisional</td>
<td>HVPSC, 30-60V, 40 pps</td>
<td>No increase in tensile strength over control</td>
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<td>Incisional</td>
<td>LVPSC, 10 µA, 60V, 1 pps</td>
<td>Increase reepithelialization</td>
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<td>Roger et al. 59</td>
<td>Pig</td>
<td>Experimental pressure sore</td>
<td>AC, 740mA, 40 pps</td>
<td>Both AC and DC showed reduced healing time. DC reduced the wound area more rapidly than AC, but AC reduced wound volume more rapidly than DC</td>
<td></td>
</tr>
<tr>
<td>Elmore et al. 60</td>
<td>Mouse</td>
<td>Full-Thickness excisional</td>
<td>LVPSC, 12.5V, 300pps</td>
<td>Increase rate of wound closure</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Direct Current Clinical Studies of Wound Healing

<table>
<thead>
<tr>
<th>Author (Reference #)</th>
<th>Stimulation Type</th>
<th>Wound Type</th>
<th>Treatment Group</th>
<th>Number of Patients or Lesions</th>
<th>% Patients or Lesions Healed/Healed</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arameshopo et al. 61</td>
<td>DC 50-100 µA/m20</td>
<td>Venous DC</td>
<td>3</td>
<td>100/94.6%</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Weil et al. 62</td>
<td>DC 240-800 µA 2 hours, 2 times/day for 36 weeks, switch to d.c. cathode</td>
<td>Case series</td>
<td>Mixed DC</td>
<td>75</td>
<td>64/64%</td>
<td>Healing rate; Pyogenic + 9.9% Perineural nerve-septate = 14.6% Vascular stasis = 16.4% Others = 100%</td>
</tr>
<tr>
<td>Gaut and Gaten 63</td>
<td>DC Regimes similar to Weil et al., except polarity reversed only once</td>
<td>Case series</td>
<td>Mixed</td>
<td>Control DC</td>
<td>100</td>
<td>50/50%</td>
</tr>
<tr>
<td>Carley &amp; Danks 64</td>
<td>DC 240-800 µA 2 hours, 2 times/day. Otherwise regimes similar to Weil et al.</td>
<td>RCT Not Specified</td>
<td>DC Control</td>
<td>15</td>
<td>Net reported</td>
<td>Healing rate; 92%</td>
</tr>
<tr>
<td>Marlow et al. 65</td>
<td>DC 20 µA/cathode</td>
<td>Comparative control</td>
<td>Venous DC/prednisone DC/sulfinpyrazone</td>
<td>4 11 5</td>
<td>Not reported</td>
<td>Healing rate (84 days); 85.5 92 45 98.1</td>
</tr>
</tbody>
</table>

RCT = Randomized Controlled Trial; DC = Direct Current; wk = week; µA = microampere
Services to allow reimbursement for ES treatment of chronic ulcers means that the dermatologic practitioner will likely become more familiar with this novel treatment approach, and that wound care centers will include this option for resistant ulcers. While no ES devices dedicated to wound healing are currently available, the large size of the potential market for such devices predicts that these devices will rapidly be offered. As the number of successful randomized controlled trials increases, the use of ES as an adjuvant therapy for wound healing will very likely become more widely accepted by physicians and wound care providers.

