

# Electrical Stimulation for Chronic Wound Treatment: Basic Principles and Current Clinical Position

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## ABSTRACT

Healing of chronic wounds is an ongoing challenge for clinicians and a worldwide issue in healthcare systems. Several issues have necessitated the development of alternative and non-medication techniques for chronic wound treatment. Electrical stimulation (ES) or electrical therapy (ET) is one of these techniques with promising outcomes. Several devices have been commercialized for wound treatment; however, studies to find more efficient treatment are ongoing. The present study aims to review the recent advances in wound treatment using ES. The basic principles of the technique, its main mechanism of actions, and the current clinical status of ES treatment in wound healing are discussed. The databases of PubMed, web of science, Cochrane central library, Embase, Google scholar, and additional databases were searched using the set terms of electrical stimulation or electrical therapy and wound treatment. The clinical trials studies on any types of wound were selected for full review.

**KEYWORDS** electrical current, electrical stimulation, electrical field, chronic wound, treatment chronic wound, clinical trials

## INTRODUCTION

Chronic wounds are serious problem to patients and healthcare professionals, affecting about 5.7–6.5 million individuals worldwide and a great cost was estimated annually. Researchers have begun to examine the influence of several therapeutic approaches designed to accelerate wound healing, including the use of antiseptics, antibiotics growth factors, pressurized oxygen, biologically engineered skin substitutes, and physical therapy modalities such as electrical stimulation (ES)<sup>1,2</sup>. Different forms of ES have been long term used to heal complicated wounds that have been used for decades, improve flap and graft survival, improve surgery outcomes and also ES has been recommended to reduce infection, improve cellular immunity increase perfusion, and accelerate wound healing<sup>3,4</sup>. Different mechanism of actions have been proposed for the wound healing enhancement of ES including enhancement of the migration of lymphocytes<sup>5</sup>, fibroblasts<sup>6–8</sup>, macrophages<sup>9</sup> and keratinocytes<sup>10</sup> and improving blood flow oxygen concentration around the wound<sup>11–13</sup>, and wound tensile

strength stimulating protein<sup>14,15</sup> and synthesis DNA reduce<sup>7,14–17</sup>, helps to reduce edema<sup>18</sup> and inhibits bacterial growth<sup>19,20</sup>. The study was aimed to review the current position of ES in chronic wound healing and to establish the effects of ES therapy as a treatment of chronic wound healing. Wound healing is a complex soft tissue repairing process. Although several new medications are introduced each year, chronic wounds have still remained as significant morbidity and mortality worldwide<sup>21</sup>. The use of electric current and electromagnetic fields (EMFs) stimulation for enhancing wound healing is not a new approach and the first line of scientific applications of these external current and fields dated back to late 1960s<sup>22</sup>.

## Chronic wounds and electromagnetic characteristic

Human soft tissues particularly skin possess unique electrical and magnetic characteristics. In the healthy skin a difference in ionic concentrations is actively maintained between the upper and lower epidermal layers under a dynamic balance of electrical charges and fields. This different ionic distribution can be measured as a difference of electrical potentials, ranging between 10 and 60 mV on different locations in the body surface. This charge difference is called epidermal battery where its positive terminal is located on the inside surface of the living layer of the epidermis<sup>23</sup>. Following the occurrence of a wound or injury where the skin layers are interrupted, the epidermal battery at the wound site is short-circuited, creating a conducting pathway that permits ionic current to move through the sub-epidermal region out of the

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wound and returns to the battery by flowing through the region between the dermis and the living layer. This current which is the injury specific can flow as long as wound surface is moist. The active role of endogenous electrical phenomena in wound healing is indirectly confirmed by the observations reporting that the healing process in the wounds whose surface remains wet is more efficient than those wounds with dry surfaces. Modeling of wound edge has shown relatively fast lateral voltage gradient across the edge indicating that the cells on the wound edge are under an electric field<sup>24</sup>. Electric fields with the magnitudes of 100–200 mV/mm are existed lateral to wounds in mammalian epidermis. Endogenous wound-induced electric fields present in the cornea plays role in the healing process by helping guide the cellular movements that close wounds.

A chronic wound does not heal in an orderly set of stages and in a diagnostic time the way most wounds do; wounds that do not heal within 3 months are often considered chronic. Chronic wounds seem to be detained in one or more of the phases of wound healing. For example, chronic wounds often remain in the inflammatory stage for too long<sup>25,26</sup>. There are many common types of chronic wounds. These common wounds have different characteristics. Some types of chronic wounds are very painful while others are not. These wounds include venous stasis ulcers, arterial ulcers, diabetic ulcers, pressure ulcers, traumatic ulcers, post-surgical wounds.

