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Bioelectrochemistry and Bioenergetics 43 (1997) 265–270

BIOELECTROCHEMISTRY AND BIOENERGETICS

DC electrical stimulation for chronic wound healing enhancement. Part 1. Clinical study and determination of electrical field distribution in the numerical wound model

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Abstract

Notwithstanding several past clinical studies demonstrating the beneficial impact of electrical stimulation with steady direct current on the healing of chronic cutaneous wounds, the basic mechanisms underlying its effects on regenerative processes remain to be elucidated and the stimulation regime optimized. In the present study, an attempt is made towards the optimization of steady direct current stimulation of wound healing with respect to the shape and positioning of stimulation electrodes. The effects of direct current stimulation on wound healing were studied in a double-blind clinical trial involving fifty patients with spinal cord injuries, suffering from pressure ulcers. The therapeutic effect of electrical stimulation was found to depend on the positioning and shape of the electrodes. Healing of pressure ulcers was significantly enhanced by direct current, with the positive stimulation electrode overlaying the wound surface and the negative electrode placed on intact skin around the wound. By contrast, stimulation by the second type of electrode configuration – which assumed positioning of both stimulation electrodes on intact skin at the opposite sides of the wound – had only a non-significant effect on pressure ulcer healing. Numerical modelling showed that direct current stimulation using two types of electrode arrangements induced different electric field distributions in the stimulated tissue in the wound area. Endogenous electric conditions in the skin were closely approached with external electrical stimulation when the wound surface was covered with the positive stimulation electrode, while the negative electrode surrounded the wound. With such stimulation, highly significant acceleration of wound healing was observed in the clinical study, leading to the assumption that endogenous electrical phenomena in injured skin are not just side effects, but play an active role in healing. The agreement of the externally induced electric field with the endogenous electric field distribution in injured skin was adopted as the basis for optimization of direct current electrical stimulation for wound healing enhancement. © 1997 Elsevier Science S.A.

Keywords: Electrical stimulation; Direct current; Wound healing; Numerical modelling; Electric field distribution

1. Introduction

Skin injury represents a menace for the organism's integrity, in response to which in an otherwise healthy organism an elegant, harmonized cascade of processes is started, leading to healing of the wound. Biological processes such as inflammation, proliferation, angiogenesis, wound contraction, epithelization – lead to the scar formation [1]. Certain systemic diseases, such as injuries of the nervous system, metabolic and ageing problems, however, significantly increase the probability of wound formation and disadvantageously influence the healing process. The course of events, which normally lead to healing, is in these cases slower or even does not progress, thus leading to chronic wound formation. Such wounds represent a vast energetic demand for the organism, constant threat of infection, undesired interaction with the patient's every-day life, hindrance for the normal course of rehabilitation, and also a financial burden for society.

The problem of chronic wound healing therefore has not lost its actuality in spite of centuries-lasting research, the goal of which, on the one hand, is to elucidate the healing process per se, and on the other to find therapeutic methods for enhancement of healing. In this sense, electrical phenomena linked with wound healing can be considered through two approaches:

– study of the endogenous electrical properties of the

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PII S0302-4598(96)05192-6

injured skin and their significance in the wound healing process, and

– application of exogenous sources of electrical currents for therapeutic purposes, i.e. for chronic wound healing enhancement.

1.1. Endogenous electrical properties of the skin

In normal, uninjured human skin, a difference in ionic concentrations is actively maintained between the upper and lower epidermal layer, which can be measured as a difference of electrical potentials, ranging between 10 and 60 mV on different locations on the body surface. The positive terminal of this so-called epidermal battery is located on the inside surface of the living layer of the epidermis [2]. After wounding, when the skin layers are interrupted, the epidermal battery at the wound site is short-circuited, producing a conducting path which allows ionic current to flow through the subepidermal region, out of the wound and return to the battery by flowing through the region between the stratum corneum and the living layer [3,4]. The injury current can only flow as long as the wound surface is moist. Drying of the wound leads to appearance of a layer with very high resistivity and thus cessation of the ionic current [2].