Table 3. Pulsed Current Clinical Studies of Wound Healing

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Current Type</th>
<th>Dosage</th>
<th>Applied/Polarity</th>
<th>Study Type</th>
<th>Wound Type</th>
<th>Treatment Group</th>
<th>Number of Patients or Lesions</th>
<th>% Patients or Lesions Healed/Time</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feodor et al. 27</td>
<td>LVPC</td>
<td>350 μA/g for 10 μs (maximum duration of 20 μs and 320 μA/g dose)</td>
<td>Double-blind RCT</td>
<td>Mixed</td>
<td>LVPC</td>
<td>10</td>
<td>80/100</td>
<td>80%</td>
<td>Healing rate: 14%</td>
</tr>
<tr>
<td>Meador et al. 29</td>
<td>LVPC</td>
<td>50–100 μA/g for 30 μs</td>
<td>Double-blind RCT</td>
<td>Mixed</td>
<td>LVPC</td>
<td>20</td>
<td>90/100</td>
<td>90%</td>
<td>Healing rate: 90%</td>
</tr>
<tr>
<td>Gantchev et al. 39</td>
<td>LVPC</td>
<td>50–100 μA/g for 30 μs</td>
<td>Double-blind RCT</td>
<td>Mixed</td>
<td>LVPC</td>
<td>10</td>
<td>70/100</td>
<td>70%</td>
<td>Healing rate: 70%</td>
</tr>
<tr>
<td>Woodward et al. 40</td>
<td>LVPC</td>
<td>50 μA/g for 600 μA/g for 30 μs</td>
<td>Double-blind RCT</td>
<td>Mixed</td>
<td>LVPC</td>
<td>44</td>
<td>90/100</td>
<td>90%</td>
<td>Healing rate: 90%</td>
</tr>
<tr>
<td>Kothari et al. 52</td>
<td>HVPIC</td>
<td>150–300 μA/g for 1 s</td>
<td>Single-blind RCT</td>
<td>EDC</td>
<td>HVPIC</td>
<td>6</td>
<td>50/60</td>
<td>50%</td>
<td>Healing rate: 50%</td>
</tr>
<tr>
<td>Griffin et al. 60</td>
<td>HVPIC</td>
<td>200 μA/g for 1 h</td>
<td>Single-blind RCT</td>
<td>EDC</td>
<td>HVPIC</td>
<td>8</td>
<td>70/100</td>
<td>70%</td>
<td>Healing rate: 70%</td>
</tr>
<tr>
<td>Cegut et al. 72</td>
<td>HVPIC</td>
<td>250 μA/g for 50 μs</td>
<td>Single-blind RCT</td>
<td>EDC</td>
<td>HVPIC</td>
<td>6</td>
<td>Not reported</td>
<td>Rate of Healing: 30%</td>
<td></td>
</tr>
</tbody>
</table>

LVPC = Low Voltage Pulsed Current; HVPIC = High Voltage Pulsed Current; RCT = Randomized Controlled Trial

Table 4. Alternating Current Clinical Studies of Wound Healing

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Current Type</th>
<th>Dosage</th>
<th>Applied/Polarity</th>
<th>Study Type</th>
<th>Wound Type</th>
<th>Treatment Group</th>
<th>Number of Patients or Lesions</th>
<th>% Patients or Lesions Healed/Time</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kasai et al. 15</td>
<td>TENS</td>
<td>150 μA/g for 10 μs</td>
<td>bathing</td>
<td>Case report</td>
<td>Mixed</td>
<td>TENS</td>
<td>10</td>
<td>70/20</td>
<td>None reported</td>
</tr>
<tr>
<td>Iwasa et al. 25</td>
<td>TENS</td>
<td>60–300 μA/g for 10 μs</td>
<td>bathing</td>
<td>Case report</td>
<td>Decubitus</td>
<td>TENS</td>
<td>6</td>
<td>30/30</td>
<td>None reported</td>
</tr>
<tr>
<td>Korda et al. 36</td>
<td>TENS</td>
<td>50–100 μA/g for 10 μs</td>
<td>bathing</td>
<td>Case report</td>
<td>Decubitus</td>
<td>TENS</td>
<td>22</td>
<td>90/20</td>
<td>None reported</td>
</tr>
<tr>
<td>Landesberg et al. 6</td>
<td>TENS</td>
<td>150 μA/g for 10 μs</td>
<td>bathing</td>
<td>Double-blind RCT</td>
<td>Lower extremity</td>
<td>TENS</td>
<td>32</td>
<td>40/12</td>
<td>Percentage of areas healed: 12%</td>
</tr>
<tr>
<td>Kofele et al. 72</td>
<td>Biphasic AC</td>
<td>150 μA/g for 10 μs</td>
<td>bathing</td>
<td>Case report</td>
<td>Mixed</td>
<td>Biphasic AC</td>
<td>14</td>
<td>80/14</td>
<td>None reported</td>
</tr>
<tr>
<td>Zatti et al. 75</td>
<td>Biphasic AC</td>
<td>150 μA/g for 10 μs</td>
<td>bathing</td>
<td>Case report</td>
<td>Biphasic AC</td>
<td>Biphasic AC</td>
<td>82</td>
<td>100/82</td>
<td>None reported</td>
</tr>
<tr>
<td>Baker et al. 78</td>
<td>Biphasic AC</td>
<td>150 μA/g for 10 μs</td>
<td>bathing</td>
<td>Biphasic AC</td>
<td>Biphasic AC</td>
<td>Biphasic AC</td>
<td>29</td>
<td>100/29</td>
<td>Healing rate: 100%</td>
</tr>
</tbody>
</table>

