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Abbreviations and Acronyms

AC= alternating current
CGRP= calcitonin gene-related peptide
DC= direct current
EA= electroacupuncture
ES= electrical stimulation
HVPC= high voltage pulsed current
LIDC= low intensity direct current
PC= pulsed current
PMN= polymorphonuclear
SEM= scanning electron microscopy
VEGF= vascular endothelial growth factor
VIP= vasoactive intestinal polypeptide

Electrical Stimulation of Wound Healing: A Review of Animal Experimental Evidence

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Significance: Electrical stimulation (ES) is a therapeutic intervention that may help specialists facilitate wound healing rates. The purpose of this section is to compile the available animal research regarding the effectiveness of ES on the injury potential, healing rate, cellular and molecular proliferation, mechanical properties, and survival rate of skin flaps.

Recent Advances: Regardless of the type of ES current and polarity used, most of the animal experimental evidence suggests that application of ES can facilitate wound healing. However, treatment time should be sufficiently long to attain good mechanical strength of regenerated tissue, because tensile strength is not consistent with augmented collagen deposition. ES improves the survival rate and skin blood flow of animal flaps, but clinical studies are needed to substantiate the findings from these animal experiments.

Critical Issues: Impaired or delayed healing is a major clinical problem that can lead to wound chronicity. ES with various strategies has been used to facilitate the healing process, but many aspects remain controversial. Despite much research, no consensus exists regarding the detailed effects of ES on wound healing. Nevertheless, ES has been approved by the Center for Medicare and Medicine Services for reimbursement of the treatment of some chronic ulcers.

Future Directions: Exogenous ES may promote the directional migration of cells and signaling molecules via electrotaxis; however, its underlying mechanism is still poorly understood. Future studies that further elucidate the mechanisms regulating electrotaxis will be necessary to optimize the use of ES in different wound states.

SCOPE AND SIGNIFICANCE

THE HEALING PROCESS of damaged skin is a complex biological event that allows the maintenance of skin continuity. Impaired or delayed healing is a major clinical problem that can lead to wound chronicity. Electrical stimulation (ES) is a non-pharmacological biophysical energy that may help specialists facilitate the skin healing rate and prevent ischemia and the formation of necrotic tissue. The purpose of this section is to compile the available animal research that has investi-

gated the effectiveness of ES on wound healing. Electronic database (PubMed and Science Direct) were searched for animal studies from the earliest year available to September 2012. In addition, references in articles were scanned for additional studies. All results from the searches were carefully scanned for animal studies related to the effect of ES on the injury potential, healing rate, wound closure, cellular and molecular proliferation, mechanical properties, and flap survival rate and its blood flow of skin wounds.

TRANSLATIONAL RELEVANCE

A variety of ES waveforms have been used to augment wound healing; the most common are low-intensity direct current (LIDC) and high voltage pulsed current (HVPC). The main effects of electrical current, which include promotion of directional migration of keratinocytes and macrophages,¹ stimulation of fibroblasts, increased protein and collagen synthesis,^{2,3} and enhanced angiogenesis,⁴⁻⁷ have been shown to be important in the mechanism that facilitates wound healing. However, its underlying mechanism is still poorly understood, but examination of ES based on the experimental evidence can provide valuable information about the potential clinical implication of this therapeutic biophysical energy.

CLINICAL RELEVANCE

The effectiveness of applied ES depends on the degree of epithelialization, wound contraction, and wound closure induced, as these processes are very important in diminishing wound susceptibility to infection and some repeated lesions. In addition, increased collagen density and mechanical strength are essential for tolerating the forces experienced in daily living. Many *in vivo*⁸⁻¹⁰ and *in vitro*^{3,11,12} studies have shown the effectiveness of ES with regard to increases in cell proliferation and collagen synthesis, but whether tensile strength is augmented after ES is still controversial. Nevertheless, ES has been approved by the Center for Medicare and Medicine Services for the treatment of some chronic wounds.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Effects of ES on endogenous potential during wound healing

Intact skin possesses endogenous electrical potentials such that the external skin surface is al-

ways electronegative with regard to the inner skin layers.¹³⁻¹⁶ A wound site, in contrast, is generally positive compared with the surrounding intact skin^{13,14,17,18} and this potentially changes during the healing process. After tissue damage, an LIDC is generated that is thought to trigger biological repair.^{15,19,20} This potential can be measured using a differential amplifier (Fig. 1).¹⁸ External ES has been proposed to help healing through the simulation of natural bioelectric currents.²⁰⁻²³ Some authors have reported that the endogenous electrical potentials of wounds remained positive compared with surrounding intact skin throughout the healing process,^{13,14,24} while others found that the charge of endogenous potentials can change during healing.^{25,26}

The effect of ES on changes in the skin potential in a wound throughout the healing process was studied by Talebi *et al.*¹⁸ in 39 guinea pigs. A micro-amperage direct current (DC) with an intensity of 600 μ A was applied for 1 h per day, three times a week, for 3 weeks in two experimental groups. In one group, negative polarity was set as the active electrode and in the other group, positive polarity was used. Although the pattern of endogenous potential was similar in the control and ES (cathodal and anodal DC) groups, the DC microamperage stimulation with positive polarity caused a later positive peak value and a faster return of the endogenous potential to the normal level (Fig. 2). The authors concluded that the greatest correlation between wound potential and wound surface area is related to an accelerating effect of positive polarity on wound epithelialization. Effective wound healing requires that cells not only become mobile, but that they also migrate in the correct direction.²⁷ Therefore, application of external ES with suitable parameters and polarity through wound healing appears to activate signaling molecules in a directional manner to accelerate healing process.

Figure 1. Block diagram of differential amplifier equipment to measure differential skin surface potential. Two surface electrodes (EL 1 and EL 2) are placed on the wound site and near skin intact area; these electrodes can be movable at specific locations. A single fixed reference electrode (Ref) is placed on the intact skin away from the two recording electrodes. Differential skin surface potential measuring technique is a non-invasive method to record endogenous potential without using any inserted electrodes.

Figure 2. The value of skin potential before, immediately after incision, and during healing period in a guinea pig full-thickness wound. Control: without electrical stimulation (ES) application, anodal and cathodal: with application of ES (was recorded by author).

