

WHAT IS THE MECHANISM OF WOUND HEALING WITH THE EFFECT OF ELECTRIC CURRENT ?

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SUMMARY : Studies searching how electric current effects wound healing, mostly starts after the 3rd day of wounding. Regeneration of wound tissue is the distinct phenomenon which is evident from the time of injury until the completion of wound healing. Concerning this phenomenon activity of many types of cells and extracellular substances is necessary. The acting cells are the polymorphonuclear leukocytes, the lymphocytes, the endothelial cells, the fibroblasts and the epithelial cells. In skin wounds, fibroblasts do not usually appear until about the third day, but thereafter their number increases rapidly. Collagen, being an important protein of the body, is synthesized by fibroblasts. Hydroxyproline, a measure of collagen concentration, increases rapidly beginning at day 4, with the highest rate seen between days 5 and 12, a lesser rate of increase between 12 and 21, and a markedly lower rate from day 21 to day 60.

Injury current, electric field and cell division are the most important mechanisms for wound healing. Effects of electric field that creates injury current may become stronger by an external current application. So, the net electric field or potential difference increases fibroblasts' cell division in the direction of the electric field and therefore they synthesize more collagen.

This article reviews the studies on wound-electric current couple and tries to find an approach to the wound healing phenomena under the effect of electric currents.

Key Words : Wound Healing, Electric Current, Collagen, Hydroxyproline, Injury Current.

Researches on how electric current effects wound healing may be gathered in two main headlines;

1. Studies in which current application had been continued until the wound healed completely :

In recent studies, decubitus ulcer and ischemic skin ulcer cases have been healed completely at the end of 9.6 weeks and 4.7 weeks respectively by applying constant currents of different intensities between 100 μ A and 800 μ A (13, 15, 22). Atalay et al. (1987) have observed complete healing of the

patient having Fournier Gangrene by applying 100 μ A-150 μ A constant current for 18 days at the end of 2 months of treatment and surgical operation (5). Healing rate of artificially created skin wounds has been reported 25 % more by the effect of current application (3).

2. Studies searching how electric current effects biochemical, histological and physiological changes in wounds at different days during healing period before complete healing occurred :

These studies are less in number compared to the studies referred in paragraph one hereabove. Recently, the effects of electric current on the cell migration and fibroblastic activity have been researched histologically at 2nd, 3rd and 5th days of wounding for skin wounds of rabbits (12). Another research group have studied on epidermal wounds of pigs and have reported that healing rates of current applied wounds, placebo electrode applied wounds and no treatment wounds were 100 %, 88.4 % and 77.1 % respectively at the 5th day of wounding (1).

The cell primarily responsible for the synthesis of collagen is the fibroblast. In skin wounds, fibroblasts do not usually appear until about the third day, but thereafter their number increases rapidly. Primitive collagen fibers are visible at the 3rd day and their numbers increase at 4th and 5th day fastly. Collagen fibers form the main structure in the wound when fibroblast cells decrease. Hydroxyproline, a measure of collagen concentration, increases rapidly beginning at day 4, with the highest rate seen between days 5 and 12, a lesser rate of increase between 12 and 21, and a markedly lower rate from day 21 to day 60 (18).

Determining the change in the hydroxyproline content of wound tissue under the effect of electric current is one of the ways to observe the healing process. The results of the investigation about constant current effect on collagen synthesis of skin wounds showed that hydroxyproline amounts of current applied wounds were higher than the control wounds at the 7th and 12th day of wounding (5, 6).

Consequently the histological examinations and collagen synthesis determinations on current applied wound healing studies were mostly done after the 3rd day of wounding. We searched whether a triggering was possible on collagen synthesis in wound healing before and on the 3rd day of wounding by the effect of two different electric current intensities of 200 μ A and 400 μ A with two different application times of 48 hours and 72 hours after wounding. Hydroxyproline contents of the skin wounds were increased by the effects of 200 μ A and 400 μ A current intensities at the end of 72 hours (7, 8).