### Types of electrical stimulation

Different modes of electrical current and electrode montage have been used for treatment of soft tissue injuries and also wound, including direct current (DC), alternating current (AC), high-voltage pulsed current (HVPC),

and low-intensity direct current (LIDC). Physicians are probably most familiar with pulsed electromagnetic field (PEMF) for the repair of fracture non-unions and transcutaneous electrical nerve stimulation (TENS) for pain control<sup>22,23</sup>. Frequency rhythmic electrical modulation systems (FREMS) is a form of transcutaneous electrotherapy using ES that automatically varies in terms of pulse, frequency, duration, and voltage (Fig. 1).

### Electrodes montage and position

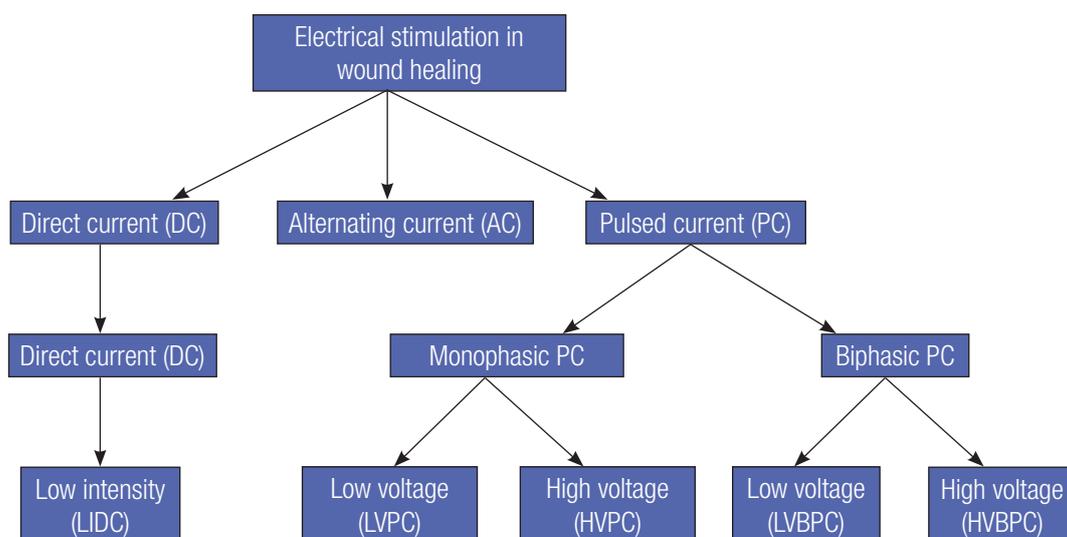
Electrodes build an electrical circuit that delivers electrical energy, with controllable dosage, into the wound tissues. The therapeutic effects of electrical current have been reportedly dependent on stimulation parameters, types of tissues, and positioning and shape of the electrodes. There are two main types of electrodes placement on the wound including direct and indirect electrode placement<sup>27</sup>:

1-Direct placement: a treatment electrode of the selected polarity placed in direct contact with the wound and the return electrode placed on intact peri-wound skin (Fig. 2B).

2-Indirect placement: one lead wire is split into two electrodes of the same polarity placed at the two opposite margins of wound on intact peri-wound skin with the return electrode of opposite polarity on intact skin (Fig. 2A).

### Endogenous electromagnetic characteristics of soft tissue

The first line of studies with scientific design and methodology on the use of direct electric current for the wound treatment has been reported late 1960s<sup>16</sup>. The first study of this kind was conducted on three patients with



**Fig. 1** The main types of electrical stimulation used in wound healing. Direct current (DC), defined as current that flows continuously for 1 s or longer; alternating current (AC) and pulsed current are the main forms of electrical stimulation. Pulsed current is the most common form of stimulation used for wound healing.

leg ulcers who were stimulated with negative polarity direct current of 0.1 mA. The field direction is a function of position. Beneath the epidermis, the field polarity has the negative pole at the wound center, and above the epidermis, the wound current is flowing in the opposite direction so that the positive pole is at the wound. In normal, there is a difference in ionic assembly between the upper and lower epidermal layer in unharmed human skin, which can be measured as a difference of electrical potentials (10–60 mV). The inside surface of the living layer of the epidermis is positive terminal<sup>28</sup>.