Effects of ES on healing rate and histological parameters

Relevant literature

Effects of DC ES on acute incision wounds. Carely and Lepley²⁸ applied DC stimulation (200–300 μ A for 2, 3, and 5 days) over 4 cm full-thickness wounds in rabbits. One wound in each animal received ES via a stainless steel cathode electrode, and a second wound, via the anode. No significant wound healing was noted at the anode and cathode, while some necrosis was observed at the anode, and a scarcity of inflammatory cells was reported at the cathode area. Interaction between the two electrical fields may have given rise to this result. Assimacopoulos²⁹ showed that complete wound closure occurred earlier in rabbits that were stimulated continuously with 50–100 μ A, 0.8–1.1 V negative polarity DC. Complete wound closure occurred after 18 and 19 days in animals treated with DC, whereas it took 25 and 26 days in untreated animals. Unfortunately, only 4 wounds were studied in each control and treatment group. Alvarez *et al.*³⁰ assessed skin wound healing in 11 pigs treated with DC (50–300 μ A) that were supplied by an energized silver-coated electrode. Wounds were excised on days 1–7 after wounding. The positive electrode was placed in contact with the wound area. The rate of re-epithelialization was significantly greater in the DC group than in the placebo (un-energized electrode) and untreated groups. The time needed for 50% closure was 2.9 days for the DC group, and the relative rate of healing was 36.7 and 29.2 compared with the untreated and placebo groups, respectively. A significant increase in collagen biosynthesis was

also observed on days 5–7 in wounds treated by DC, due to an augmentation of collagen-producing cells.

Steckel *et al.*³¹ assessed skin wound healing in horses using low-level DC. Full-thickness wounds were surgically produced and ES at 10 or 20 μ A was delivered via implanted stainless steel electrodes. The anode was embedded in the subcutaneous tissues under the wound, and the cathode was placed in the center of the wound. After 4 weeks of treatment, no differences in wound appearance were noted between stimulated and non-stimulated wounds. The wounds with embedded electrodes healed more slowly (whether stimulated or not stimulated) than did the wounds of control animals with no electrodes. Implanted electrodes can induce severe tissue reactions and lead to local infection that may be detrimental to wound healing.

Application of charged particles directly to the wound surface is an alternative method for creating a charged environment in place of conventional ES. Mustoe *et al.*³² applied positive, negative, and neutral surface-charged particles to incision wounds in rats. When observed 10 days after wounding, wounds with positively charged particles were characterized by large quantities of collagen-rich connective tissue, more fibroblasts, and prominent bead-associated giant cells. The researchers suggested that the positively charged beads created a localized ionic environment similar to that produced by an anodal ES in the wound area, and this localized charge area may have attracted or activated macrophages that subsequently stimulated fibroblasts to enhance connective tissue formation. This method is invasive; however, it may promote the development of some inflammatory reactions and foreign-body type reactions.

Jiang³³ showed more rapid rate of epidermal cell proliferation and wound healing with DC stimulation in guinea pigs, especially at the negative electrode. In this study, 2 full-thickness skin defects were made in 44 animals. DC stimulation at different intensities (10, 30, 50, and 0 μ A) was delivered to one of the wounds in each animal. The results also indicated a systemic effect of ES on tissues located away from the electrodes and indicated the importance of using separate animals as a control group in this type of study.

Canseven and Atalay⁸ examined the possibility that a direct micro-current could trigger collagen synthesis by applying ES to circular skin wounds in rabbits for 3 days, for 8 h daily. At the end of 72 h, the hydroxyproline content was increased in the stimulated wounds. The authors suggested that DC promotes collagen synthesis.

Taşkan *et al.*⁹ applied DC ES (300 μ A, 30 min daily, 7 days with negative polarity for the first 3 days) to treat 6-cm linear sutured incisions in rats. At 4 and 7 days, DC stimulation caused a significant decrease in polymorphonuclear (PMN) cells and macrophages and a significant increase in fibroblasts and wound tissue hydroxyproline content. On the seventh day, mast cells decreased significantly, and the collagen was denser and more regular.

Demir *et al.*³⁴ treated sutured wounds 2 h after the surgical procedures, and continued this treatment for 30 min daily for 10 days. An active electrode was placed on the incision: It was set as negative for the first 3 days and then positive for the remaining days. DC was effective in decreasing the duration of the inflammatory phase; a significant decrease in PMN and macrophages was seen at the 4th and 10th days. On the 10th day, mast cell numbers also showed a significant decrease compared with the sham ES group. Increases in the fibroblast cell number and hydroxyproline level were obtained in the proliferation phase at the 4th and 10th days after application of DC.

Talebi *et al.*³⁵ mimicked the natural endogenous bioelectric current by applying micro-amperage DC (600 μ A, 1 h/day, three times a week, for 3 weeks) to guinea pigs. In one group, the ES was delivered as cathodal stimulation; while the other group received anodal stimulation. The wound surface area decreased significantly in the anodal and cathodal groups, from 15th and 17th days, respectively, when compared with the control group. The cathodal stimulation used in this protocol increased the number of fibroblasts compared with the control group. The collagen density was significantly greater in the cathodal group than in the control and anodal groups. No statistical difference was observed in the number of microvessels or in the collagen orientation among the groups. Cathodal DC appeared to be effective at decreasing the

duration of the inflammatory phase and at promoting a more rapid initiation of the proliferation phase.

Effects of pulsed current ES on acute incision wounds. Various types and waveforms of pulsed current (PC) ES were used in animal studies (Fig. 3). Stromberg³⁶ made 13 wounds (8 cm in diameter through fascia) in 7 pigs; 7 wounds as controls, 3 wounds with a negative current, and 3 wounds received a positive current alternating with a negative current on 3 day cycles. A monophasic square wave pulse (35 mA and 128 pulses per second [pps]) was used for 30 min, twice a day, for 4 weeks. A delay in wound contraction was seen in wounds that received a negative current, but the alternating polarity caused an increase in the wound closure rate.