What are the important parameters applying current to living organisms?

The shape and dimension of the electrode are important parameters for electric current application to living organisms. Because, the body and tissues are electrical volume conductors and local effects of current in the body or tissues depend on their electrical charge density (19). Electrode positions are determined by taking the head as reference; positive electrode is proximal, negative electrode is distal and the electrode axis is kept quite away from the axis of the heart itself (13, 15, 22).

In the studies of wound healing acceleration by electric current, a standart has been built up for 10 years or more : Current generator must be a constant current generator since the conductivity of wound tissue changes along with the healing process (13, 15, 22). Wound can be considered to be an area less dense than the surrounding skin, and it is covered with electrolytes. Therefore it should exhibit lower electrical resistance than the intact skin. Along with the healing process, electrolytes in the wound decreases, and the electrical resistance of the skin returns to its normal value (17).

How does the electric current effect wound healing?

What are the electrical effects that increase the collagen synthesis at the third day (72 hours) and after the third day and decrease the collagen synthesis in the first 48 hours of the wounding? Finding the answers to these questions requires investigation of wound healing mechanism in the bioelectrical aspect.

Regeneration of wound tissue is the distinct phenomenon which is evident from the time of injury until the completion of wound healing. Concerning this phenomenon activity of many types of cells and extracellular substances is necessary. The acting cells are the polymorphonuclear leukocytes, the lymphocytes, the endothelial cells, the fibroblasts and the epithelial cells. Enzymes, fibrin, mucopolysaccharides, ions, antibodies, nutritional elements, aminoacids and collagen are some of the important extracellular substances. Collagen, being an important protein of the body, is synthesized by fibroblasts as a fundamental unit called tropocollagen. The tropocollagen molecules are polymerized to fibrils and then to the connective tissue fibers (3).

Grillo et al (1958) have searched the collagen synthesis in the wound by determining the hydroxyproline content of the granulation tissue formed on the base of the wound (16). They have reported that there were no measurable amounts of collagen at the first two days, less amounts at the 3rd and 4th days of wounding. Collagen contents of wound increased at the 5th day fastly, reached to its maximum value at the 8th day and then decreased slowly until turning its normal value at the end of second week nearly.

In response to injury there is locally a loss of electronegative colloid-charge density, cation-binding capacity and redistribution of electrolytes. The loss of negative charge after injury renders the ground substance more closely equilibrated with plasma over which it normally maintains a binding capacity many times greater for most cations. The stronger scar depends on the local re-establishment of the lost negative charge and the quicker return to the injured place of physiologic and bioelectric conditions in addition to the special influence of the precursors of collagen (3).

Becker conceptualized the existance of a direct current electrical system controlling in tissue healing (10, 11). When electrical balance of the body is disturbed in an injury, the resulting shift in current flow-current of injury-triggers a biologic repair system. As healing continues, the direct current potential difference will approach the normal electrical balance relative to surrounding tissues. Based on these concepts, externally applied LIDC could stimulate biologic homeostasis feedback mechanism and hence the events which result in tissue repair and replacement.

A characteristic increase in the collagen biosynthetic capacity after wounding is observed in the dermis of excised wounds. This initial increase in collagen biosynthetic capacity is a normal response to healing and has been observed in both superficial and fullthickness wounds. It is known that during dermal wound repair, fibroblasts, mesenchymal, and endothelial cell adjacent to the site of injury increase their migratory, synthetic, and proliferative activities (1).

Cells have complex electrical systems which are sensitive to electrical field changes (1). It was reported that electric field causes the increasing cell divisions and DNA synthesis in cartilage cells 4 to 6 hours after 15 minutes' electrical stimulation (20).

Cultured fibroblasts (3T-6) subjected to an external electrical field not only proliferated more rapidly (20 % increase in DNA) but also increased their collagen biosynthetic activity (100 %) when compared to unenergized controls and this increase in DNA synthesis has also observed in other cells (1).