The measurements have shown that the injured tissue is characterized by a higher potential compared with the surrounding intact skin [5]. The transepithelial potential is low at the wound and increases with the distance from the wound, reaching the value which is normal for the unwounded skin at the distance of a few millimetres [2]. The wound edge is thus characterized by a relatively steep lateral voltage gradient which means that the cells on the wound edge are situated in an electric field. Physiological meaning of these lateral fields is not completely known, but they are believed to play a role in the healing process by helping guide the cellular movements that close wounds [2]. It has been shown that electrical fields of such 'physiological' intensities can affect orientation, migration and proliferation of cells, which are of key importance for healing, such as fibroblasts and keratinocytes [6,7].

1.2. Application of externally applied electric fields for enhancement of chronic wound healing

Endogenous electrical skin phenomena exert a steady direct character, therefore out of the various types of electrical and electromagnetic stimulation which were examined for their wound healing promotion capacity [8], this article will focus on stimulation with constant direct currents.

The first report on the use of direct electric current for stimulation of wound healing was published in 1968 [9]. It dealt with only three patients with leg ulcers, who were stimulated with negative polarity direct current of 0.1 mA. This study was followed by several studies in which the polarity of the stimulation electrode on the wound was changed during the course of healing [10–13]. In these studies, the stimulation program was always started with the application of the negative electrode to the wound due to its assumed antimicrobial effect. Thereafter the polarity was reversed and the application of the positive electrode to the wound was supposed to lead to accelerated healing. The amplitude of the stimulation current was up to 1 mA. The regime of polarity changes was repeated whenever the plateau in healing was observed. The beneficial effects of weak constant direct current stimulation on wound healing were reported in all the above mentioned studies, yet the explanation for the study protocol with electrode polarity changes was not given.

Stimulation with weak direct electric currents does not provoke any easily identifiable reactions in the tissue which could be used as a basis for selection of optimal parameters and regime of stimulation. Ignorance regarding the basic mechanisms of the effects of external electrical signals at the cellular level, however, renders this task still more difficult.

The primary aim of our study was to make a step towards optimization of the constant direct current stimulation regime for wound healing enhancement. The principal question arising certainly relates to the optimization criterion. Being aware of endogenous electrical properties of the injured skin and assuming that they are beneficial and necessary for the normal course of healing, the possibility is given for using them for determination of therapeutic electrical stimulation parameters.

In our clinical study, which involved a uniform population of spinal cord injured patients with pressure ulcers, electrical stimulation was delivered through surface electrodes. Two different electrode configurations were used, which clearly induced significantly different electric field distributions in the stimulated wound area. We studied the effect of DC electrical stimulation on healing of pressure ulcers and the differences ensuing from different electrodes arrangements.

We further built a three-dimensional anatomically-founded model of the cutaneous wound, taking into account different tissue types constituting the skin layers. It was used for determination of electric field distribution in the wound area, resulting from DC electrical stimulation, as well as for determination of electric conditions induced by endogenous epidermal battery.

From the comparability of externally induced electrical fields with endogenous electrical conditions and the clinical results obtained, an attempt was made to derive a criterion for optimization of DC electrical stimulation for wound healing enhancement.

2. Materials and methods

2.1. Clinical study

The clinical study was conducted in the double blind manner. Fifty hospitalized patients with spinal cord injuries having pressure ulcers participated. All patients received equal conventional treatment of their ulcers (daily cleaning and dry gauze dressing exchanges). Stimulation electrodes were applied for two hours daily in all patients. They were divided into three groups with regard to electrode placement and applied electrical stimulation.

In the first group of patients (DC +, $N = 16$), the positive stimulation electrode overlaid the ulcer. The ulcer surface was covered with sterile gauze, soaked in physiological solution, on top of which a conducting rubber electrode was applied. This assured uniform current distribution throughout the entire wound area. Four self-adhesive electrodes (Encore TM Plus, Axelgaard Manufacturing Co., Ltd.) were attached to the intact skin around the wound, representing the ring-shaped negative electrode. The electrical stimulation programme consisted of 2 hours application of constant direct electric current of 0.6 mA.

The second group of patients (DC + / −, $N = 18$) received the same electrical stimulation programme, but the electrode placement was different. Two self-adhesive electrodes were positioned on the healthy skin at the ulcer edge across the wound, one of them being positive and the other negative. This type of electrode arrangement was used in our previous study for the application of pulsed currents, which proved beneficial for wound healing acceleration [14].

In the third group of patients (SHAM, $N = 16$), the electrodes were also applied to the intact skin on both sides of the wound for two hours daily and connected to the stimulators, in which, however, the power source was disconnected and they delivered no current.