Brown *et al.*³⁷ evaluated the effects of HVPC stimulation, after 4 and 7 days, on wound healing using positive polarity for 4 h daily. The current intensity was set to provide barely palpable contraction. The percentage of wound closure on the fourth and seventh days showed no significant difference between the HVPC and control groups; however, on the fourth day, the wounds in HVPC group showed a trend toward delayed healing compared with the control group. The rates of epithelialization on the fourth and seventh days were faster after HVPC than in the control groups. In addition, fibroblasts and collagen fibers were arranged regularly in the dermis on the seventh day after using HVPC. Brown *et al.*³⁸ complemented their early studies by conducting a further study to delineate the role of HVPC polarity switching on wound healing. They applied HVPC 24 h after full-thickness wounding in 36 rabbits in order to deliver a twin-peaked monophasic wave (100 μ s pulse duration, 80 pps, and voltage range 30–60 V). The treated animals received ES for 4 h daily with a threshold current that produced a barely palpable

Figure 3. Various waveforms of pulsed ES that are used in animal studies, including (A) high voltage, (B) monophasic, (C) balanced biphasic, (D) unbalanced biphasic, and (E) biphasic sine wave or alternative current.

contraction. The current polarity was negative for the first 3 days and positive for the remaining 4 days. Although wound closure values were significantly higher in the treated animals than in the control group, histological evidence showed no significant increase in the rate of epithelial cell migration.

Cruz *et al.*³⁹ applied HVPC stimulation (10 min stimulation with 175 V at 60 pps) to full-thickness thermal burns in pigs. The active electrodes with negative polarity were placed on either side of the burn wounds (2 burns in each pig), and a large dispersive electrode was placed over the abdominal skin. Weekly wound contraction rate and fibroblast population showed significant increases in the ES group compared with control animals over the 4-week study.

Leffmann *et al.*⁴⁰ examined wound reduction, epithelial thickness, vascularity, and fibroblast density in rats after microamperage stimulation. Six rats received monophasic rectangular 100 μ A pulses at 0.3 pps at a 50% duty cycle, for 2 h a day for 14 days. On the first 3 days, a negative electrode was placed at the wound site, and then, polarity was reversed. No effects were seen over the 14-day treatment period.

Byl *et al.*⁴¹ examined the effect of a low-voltage pulsed microamperage current (100 μ A, 0.3 pps, 50% duty cycle, each cycle consisting of 3 s on and 3 s off) on wound healing. Four sets of surgical wounds were induced on each pig, and each wound set was covered with a sterile electrode and kept covered for 7 days. Sham treated wounds prepared on the nontreatment side were also kept covered in a similar manner. Positive polarity stimulation was administered for 1 h per day for 5 days. At 7 days post injury, no differences were noted in density, maturity, and deposition of collagen or in the wound size between the sham treatment and ES treatment lesions. The authors suggested insufficient current delivery, low current density, and no preliminary cathodal stimulation as reasons for the lack of acceleration of wound healing. A systemic effect of ES appeared to complicate the comparison of treated wounds and sham wounds when evaluating the effects of ES on the healing process.

Brown *et al.*⁴² examined the effects of HVPC on histological changes in guinea pigs. Two 2.5 cm incision were made on the dorsal aspect of the thoracic area; the left side incision was considered the untreated intra-animal control. The ES protocol was consistent with that used in their previous study.³⁸ They showed a noticeably more advanced epidermal closure in animals after 2 weeks of

treatment and also showed higher scores for dermal closure after 4 weeks. No indication of inflammation was evident in any of the ES or control groups.

The effect of microamperage ES on the fibroblast, neutrophil, and blood vessel numbers in sutured surgical wounds was also investigated in rabbits by Bayat *et al.*,⁴³ who applied ES (200 μ A, 50% duty cycle, and 0.5 pps) for 2 h daily for 3, 6, or 14 sessions in different groups. In all groups, the active polarity was set as negative for the first 3 days, and tissue sampling was done 24 h after the last ES session. Application of ES significantly increased the number of fibroblast cells compared with the sham-treated group, after 6 sessions. Blood vessel counts showed no significant differences in the ES groups.

Mehmandoust *et al.*⁴⁴ compared the effects of anodal and cathodal ES on wound closure in guinea pigs. They used a monophasic PC of 300–600 μ A, 80 pps, and 0.3 ms pulse duration, at 1 h a day for 14 or 21 days. The percent decrease in wound surface area was greater at the 14th and 21st days in both the anodal and cathodal ES groups when compared with the control group. These results indicated that the application of ES, regardless of the applied polarity regimen, could lead to greater and faster decreases in wound surface area.

Cinar *et al.*¹⁰ investigated the exposure of 3 different electric field intensities (10, 1.9, and 0.9 kV/m) on wound healing in 32 mice. Pulsed ES was applied for 20–22 h during 8 consecutive days using the parallel plate exposure system around the polyvinyl chloride cages. The measurements were not numerical, but they suggested that the intensity of 0.9–1.9 kV/m accelerated healing; whereas ES with an intensity of 10 kV/m suppressed the wound healing process.

Effects of DC and PC ES on burn, pressure ulcer, diabetic, and ischemic wounds. Chronic ischemic wounds are a significant healthcare burden worldwide, especially for patients with immobility and vascular impairment. Studying the ability of ES to stimulate the healing rate of ischemic wounds is essential, using appropriate animal models. Morris *et al.*⁴⁵ used the ischemic rabbit ear model to study the effect of square-wave pulsed DC (11 mA amplitude, 40 ms interpulse interval, 5 or 110 μ s pulse duration) on the healing of ischemic wounds. Stimulated wounds showed increased healing activity relative to non-stimulated wounds on the 7th and 14th days after wounding. At the 14th day, ES with 110 μ s pulse duration caused a significant increase in vascular endothelial growth

factor (VEGF) and COL-IV levels compared with 5 μ s pulse duration. Both collagen-I and collagen-V showed statistically significant increased activity between 7th and 14th days with a 110- μ s pulse duration stimulation. Full re-epithelialization of induced wounds by 10 days suggested that this model may not be valid for inducing chronic wounds. However, the increase in VEGF level, as an effective factor for the promotion of angiogenesis, indicated the effectiveness of ES in the improvement of wound healing.

Reger *et al.*⁴⁶ reported changes in surface area and volume of induced pressure ulcers after using DC (current amplitude about 0.7 mA and current density of 30–200 μ A/cm²) and alternating current (AC; 300 μ s pulse duration, 40 Hz, and current density of $1,189 \pm 219$ μ A/cm²) stimulation. Wound contraction occurred more rapidly in stimulated animals than in the controls. No histological changes were noted between the AC and DC stimulated wounds in the early phase of healing. Tissue perfusion was enhanced more by DC than by AC stimulation. A shorter wound area time constant and a higher rate of wound area reduction were noted after DC compared with AC ES. AC stimulation reduced wound volume more than DC.