In this regard, externally applied electrical fields with the intensities in the order of such endogenous fields, known as physiological intensities, is expected to alter orientation, migration, and proliferation of the exposed cells such as fibroblasts and keratinocytes<sup>29</sup> that are of pivotal elements in the healing process<sup>10,30–32</sup>. Several studies have shown that externally induced electrical fields with physical parameters comparable with the endogenous electrical characteristics, positive electrode on the surface of wound, and negative on the healthy skin around the wound, can enhance the wound healing process. Electrical currents ranging 0.2 mA to 1 mA have been mostly used intensities for wound healing. The negative electrode has shown antimicrobial effects, which in turn can enhance the wound healing<sup>33,34</sup>. After wounding, injured tissues produce significant electric fields and currents that play important roles in triggering and enhancing the healing process through initiating division, augmentation, and directional migration of cells into the wound<sup>35</sup>. Immediately following a wound, transepithelial potential generates an electric field which is the wound specific. This electric field directs and forces charges in the form of current to flow out the wound and passes through a low resistance pathway. This migration which is driven by wound specific electric field is known as galvanotaxis and

has been studied extensively in human keratinocytes and mammalian corneal epithelial cells<sup>10,36</sup>.

### Antibacterial effects

Bacterial growth in wound tissue is often a considerable factor that contributes to delayed healing or failure to heal<sup>37</sup>. Bacteria are a strong source of inflammatory stimuli over a prolonged period, resulting in chronic inflammation and chronic wound for this reason, resolution of any bacterial imbalance is considered to be a basic process to the healing of chronic wound<sup>38</sup>. The type of ES, its polarity, and the intensity of the current play an effective role in the establishment of antibacterial effects. Both direct current (DC) and high voltage pulse current are more effective at inhibiting bacterial growth than other types of ES (Fig. 3)<sup>39</sup>. The negative electrode placed on wound surface has reportedly antimicrobial effects that are beneficial effects for wound healing particularly during the initial stages of wound development<sup>33,34</sup>.

### Direct and indirect effects of ES

Several *in vitro* and *in vivo* studies have suggested that plasma transmembrane potential is related to the cell cycle processes. Low transmembrane potential facilitates cell proliferation, while high potential tends to inhibit it. Transmembrane potential of microbes differs from other cells, such as fibroblasts. Therefore, different characteristics of the membrane of microbes might be responsible for inhibition of microbe proliferation by ES<sup>40</sup>. The main mechanism of actions of these studies have been reported as enhancing skin blood flow, migration of cells in and around the wound, and altering PH of the wound tissue. It is suggested that plasma transmembrane potential is related to the cell cycle processes. Low transmembrane potential facilitates cell proliferation, while high potential tends to inhibit it. Transmembrane potential of microbes differs from other cells, such as fibroblasts. Thus, different characteristics of the membrane of microbes might be responsible for inhibition of microbe proliferation by ES<sup>41</sup>.

Several hypotheses have been proposed as the underpinning mechanism of actions of ES in wound treatment. One hypothesis proposed that the lateral electrophoresis and local clustering of membrane ion channels such as calcium channels increase local fluxes of ions, possibly inducing the cell to form local lamellipodia. Changes in actin stress fibers and microtubules can alter the cell shape and orientation<sup>42,43</sup>. The direct current induced migration depends on the variations of intracellular  $Ca^{2+}$  concentration and induction of alterations of membrane potential<sup>44,45</sup>. It should be noted that the endogenous electric and magnetic characteristics of target tissue are important factors influencing the outcomes of ES in wound treatment<sup>46,47</sup>.

The main limitation for a systematic review of these studies is the high level of heterogeneity and variance