The double blind study protocol could be conducted since the weak constant direct current of 0.6 mA cannot be felt even on a normally innervated skin, so neither the patients nor the therapists were aware of the deactivated stimulators in the third group of patients.

Healing was evaluated using weekly measurements of the ulcer area. The parameter "relative healing rate" θ was calculated for each wound after the respective ulcer area time plot was fitted by an exponential curve and described by the equation $S(t) = S_0 \exp(-t.\theta)$, where $S(t)$ is the ulcer area at time t and S_0 the initial ulcer area [15]. Student's t-test was applied to test the hypotheses regarding the equality of average relative healing rate in the SHAM group with average relative healing rates in DC + and DC + / − groups.

2.2. The cutaneous wound model

Skin is composed of two layers: epidermis and dermis. Epidermis is the upper, protective layer, while dermis provides strength and elasticity. The epidermal layer is relatively thin (0.006–0.8 mm), while the dermis is approximately seven times thicker. Below the dermal layer lies the subcutis, and deeper down the fat layer, reaching down to the muscle tissue. A three dimensional finite element model of the wound and its surroundings was built using MSC/EMAS and MSC/XL Electro-Magnetic Analysis System software packages [16–18]. The wound and the surrounding tissue were modelled as a cylinder with the spherically shaped cut-out representing the wound. The model consisted of five layers of homogenous, isotropic materials representing layers of skin and subcutaneous tissue: epidermis, dermis, subcutis, fat and muscle. A detailed description of the model with respect to geometry definition, tissue characteristics and determination of boundary conditions is given in Part 2 of this series [20].

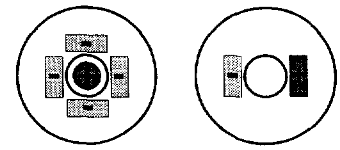

Fig. 1. DC + (left) and DC + / − (right) electrode arrangements studied for their effect on electric field distribution in the wound model.

The model was first used for the study of endogenous electrical skin phenomena. The electric field was determined, which arises as a result of setting the potential difference of 30 mV between the top and bottom of the epidermal layer. In our model in this case the potential of 0 V was placed on the surface of uninjured skin in the wound surroundings (top of epidermis) and the potential of 30 mV on the boundary between epidermal and dermal layers.

The numerical model was further employed for studying the effects of different arrangements and shapes of surface stimulation electrodes which were used in the clinical study on electric field configuration in the model. The computations were obtained using the same model with different boundary conditions. They are shown in top view in Fig. 1. In the DC + case, the potential difference of 66 mV was set between the positive circular electrode (diameter of 30 mm) covering the wound surface and four rectangular negative electrodes (60 mm × 25 mm) on intact skin in the wound surroundings, in order to obtain the total current of 0.6 mA as used in the clinical study. The DC + / − assumed two rectangular surface electrodes (60 mm × 25 mm) of opposite polarity placed on the intact skin symmetrically on opposite sides of the wound. In this case a total current of 0.6 mA was obtained by setting the

Table 1
Results of the clinical study

Group	Number of cases	Initial ulcer area [a] (mm^2)	Relative healing rate θ [a] (% per day)
DC +	16	1332 ± 285	7.4 ± 1.6
DC + / −	18	1078 ± 272	4.8 ± 1.5
SHAM	16	1111 ± 291	4.2 ± 1.1

[a] Mean ± S.E.

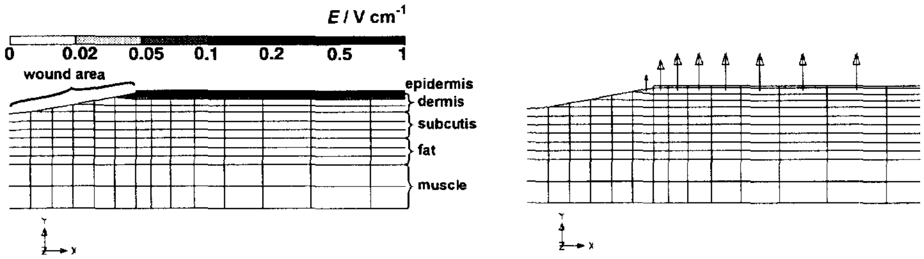

Fig. 2. Electric field intensity (left) and direction (right) in the wound model due to endogenous epidermal battery or potential difference of 30 mV between top and bottom of epidermal layer.

potential difference of 184 mV between the positive and negative electrodes.