Castillo *et al.*⁴⁷ applied an ES (positive/negative [biphasic] square wave pulse of 0.04 mA, 67 Hz, and 300 mV) to burns with at least 60–80% of dermis depth in rats and evaluated the healing process by scanning electron microscopy (SEM). ES was delivered immediately after the induced burn and continued for 20 days for 20 min daily. The collagen architecture in the ES group was similar to that of normal skin, but the number of capillaries was significantly higher in the ES group compared with untreated burn and normal groups. The SEM images obtained after 20 days showed that skin only from the ES and normal groups appeared homogeneously similar.

Greenberg *et al.*⁴⁸ evaluated the effect of ES polarity on epithelialization and angiogenesis in burn wounds of pigs. They found that epithelialization began faster in wounds treated by an anode when compared with cathode-treated or control-treated wounds. In addition, prominent neovascularity was seen on day 10 in wounds treated by the cathode compared with anode-treated wounds.

Thawer and Houghton⁴⁹ compared the effect of ES in healing of diabetic and nondiabetic wounds in mice. A 1 cm² full-thickness incision wound was made, and 24 h later, monophasic PC with negative polarity (pulse duration of 200 μ s and pulse frequency of 200 pps) was delivered for a period of 15 min on alternate days to the wound site. The

effect of varying doses of ES (sham, 5, 10, and 12.5 V) on wound healing was assessed on the 16th day after wounding. A significant increase in collagen deposition in the deep dermis was seen in nondiabetic animals at low-dose ES (5 V) and in diabetic animals with higher-dose ES (12.5 V). No significant differences were seen in epidermal thickness or cell counts of superficial and deep layers of dermis after the application of different intensities of ES or for 12.5 V ES on the 2nd, 8th, and 16th days, in either diabetic and nondiabetic animals. On the 16th day, a 12.5 V ES caused a significant increase in the collagen/noncollagen protein ratio in diabetic animals compared with the sham group. The authors suggested that higher doses of ES were required to stimulate collagen deposition in diabetic animals.

Effects of PC ES on mast cells in acute wounds. Increases in mast cell numbers is often observed after wounding, generally around the vessels, and the cell levels return to normal during the wound healing process. The duration of these changes depends on the kind of wound and its status at each healing phase. Reich *et al.*⁵⁰ designed one study to examine the effects of ES on the proliferation of mast cells in acute wounds. They made 80 wounds in 4 pigs (20 wounds in each animal): The wounds of 2 animals were treated using positive monophasic pulsed ES (38 mA, 140 ms pulse duration, and 128 pps), twice a day, for 1.5 h in each treatment session. The number of mast cells was significantly lower in these ES treated wounds than in the control wounds at days 1, 2, and 3. They speculated that this decrease may be related to a reduction in either proliferation or migration of mast cells. Many other studies have also shown a decrease in mast cells after application of ES.^{9,34,45} Positive pulsed ES reduces wound vascularity and may be responsible for mast cell reduction.^{51,52} Keloids and hypertrophic scars, in particular, are often associated with increased numbers of mast cells.⁵³ Surgical flap survival rate is increased in mast cell deficient rats,⁵⁴ indicating that ES may affect scar formation and should be considered in future animal studies. Proposed mechanisms of ES on mast cells in the wound healing process are summarized in Fig. 4.

Effects of preoperative PC ES on wound healing. In all of the animal studies mentioned earlier, ES was used after wounding and continued throughout the healing process. However, Borba *et al.*⁵⁵ revealed a different strategy by which ES with positive polarity was applied before incision.

Figure 4. Proposed mechanisms of ES on mast cells in wound healing process.

They postulated that delivery of positive charges before skin incision could change the bioelectric potential and alter the healing process. In their study, a pulsed monophasic current (frequency of 7.7 pps and 8 mA intensity) was applied for 30 min; then, 2 min after removing electrodes, an incision was made and then sutured. On the seventh day, the number of blood vessels and fibroblasts were greater in the ES group than in the control group. No significant differences were found in the number of lymphocytes, eosinophils, and mast cells at any postoperative day. The stimulated group had a smaller amount of type III collagen on the seventh postoperative day, but no significant changes were noted for type I collagen on the 7th and 14th days. The authors concluded that preoperative ES may promote electrotaxis and attract or repel different cells and tissue proteins at the incision site, but detailed studies are still needed to clarify the mechanism underlying this method for wound healing.

Discussion of findings

Regardless of the kind of wound or the ES current and polarity, most of the evidence from animal studies suggests that the application of ES, especially LIDC and low-intensity PC, can facilitate wound healing.^{8,9,18,35,42,47,49} Table 1 summarizes the animal studies in which ES has been used to assess its effect on wound closure and histological parameters. Positive polarity appears to enhance the migration of epithelial cells and leads to faster closure of the wound (Fig. 5), which can be useful in

preventing bacterial infection.^{18,48,56} Application of the cathode as the active electrode, compared with the anode, can be more effective in attracting fibroblasts to the wound area (Fig. 6) and can give rise to more collagen synthesis,³⁵ although more treatment time is needed for realignment and proper orientation of the collagen fibers. Electrical current may also decrease the duration of the inflammatory phase,^{9,34} thereby facilitating the proliferation phase for the synthesis of collagen and the extracellular matrix. The meta-analysis human studies by Gardner *et al.*⁵⁷ support the idea that ES is an effective adjunct therapy for chronic wound healing. Based on the overall average rates of healing, ES increases the rate of human chronic wound healing by 144% (regardless of the kind or polarity of ES device or the type of chronic wound); however, it is still necessary to investigate the effects of DC stimulation on signaling pathways and signaling molecules in different phases of wound healing process. This step is very important for the clinical application of ES as a therapy to facilitate the healing process, especially in ischemic and chronic ulcers.