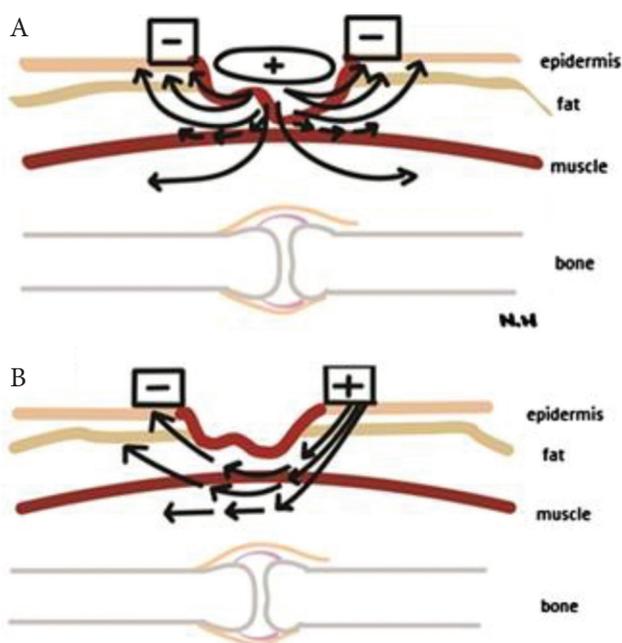


Fig. 2 Direct and indirect placement of electrodes (adopted from ref (27)).

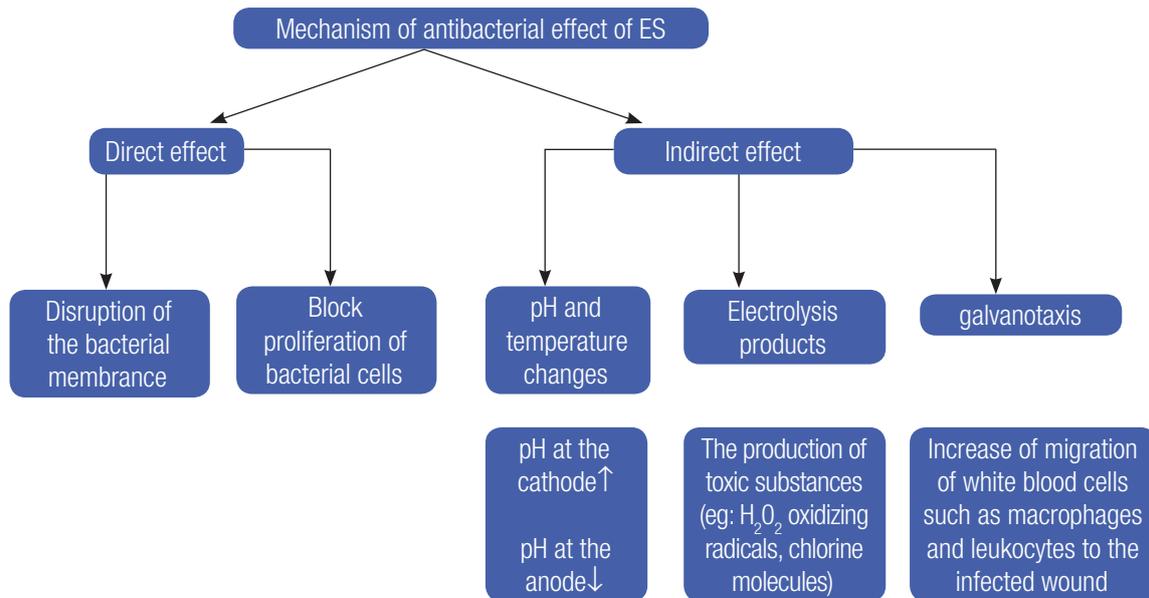


Fig. 3 A schematic diagram of direct and indirect effects of ES on microorganism growth.

in the study methodology and the stimulation parameters including the electrode montage, current intensity, treatment period, type of current, and type of wounds. These variances make it difficult to reach an unbiased conclusion regarding the efficacy of the electric stimulation for wound healing. However, the findings of the reviewed studies indicate the therapeutic efficacy of electric stimulation for enhancing wound treatment. Although the U.S. FDA has not approved any ES devices for the skin wound healing, findings of preclinical and clinical studies demonstrated efficacy of this technique. Furthermore, several clinical trials have reported the therapeutic efficacy of several ES based devices as alternative or adjunctive treatment for some types of chronic wounds.

## CONCLUSIONS

ES techniques have shown promising outcomes in chronic wound healing. ES is a simple and safe intervention to improve surgical wound healing. Induction of lateral electrophoresis and local clustering of membrane ion channels such as calcium channels are among the main biological interactions of ES and cells. Furthermore, different parameters influence the therapeutic performance of ET and EMFT including electrical intrinsic properties of living organs as well as physical parameters of stimulations. For further development of ES techniques for wound healing, developing quantitative objective assessments of wound healing process as well as conducting controlled dose-response studies are necessary. In this regard, multi-center and randomized clinical trials with larger sample size play an pivotal role in developing this technique for clinical applications as well as to understand the mechanism of action of ES in wound healing to define an exact dose-response relation.

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