3. Results

3.1. Clinical study

In Table 1, the average values of relative healing rate θ with standard errors for DC +, DC + / − and SHAM groups are given. Data concerning the initial average ulcer areas are presented as well.

The criteria for inclusion of treated pressure ulcers into the analysis of the efficacy of the particular treatment were: initial ulcer area of at least 500 mm^2, ulcer stage 3 or 4, no previous plastic surgery at the same location, no additional illnesses such as diabetes or cancer. The number of ulcers in the groups hence is not large, but with regard to the above requirements and uniform ulcer aetiology, a high level of comparability is provided between groups. The differences in initial pressure ulcer areas between the groups are non-significant.

The hypothesis that the ulcers treated with dummy equipment (SHAM group) heal with the same average relative healing rate as those treated with direct current applied across the wound (DC + / − group) could not be rejected (Student's t-test; $p \leq 0.05$ was considered significant). The average relative healing rates were 4.2% and 4.8% per day, respectively. Much better therapeutic effects than in the DC + / − group, however, were obtained with direct current stimulation applied directly to the wound, i.e. in the DC + group. The difference in average relative healing rates of DC + ($\theta = 7.4\%$ per day) and SHAM ($\theta = 4.2\%$ per day) groups was found to be statistically significant ($p = 0.028$).

3.2. The cutaneous wound model

Endogenous electric field distribution due to activity of the epidermal battery is shown in Fig. 2. Represented here is one half of the wound model cross-section, showing electric field intensity (left) and direction (right). The modelled endogenous potential difference of 30 mV across the epidermal layer resulted in a homogenous electric field of 1 V cm^{-1}, directed from the bottom to the top of epidermis.

Fig. 3 represents the calculated electric field intensity (left) and direction (right) for external DC electrical stimulation with electrode arrangement DC +. A current of 0.6 mA in this case induces in the epidermis at the wound edge an electric field of 0.03 V cm^{-1}, which is much lower than the endogenous field intensity. The direction of the electric field in this skin layer (from the bottom towards the top of the epidermis), on the other hand, closely resembles the endogenous conditions. With electrode arrangement DC +, the electric field is obtained not only in the epidermal layer, but also in tissues below the wound surface, its direction being from the center towards the edge of the wound.

The same electric current applied through electrodes in

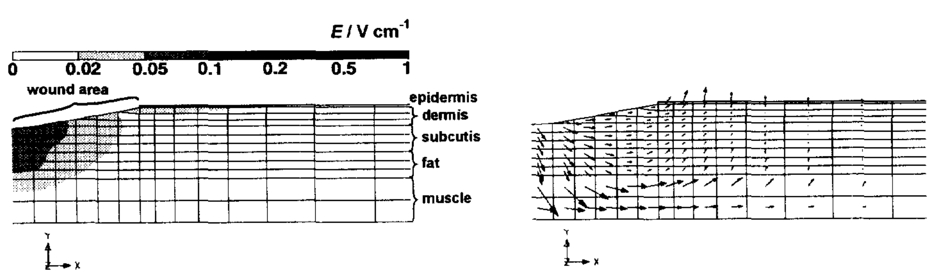

Fig. 3. Electric field intensity (left) and direction (right) in the wound model due to external electrical stimulation with electrode arrangement DC +.