Effects of ES on the mechanical strength of wounds

Relevant literature

Assimacopoulos²⁹ used the negative polarity of DC for the healing of incisional wounds of rabbit ears and showed enhancement of wound tensile strength in the ES treated group. Wu *et al.*⁵⁸ studied the effect of DC on the tensile strength of full-thickness incision wounds in rabbits. They made a bilateral incision on the abdomen of 26 rabbits and then sutured the wounds. A positive current was applied through one incision, and a negative current was applied through the contralateral wound. Current intensity, delivered from a 1.5-V battery, ranged from 40 to 400 μ A. They reported that neither the polarity nor the current intensity had any apparent effect on wound tensile strength after 7 days. Unfortunately, no control group was used in this study. Konikoff⁵⁹ continuously delivered 10 μ A current for 7 days with a cathodal electrode to full-thickness wounds in rabbits. The resulting tensile strength was twice as high as in the untreated wounds.

Bigelow⁶⁰ made incisions in dogs and placed electrodes alongside the injury. His results showed an early increase in tensile strength when a week DC field was applied, but at later time points, it was indistinguishable from the no-current control wounds. Smith *et al.*⁶¹ reported that 10 days application of ES increased the tensile strength of treated wounds in healthy and diabetic mice.

Table 1. *Animal studies to investigate the effect of electrical stimulation on wound closure and histological parameters*

Reference	Current type	Wound/Animal	Finding
Carely and Lepley (1962) ²⁸	DC (+ or -), 200–300 μ A	Incision wound/Rabbit	No significant wound healing in anode or cathode
Assimakopoulos (1968) ²⁹	DC (-), 50–100 μ A	Incision wound/Rabbit	Earlier wound closure
Alvarez <i>et al.</i> (1983) ³⁰	DC (+), 50–300 μ A	Incision wound/Pig	Increase of re-epithelialization, rate of healing, and collagen biosynthesis
Steckel <i>et al.</i> (1984) ³¹	DC (-), 10 or 20 μ A	Incision wound/Horse	No difference in wound healing
Stromberg (1988) ³⁶	Unipolar square pulse, (+ or +/ -), 35 mA	Incision wound/Pig	Increase of wound closure with alternating polarity, delay in wound contraction in negative polarity
Brown <i>et al.</i> (1988) ³⁷	HVPC (+), barely palpable contraction	Incision wound/Rabbit	No difference in wound closure, increase of epithelialization, and regular arrangement of collagen fibers
Brown <i>et al.</i> (1989) ³⁸	HVPC (-/ +), barely palpable contraction	Incision wound/Rabbit	Increase of wound closure, faster epithelialization, no difference in epithelial cell migration
Cruz <i>et al.</i> (1989) ³⁹	HVPC (-), 175 V	Thermal burn/Pig	Increase of wound contraction rate and fibroblasts population
Reich <i>et al.</i> (1991) ⁵⁰	Monophasic pulsed ES (+), 38 mA	Punched wound/Pig	Decrease the number of mast cells
Mustoe <i>et al.</i> (1992) ³²	Negative/positive charged particles	Incision wound/Rat	Collagen-rich connective tissue and more fibroblasts with positively charged beads
Leffmann <i>et al.</i> (1994) ⁴⁰	Monophasic pulsed ES (-/ +), 100 μ A	Incision wound/Rat	No effect
Byl <i>et al.</i> (1994) ⁴¹	Low voltage pulsed ES (+), 100 μ A	Thermal burn/Pig	No difference in density and maturity of collagen and wound size
Brown <i>et al.</i> (1995) ⁴²	HVPC (-/ +), 100 μ A	Incision wound/Guinea pig	Higher scores for dermal closure
Castillo <i>et al.</i> (1995) ⁴⁷	Biphasic square pulsed ES (+/ -), 0.04 mA	Induced burn/Rat	Increase the number of capillaries, no difference in collagen architecture
Cansevan and Atalay (1996) ⁸	Direct micro-current 200–400 μ A	Circular skin wound/Rabbit	Increase of hydroxyproline
Tagkan <i>et al.</i> (1997) ⁵	DC (-/ +), 300 μ A	Incision wound/Rat	Decrease of PMN and macrophages, increase of fibroblasts and hydroxyproline
Reger <i>et al.</i> (1999) ⁴⁶	DC, 7 mA, 30–200 μ A/cm ² or AC 1189 $\pm$ μ A/cm ²	Pressure ulcer/Pig	rapidly wound contraction with ES, enhance of tissue perfusion, and wound reduction area in DC, higher wound volume reduction in AC
Greenberg <i>et al.</i> (2000) ⁴⁸	DC (+ or -)	Burn wound/Pig	Faster epithelialization in anodal ES, prominent neovascularity in cathodal ES
Thawer and Houghton (2001) ⁴⁹	Monophasic pulsed ES (-),	Incision wound/diabetic mice	Increase of collagen deposition and collagen/noncollagen protein ratio
Demir <i>et al.</i> (2004) ³⁴	DC (-/ +), 300 μ A	Incision wound/Rat	Decrease of PMN, macrophages and mast cells, increase of fibroblasts, and hydroxyproline
Bayat <i>et al.</i> (2006) ⁴³	PC (-/ +), 200 μ A	Sutured wound/Rabbit	Increase of fibroblasts, no difference in blood vessels
Mehmandoust <i>et al.</i> (2007) ⁴⁴	PC (-/ + or +/ -), 300–600 μ A	Incision wound/Guinea pig	Greater and faster wound surface area
Talebi <i>et al.</i> (2007) ³⁵	DC (+ or -), 600 μ A	Incision wound/Guinea pig	Increase of fibroblasts collagen in cathodal ES, no difference in microvessel number
Talebi <i>et al.</i> (2008) ¹⁸	DC (+ or -), 600 μ A	Incision wound/Guinea pig	Faster wound closure in anodal ES
Cinar <i>et al.</i> (2009) ¹⁰	Pulsed ES, 0.9, 1.9, and 10 kV/m	Triangular incision/Mice	Acceleration of healing in 0.9–1.9 kV/m and suppression in 10 kV/m
Morris <i>et al.</i> (2009) ⁴⁵	Pulsed DC, 11 mA	Ischemic ear model/Rabbit	Increase of VEGF and COL IV and activity of collagen I and V with longer pulse width
Borba <i>et al.</i> (2011) ⁵⁵	Preoperation pulsed ES, 8 mA	Incision wound/Rat	Increase of blood vessels and fibroblasts, decrease of type III collagen, no difference in inflammatory cells

DC, direct current; HVPC, high voltage pulsed current; ES, electrical stimulation; PMN, polymorphonuclear; AC, alternating current; PC, pulsed current; +/ - or -/ +, alternating polarity; VEGF, vascular endothelial growth factor.