AC = Alternating Current; RCT = Randomized Controlled Trial; TENS = Transcutaneous Electrical Nerve Stimulation
Table 5. Device Specifications of Electrical Stimulators 1

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Type of Unit</th>
<th>Waveforms</th>
<th>Amperage</th>
<th>Voltage, Volts</th>
<th>Delivery Mode</th>
<th>Frequency Range, Hz</th>
<th>Intended Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avta Tronics</td>
<td>Galvanostat 770</td>
<td>PC</td>
<td>Monophasic</td>
<td>N/A</td>
<td>0-500</td>
<td>Pulsed</td>
<td>4-80</td>
<td>Neuromuscular stimulation</td>
</tr>
<tr>
<td>Chattanooga</td>
<td>InflecLegend</td>
<td>HVPC</td>
<td>NMES</td>
<td>Monophasic</td>
<td>0-2000 mA peak</td>
<td>0-90</td>
<td>Pulsed, intermittent</td>
<td>1-120</td>
</tr>
<tr>
<td>Dynavolt</td>
<td>Dynawave Model 11</td>
<td>Microcurrent</td>
<td>NMES</td>
<td>Monophasic</td>
<td>Microamp</td>
<td>0-900</td>
<td>Pulsed, intermittent</td>
<td>1-105</td>
</tr>
<tr>
<td>ElectroMedical Inc.</td>
<td>ElectroAnoscope 95</td>
<td>TENS</td>
<td>Biphasic</td>
<td>25-500 microamp</td>
<td>N/A</td>
<td>Pulsed</td>
<td>0.5-320</td>
<td>Pain management</td>
</tr>
<tr>
<td>ElectroTherapeutic Devices</td>
<td>Accu-O-Matic</td>
<td>TENS, microcurrent</td>
<td>Biphasic</td>
<td>250-500 microamp</td>
<td>55 peak</td>
<td>Pulsed</td>
<td>0.5-320</td>
<td>Pain management</td>
</tr>
<tr>
<td>Erbip</td>
<td>Epleren TENS</td>
<td>Biphasic</td>
<td>0.2-0.3 mA</td>
<td>N/A</td>
<td>Pulsed</td>
<td>2-125</td>
<td>Pain management</td>
<td></td>
</tr>
<tr>
<td>Rehabilitronics</td>
<td>GV II</td>
<td>PC</td>
<td>Monophasic</td>
<td>0.2-0.3 mA</td>
<td>0-150</td>
<td>Pulsed, intermittent</td>
<td>1-100</td>
<td>Neuromuscular stimulation</td>
</tr>
<tr>
<td>NeuroCare Inc.</td>
<td>NC 1000</td>
<td>NMES</td>
<td>Biphasic</td>
<td>0.1-2.0 mA</td>
<td>20-440</td>
<td>Pulsed</td>
<td>47</td>
<td>Neuromuscular stimulation, Soft tissue injuries, Decubitus ulcers stage IV, Diabetic Neuropathy</td>
</tr>
<tr>
<td>Strydom</td>
<td>Dermazosthe 5000</td>
<td>PC, NMES</td>
<td>Monophasic</td>
<td>0.2-0.3 mA</td>
<td>N/A</td>
<td>Pulsed</td>
<td>64, 128</td>
<td>Wound management</td>
</tr>
<tr>
<td>Universal Technology Systems, Inc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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References