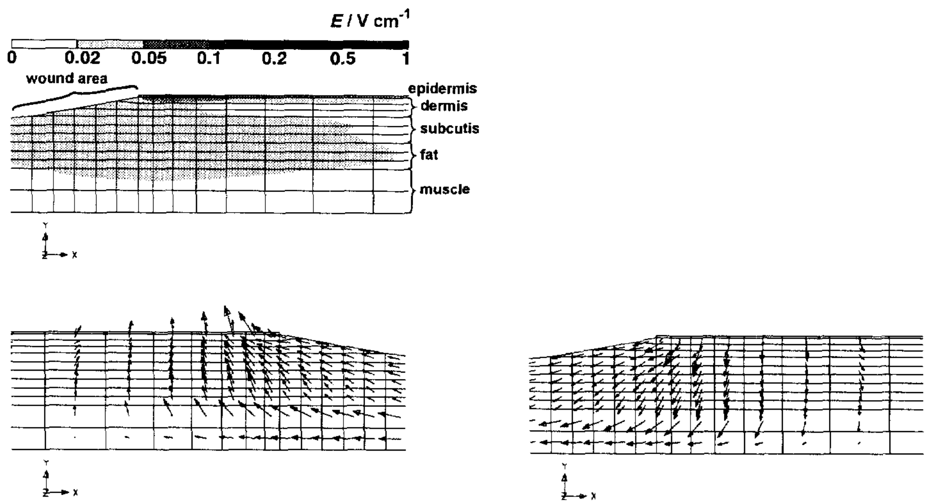

Fig. 4. Electric field intensity (top) and direction (bottom) in the wound model due to external electrical stimulation with electrode arrangement DC + / −. Bottom left and right illustrations show electric field direction on the opposite sides of the wound under the negative and positive stimulation electrodes, respectively.

configuration DC + / − induces in the epidermis at the wound edge below the surface stimulation electrodes an electric field of 0.055 V cm^{-1} (Fig. 4, top). Its direction depends on the polarity of the electrode and is thus opposite on both sides of the wound, as shown in bottom illustration of the Fig. 4. Direction of the electric field in the tissue below the negative and positive stimulation electrodes is shown on the left and right sides, respectively. Comparison with the endogenous situation reveals that distributions of electric fields in endogenous and DC + / − cases are significantly different.

4. Discussion

In the clinical study employing DC electrical stimulation for enhancement of pressure ulcer healing, two electrode arrangements were used, which induced different electric field distributions in the stimulated tissue. Significant differences were also observed concerning their clinical value when used for stimulation of pressure ulcer healing. The numerical modelling of electric field distribution in the computer cutaneous wound model revealed that by the application of direct current using two rectangular surface stimulation electrodes placed on opposite sides of the wound (DC + / −) an electric field is induced in the tissue, the form and distribution of which strongly deviates from the endogenous field. With this electrode arrangement, the result of pressure ulcer stimulation in the clinical study hardly surpassed the control placebo effect obtained by sham equipment. Significantly better results, i.e. faster healing, however, have been obtained using the electrodes configuration, with the positive stimulation electrode covering the wound and four negative electrodes overlaying the intact skin in the wound surroundings (DC +). At the same time, numerical modelling showed that with this electrode configuration, the endogenous electrical conditions in the epidermal layer at the wound edge are closely approached.

This agreement can be observed as confirmation of the assumption that endogenous electrical phenomena in the skin are not just side effects, but play an active role in healing. The endogenous battery which induces the injury currents in the wound is located in the epidermal layer of the skin. Distribution of the electric field, which is induced in epidermis by the application of external electrical stimulation, or else its accordance with endogenous field distribution, can thus be adopted as a criterion for optimization of DC electrical stimulation for wound healing enhancement.

The active role of endogenous electrical phenomena in wound healing is also indirectly confirmed by the fact that the healing of wounds, the surface of which is kept moist, is more successful than in wounds which are left to dry out. Winter was the first who demonstrated significantly faster wound epithelization in occluded experimental wounds in pigs compared to air-exposed controls [19]. Looking at the phenomena of more successful wound healing in a moist environment from the described endogenous electrical activity point of view, it can be noticed that the injury currents cannot exist when the wound surface is left to dry out due to the existence of a dry top layer representing very high resistivity. Wound surface moisture is thus essential for the existence of injury currents driven by the endogenous epidermal battery.

The endogenous potential difference between the wounded tissue and intact skin in the wound surroundings, which has been measured during the healing of acute and chronic wounds, has not been found to change the polarity. The wound surface was consistently positive (having higher potential) compared with the intact skin [5]. Assuming that externally applied therapeutic electrical stimulation with direct current is supposed to support endogenous electrical phenomena for wound healing enhancement, alteration of the stimulation electrodes polarity during healing, as reported in several studies [10–13], does not seem to be necessary. The application of negative electrode, however, could be useful in the initial stage of treatment of infected wounds due to its reported antimicrobial effect [10,12].

Acknowledgements

This study was supported by the Ministry of Science and Technology of the Republic of Slovenia, and by the Commission of the European Communities, Directorate-General for Science, Research and Development, international Scientific Cooperation, Brussels, Belgium (grant No. CI1-0349).

One of the authors (D.Š.) wishes to acknowledge the fruitful and helpful discussions with professor Vojko Valenčič during the preparation of the manuscript.

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