Figure 5. Schematic illustration showing the effect of ES on wound closure.

Brown and Gogia⁶² treated full-thickness wounds in rabbits with HVPC: ES was used for 2 h and twice daily until 4 or 7 days after incision. The intensity of stimulation (30–60 V) was adjusted to induce palpable contraction. After 4 days, the tensile strength value showed no significant difference, but the wound failure value at the seventh day was significantly less than in the control group. Brown *et al.*³⁸ re-examined the effects of HVPC on the tensile strength in order to clarify

the role of switching polarity during the wound healing. The current polarity was set as negative for the first 3 days. No significant differences were obtained for the mechanical measurements, although histological evidence showed more collagen synthesis in the dermis of experimental wounds. The authors suggested that the duration of the applied stimulation was insufficient to allow for collagen maturation and increases in tensile strength.

Figure 6. Light micrograph (hematoxylin and eosin, 100 $\times$) of full-thickness wound in guinea pig 7 days after incision: *left*, control; *middle*, cathodal ES; *right*, anodal ES. Cathodal and anodal direct current (DC) ES (sensory intensity) was applied for 1 h per day, every other day, for 7 days. The number of fibroblasts (dark fusiform cells, F) was significantly higher in cathodal ES group compared with control group. (Unpublished data were recorded by author.)

Bach *et al.*⁶³ investigated the effect of AC (sinusoid with sequence 300 Hz, peak value 1 V, and current 100 μ A for 15 min daily from days 2 to 4 after incision) and DC (1 V, 20 μ A, 60 min daily from days 4 to 8 after incision) on healing of a 6-cm-long incision of the dorsum of rats. Both AC and DC stimulation caused significant increases in the collagen content around the incision line, but this increase did not affect the subsequent tensile strength and energy absorption. Mustoe *et al.*³² applied charged particles to incision wounds in rats and showed that, at 10 days after wounding, the maximum load tolerated was 53% greater in wounds treated with positively charged beads than in control wounds. No significant differences in tensile strength were seen in wounds that received negatively charged or uncharged beads when compared with the control group.

Kambic *et al.*⁶⁴ compared the effect of DC and AC on the biomechanical properties in 20 mini-pigs with grade III trochanteric pressure ulcers. ES was applied 9 days after wounding, at 2 h daily, and 5 days per week, and continued until termination of the study 30 days later. For the first time, mechanical testing was performed carefully at a controlled extension rate (150 mm/min), temperature, and gauge length. Stress and the elastic modulus for healing wound samples (that oriented parallel to the current flow) were significantly reduced in the DC, AC, and untreated control wounds than in normal control skin wounds. In another study, the application of a low-voltage pulsed microamperage current did not increase the tensile strength at 7 days post injury.⁴¹ Brown *et al.*⁴² showed a greater peak force to failure and energy absorbed to failure in high voltage treated and untreated contra-animal wounds at either 2 or 4 weeks after incision than in control wounds, but these changes were not statistically significant. HVPC applied to the treated side incision also had a spill-over effect to the opposite side.

Taşkan *et al.*⁹ reported the effectiveness of DC ES on the increase in breaking strength on the 25th day. This significant increment may suggest that at least 3 weeks is necessary for progression of the proliferation phase and for collagen fiber realignment in the wound healing process, and that the role of collagen arrangement is more important than the amount of collagen deposition. Reger *et al.*⁴⁶ determined the effect of AC and DC stimulation on healing and mechanical properties of pressure ulcers created on denervated pig skin. After 3 weeks, the properties of the healing skin were evaluated by a uniaxially loaded tension test. Significant differences were reported for stress and modulus values, but the stiffness values did not

approach that of normal skin. The healed skin stiffness oriented parallel to current flow was nearly half that of the normal control values. No statistically significant differences were obtained from perpendicular sites.

Demir *et al.*³⁴ used DC to show an increase in the wound breaking strength after 25 days. The cross-head speed was 250 mm/min, which is very high for a skin uniaxial tensile test. Bayat *et al.*⁴³ showed that, after 14 sessions of ES, tensile strength increased significantly. Mehmandoust *et al.*⁴⁴ evaluated the biomechanical properties of a full-thickness healed wound after the application of a unidirectional PC. Anodal stimulation for the first 3 days and cathodal stimulation for the remaining days led to stronger tissue repair due to the effectiveness of cathodal stimulation in the proliferative phase and greater proliferation of fibroblasts and collagen deposition in the wound area. In another study, application of the anodal and cathodal DC to full-thickness wounds of guinea pigs did not significantly increase the tensile strength; however, collagen density was significantly greater in the cathodal group than in the control and anodal groups.³⁵

Asadi *et al.*⁶⁵ reported that neither sensory nor motor intensities could improve the biomechanical properties of repaired wounds. They concluded that the mechanical environment induced by sensory and motor intensities of ES could not simulate the role of normal daily stress and strain to promote the maturation of collagen fibers and formation of their cross links. Naeini *et al.*⁶⁶ applied microamperage low-voltage DC (100 μ A, 105 V) on deep and superficial wounds in rats for 14 days. The yield and ultimate tensile strength of the treated wounds showed no significant differences when compared with open and sutured non-treated wounds after 21 days.

Discussion of findings

Wound toleration for incoming daily living forces should be evaluated by considering the effect of ES on the tensile strength as well as fibroblast proliferation, collagen synthesis, and collagen fiber orientation. Most of the evidence confirms that achieving good mechanical strength requires that enough time is passed. The mechanical environment is the most important factor that affects the realignment of newly synthesized collagen fibers. Tensile strength values are quite variable and have not been consistent with augmented collagen deposition. This may indicate that ES, in a short period, may increase the collagen deposition but it has little or no effect on the formation of cross-linking and collagen realignment in a congruous

manner. Collagen fiber alignment is perhaps a later phenomenon, and a longer time interval is needed for the newly synthesized fibers to reorganize. Mustoe pointed to this subject, indicating that a value of 70–80% of normal skin tensile strength in rat wounded skin will be obtained even 3 months after wounding.³²

Unfortunately, most of the studies have not assigned a normal skin group and a separate control group to compare the obtained mechanical properties after using ES. Scientifically designed and well-controlled experimental animal studies are necessary to determine the true effects of ES on wound healing. Further, proper lengths of the skin samples, assessments of deformation rate, accurate calculations of the normalized values (e.g., stress, strain, and elastic modulus [Fig. 7], instead of tensile strength, deformation, and stiffness), and proper direction for skin mechanical tests based on the natural collagen alignment and direction of incision should be considered in future studies. The effect of ES on the mechanical strength of wounds is illustrated in Fig. 8.