Alvarez et al. (1983) have also reported that; the excised dermis from wounds subjected to 50-300 μ A electric current demonsrated not only a 28 % increase in protein content but also 109 % increase in labelled collagen between days 4 and 5 after wounding. This rise in collagen biosynthesis observed in DC-treated wounds could be due to either a local increase in the number of collagen - producing cells present (either by migration or mitosis) or to an increased ability to synthesize collagen by the cells already there. To answer this question, they expressed collagen production per DNA content and found that when collagen synthesis is corrected for cell numbers (DNA) there were no differences among the treatment groups. Therefore, the increase in the collagen synthetic capacity in the dermis of DC-treated wounds was due to augmentation of collagen-producing cells. Increased number of cells present at the wound site could be the result of proliferation and / or chemoattraction (1).

Electrical properties of collagen of achilles tendon have studied by Anderson and Eriksson (1968). They reported that, isoelectric pH point of the wet collagen of tendon have been found as 4.7. It was concluded that the piezoelectric effect was absent from the completely wet collagen, and due to the design of experimental set up, isoelectric pH point was independent from piezoelectricity of collagen at pH = 4.7 value (2).

Becker et al have solved bone collagen in acid solution, and applied low intensity direct current (approximately 1 μ A) to this solution. They have observed concave collagen band near to the cathode after 5 minute (10, 11). Collagen band was very near to the cathode than the anode, and disappeared when current was off, and appeared at the anode side when current polarity was reversed. They concluded that piezoelectric field created from piezoelectricity of the bone arranges the collagen fibers in the bone structure in a row (23). Hence, it is obvious that collagen molecule behaves like a cation in the aqueous medium.

One of the most important mechanism of wound healing is the process of reepithelization. Recent

studies have shown that the cells migrating across a wound come from a strip of intact skin approximately 0.5 mm wide around the wound and substantial voltage gradient occur in this area. The mechanisms by which cells migrate are not understood but one possibility is that they may move more under the influence of voltage gradients either passively, for example by electrophoresis, or by active polarization of charged molecules in the cell membranes. Some cells are known to become oriented in voltage gradients as low as 7 mV / mm which is considerably lower than the expected voltage gradients at the wound margin (9).

The various layers of skin also differ among themselves in their electrical properties. The two main measurements used have been the electrical resistance of the skin, and surface potential measurements. The base levels of the skin resistance range from under 10 K Ω . cm² (Kilo ohm. cm²) for damp skin, to over 500 K Ω . cm² for very dry and scaly skin (14). Human skin potentials from the stratum corneum with respect to the dermis have been recorded as -23 ± 9 mV by Foulds and Barker (9). By using a transcutaneous recording system, they have obtained results which will combine potentials due to structural characteristics of the epidermis and due to electrical activity originating from eccrine sweat glands (9).

For practical reasons, it has not been possible to measure voltage gradients in the vicinity of experimental wounds in human. However, the fingertip current measurements made in children showed that human skin batteries are capable of driving substantial currents into wounds and voltage gradients similar to these measured in the guinea-pig can be expected to exist. These voltage gradients may have a significant effect on cellular function at wound margin (9).

Electrical circuit formed by the cells in the wound base is very important for healing process. Migrating fibroblast cells synthesize the collagen, and collagen accumulates in the wound starting from the 3rd day. Fibroblasts' cell division increase in the electric field direction and therefore they synthesize more collagen. Naturally, by the effects of injury currents, and bioelectrical properties of cells, tissues, skin and wounds; this process continues during wound healing like a positive feedback. Externally applied electric current may interact with the bioelectrical properties of these formati-

ons included collagen in the wound during healing period and collagen molecules behave like positive ions if there is a potential difference in the wound medium. Effects of electric field created by the injury current may become stronger by external current application. As a result, the net electric field or potential difference increases collagen production.

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