Figure 7. A schematic illustration of stress–strain curve to measure the mechanical strength of wound site. Ultimate stress is force/cross-section area, and strain is percent of tissue deformation.

Effects of ES on survival rate and viability of skin grafts, donor sites, and musculocutaneous flaps

Relevant literature

Skin and musculoskeletal flaps are frequently used in reconstructive surgery. Ischemia is the most severe complication of this surgery, as it leads to tissue necrosis and flap failure. Many different drugs and therapeutic methods have been suggested for diminishing this complication. Several animal studies have investigated the effects of ES on the viability of skin grafts and of skin and musculocutaneous flaps.

Kjartansson *et al.*⁶⁷ investigated the effect of segmental and extrasegmental transcutaneous electrical nerve stimulation (monophasic PC) with a different frequency and amplitude on survival of the dorsal musculocutaneous flap in rat. They raised the flaps (2 cm × 7 cm) from the deep fascia of the muscles and then sutured these back into position. ES was delivered as monophasic PC with a 0.2 ms pulse duration, a frequency of 80 or 2 pps, and an intensity of 20 or 5 mA. In the segmental mode, ES was delivered to the base of the flap; in the extrasegmental method, ES was delivered at the base of the animal's tail. Preoperative ES did not increase flap survival area when compared with the untreated control group. The highest flap survival was obtained with repeated segmental ES applied postoperatively with a high intensity. The authors showed that flap survival was not related to the frequency used.

In another study, Kjartansson *et al.*⁶⁸ compared the effect of transcutaneous electrical nerve stimulation (monophasic PC) and calcitonin gene-related peptide (CGRP) on the blood flow in the musculocutaneous flap of rats. A musculocutaneous flap (2 cm × 7 cm) from the deep fascia was raised, and blood flow was measured before, during application, and 20 h postoperatively using a laser Doppler flowmeter. Monophasic square wave pulses (80 pps with 0.2 ms pulse duration and high intensity, 20 mA) were delivered to the base of the flap on postoperative days 1, 2, and 4. ES induced a gradual increase in blood flow from day 1 to day 4 that was started 10–15 mm after commencement. ES (high intensity, high frequency, and segmental at the base of the flap) and CGRP (given locally via dorsal central vein) increased the blood flow in the rat musculocutaneous flap.

Politis *et al.*⁶⁹ used exogenous DC to promote the survival of total-thickness skin grafts in rats. After having removed a 2 cm × 2 cm graft of full thickness of skin and reattaching it to its original site, DC

Figure 8. Schematic illustration shows the effect of ES on the mechanical strength of wounds.

was delivered using an anode or cathode above the graft. Current delivery ($405\ \mu\text{A}$) was discontinued on postoperative day 4. Quantitative assessment at postoperative day 7 showed 80–90% of skin necrosis in the animals treated with the cathode or with no current. In animals treated with the anode, skin necrosis was about 50%, and the dermis contained more cell-lined hair follicles and dermal glands. The maximal and mean dermal thickness was also greater in the anode group. In this research, the most efficacious results were obtained when the anodal electrode was placed on the top of the skin.

Im *et al.*⁷⁰ used ES on bipedicle skin flaps ($4\text{ cm} \times 20\text{ cm}$) that were created bilaterally on the flanks of 12 pigs and sutured back into position at their donor sites. The ischemic central portion of the flaps was treated using monophasic pulsed ES (35 mA and 128 pps) with negative stimulation at 0.5–2.5 h after operation for 9 days. In 3 animals, ES was applied 30 min twice daily and in 4 animals, on the first day, only one session was used. In the first and third 3 days, negative polarity was applied to the flap and for the next 3 days, positive polarity was used. 50% of the flaps in the stimulated group demonstrated significant improvement, as the necrosis area in these animals was significantly reduced to an average of 13.2%. Animals that received only one session on the first day demonstrated a lower skin-flap survival rate than did animals which received two sessions, at 19% and

92%, respectively. The authors suggested that chemical reactions elicited by the electrodes may be a primary stimulus for the tissue response, and the beneficial effect of ES may be related to that early response to stimulation.

Niina *et al.*⁷¹ compared the effects of electroacupuncture (EA) and ES on the surviving areas and blood flow in musculocutaneous flaps in rats. Each flap was raised from the muscles and then sutured in a donor site. In EA and ES groups, the different combinations of intensity and frequency (20, 10, or 2 mA with 2 or 80 Hz) were used. In the EA group, 2 acupuncture needles were inserted at the base of the flap and in the ES group, surface electrodes were used. Stimulation was delivered for 1 h just after surgery and on the next 2 days, with a pulse duration of 0.2 ms. The EA treatment did not increase the survival area in the flaps, but the ES group showed significant increases in the surviving flap area compared with the control group, and blood flow in the periphery was significantly higher than at the base. The increase in the surviving area after the ES treatment was not related to the intensity or frequency of the stimulus, whereas high-frequency stimulation tended to increase the flap survival. Since ES stimulates an area, while EA stimulates only a point, the authors suggested that the survival of the flap might depend on the number of sensory nerve fibers that are stimulated.

Liebano *et al.*⁷² investigated the effect of high-frequency ES with a different intensity on the viability of skin flap in rats. In 75 rats, skin flaps (measured 10 cm × 4 cm) were elevated through the deep fascia, and a plastic barrier was interposed between the flap and donor site and sutured. The base of the flap was stimulated by high-frequency ES (symmetrical biphasic pulses with 200 μ s pulse duration and 80 Hz frequency) with different intensities in 5 groups composed of 0 mA (sham), 5, 10, 15, and 20 mA. ES was applied 1 h after the operation and repeated on the next 2 days. The percentage of skin flap necrosis area showed a significant decrease for the 15 mA treatment compared with the sham group. In this study, no significant differences were reported between the other groups. The differences in the operation and treatment procedures (especially the existence of a barrier between the flap and donor site) was considered by the authors to account for the observed differences from the work of Kjartansson *et al.*,⁶⁷ who observed better results for viability of the flaps with 20 mA treatments compared with 5 mA treatments. Liebano *et al.*⁷² did not analyze the results between treatment groups (ES groups with different intensity),

but no consistent changes were noted in response to different intensities.

Russo *et al.*⁷³ investigated the ability of ES to reduce necrosis in random skin flaps in rats treated with nicotine. Sixteen rats were given nicotine (102 mg/kg per day) subcutaneously 7 days before the surgical procedure. A flap (10 cm × 4 cm) was raised on the back of the animal and sutured back in position after the interposition of a plastic film between the flap and the donor site. Immediately after surgery and on the 2 next days, ES (biphasic, rectangular, and symmetric pulses with a 200 μ s pulse duration, a frequency of 80 Hz at intensity in sensory level) was applied for 1 h to the base of the flap. The mean percentage of flap necrosis in the ES group was 21%, which was significantly lower than in the sham ES group (45%). The authors suggested that ES improves the blood flow and increases the flap viability in nicotine-treated rats.

Uema *et al.*⁷⁴ evaluated the effect of EA to increase skin flap survival in rats. In 40 rats, a skin flap (10 cm × 4 cm) was raised through the deep fascia, and a plastic barrier was placed between the flap and donor site. Ten of the rats received 20 min EA (2 Hz, asymmetrical spike-wave, and 50 mA) on acupoints of DU-14, DU-2, and Liv-13 for 8 days

Figure 9. Effective elements to increase the blood flow and flap viability after the application of ES. Release of some vasodilating neuropeptides such as substance P (SP) calcitonin gene-related peptide (CGRP), and vasoactive intestinal polypeptide (VIP), or the release of opioids, especially after low-frequency ES may be effective to increase blood flow and flap viability. In addition, muscle pumping may increase blood flow when stimulation is performed at the motor level.

after surgery. EA resulted in the greatest percentage of survival and the lowest rate of necrosis compared with the other groups. These differences were significant compared with the control and anesthetized sham groups. The authors suggested that EA is an efficient method for preserving the viability and decreasing skin flap necrosis.

Based on the findings of the effectiveness of low frequencies of ES at increasing blood flow,⁷⁵ Liebano *et al.*⁷⁶ evaluated the effect of low-frequency ES (2Hz) on the viability of ischemic skin flaps in rat. The procedures and groups were designed similar to the previously described work of these authors⁷² that was done using high-frequency ES. ES was applied for 1 h per day for 3 subsequent days with different intensities (0, 5, 10, 15, and 20 mA) in 5 groups. The application of ES at 15 mA intensity resulted in a significant decrease in the percentage of necrosis compared with sham (control) group. No significant differences were noted among the ES groups. The authors suggested that low-frequency ES may increase opioids, and this may explain the increase of flap viability.

Discussion of findings

Some hypotheses have been proposed to explain the mechanism by which electrical current increases skin blood flow. Stimulation of large mechanosensitive fibers and inhibition of the sympathetic vasoconstrictor neurons,^{77,78} alteration of sympathetic vasomotor activity,⁷⁹ liberation of some vasodilating neuropeptides such as the substance P, CGRP, and vasoactive intestinal polypeptide,^{68,80} or the release of opioids, especially after low-frequency ES⁷⁷ may be effective to increase blood flow and flap viability. The effect of muscle pumping to increase blood flow when stimulation is performed at the motor level was suggested as a mechanism underlying this effect. Higher VEGF expression has been reported after the application of ES,^{5,7,45} suggesting that ES may up-regulate genes that are responsible for angiogenesis during wound healing.

The evidence cited from animal studies suggests that ES improves the survival of skin and musculocutaneous flaps; the critical ES parameters, especially frequency and amplitude, are not yet clear. Clinical studies are still needed to substantiate the findings derived from animal experiments. Effective elements of ES on the

TAKE-HOME MESSAGES

Basic science advances

- The skin possesses endogenous electrical potentials that change during the wound healing process.
- Exogenous DC appears to promote the directional migration of cells and signaling molecules via electrotaxis.
- Exogenous DC with positive polarity accelerates wound epithelialization and leads to faster wound closure. Negative polarity increases the synthesis of collagen fibers.
- Skin mechanical strength is quite variable and is not consistent with ES-augmented collagen deposition.
- Inhibition of the sympathetic vasoconstriction and liberation of vasodilating neuropeptides may increase the survival rate of musculocutaneous flaps.
- No direct relationship is evident between an increase in the intensity of ES and its benefit on the healing process.

Clinical science advances

- Exogenous ES is a non-pharmacological biophysical energy that may help specialists facilitate healing rate, to decrease ischemia and necrosis, and to prevent wound chronicity.
- Bio-electric dressings may offer a novel approach to improve wound healing without using additional devices.

Relevance to clinical care

- ES was approved by the Center for Medicare and Medicine Services for the treatment of some chronic wounds.
- Animal experimental evidence suggests the efficacy of LIDC and low-intensity PC on promoting and accelerating wound healing.
- Multidisciplinary *in vitro* and animal experimental studies are needed to elucidate the potential clinical implications of this therapeutic, biophysical energy.

increase of blood flow and flap viability are illustrated in Fig. 9.

CONCLUSION

Exogenous ES has been shown to benefit tissue repair in a variety of wound types. Regardless of the kind of ES, application of ES—especially continuous LIDC and monophasic PC—can facilitate wound healing.⁸¹ However, the tensile strength values are quite variable and are not consistent with augmented collagen deposition. This may indicate that ES, over the short term, may increase collagen deposition, but it has little or no effect on the formation of cross-linking and collagen realignment in a congruous manner. The evidence suggests that ES improves the survival of skin and musculocutaneous flaps, but variations in study designs, administration, and parameters render its application in clinical practice somewhat impractical at present. Bio-electric dressing⁸² would

represent an easy method for the delivery of ES to a wound area, and this may facilitate the clinical use of ES for wound healing. However, randomized clinical trials are required to elucidate the potential clinical implications of this treatment modality.

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The author has no competing interests. No ghostwriters were used to write this article.

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