Electromagnetic Field Effects on Wound Healing

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Abstract

Much research has been done to determine the effects of electromagnetic fields and radiation on wound healing. In this paper, I review experimental findings that attempt to quantify these effects, as well as discuss some of the known and proposed mechanisms for such results.

Naturally Existing Wound Currents

Injury currents, or localized electrical currents at a wound site, were discovered in 1860 and further investigated and characterized in the mid-1900's [1]. Electrical currents at a wound site vary from about 1 μA to a peak of about 22μA in magnitude, and their strength depends on the stage of wound healing. Injury currents tend to increase initially until they reach their peak midway through the healing process, then the current decreases to until it reaches zero when the wound is fully healed [1, 2]. More recent studies have found that the center of the wound makes a cathodal, or negative, pole, such that the natural field polarity is oriented toward the center of the wound [3]. This orientation is thought to play a role in directing certain cells and molecules into the wound in the process of healing.

Important Mechanisms of Wound Healing

Wound healing is a complex process that involves inflammatory and immune responses, cell migration and proliferation, and restoration of the extracellular matrix [4]. The process of wound healing can be broken into two more general processes: contraction and epithelialization [5]. Contraction consists of healthy skin or other cells near the wound being pulled toward the wound center, which is primarily caused by myofibroblast contraction [5]. Myofibroblast concentration increases when tissue is wounded. Epithelialization is when epithelial cells, keratinocytes, fibroblasts, stem cells, or other cells proliferate and migrate to cover the wound [3]. The migration of these replacement cells has been found to be directed at least partially by the natural electric fields produced by injury currents [2, 3].

Cells detect the surrounding electric field using multiple chemical pathways and interactions. Two chemicals, PI3 kinase and Pten, are known as "compass molecules" because their activation in an electric field causes them to polarize to opposite poles of the cell, allowing directional sensing [2]. Other pathways including EGFR, MAPK, ERK, Src, Akt-GFP, and ERK1/2 are also activated by electric fields [2, 3]. These pathways and molecules serve various purposes in polarizing cells and initiating cell migration.

Another important factor in wound healing in the influence of inflammatory responses. Inflammation decreases blood flow to the wound with the purpose of preventing the wound site from bleeding out. However, increased blood flow promotes and increases wound healing a little later in the healing process, so inhibiting or decreasing the inflammatory response in necessary after the initial stages of healing.

It is also notable that diabetes causes decreased rate and ability to heal wounds. This is thought to be due in part to high blood glucose levels [6].

Effects of Applied Currents on Wound Healing

Much of the early research regarding electromagnetic effects on wound healing dealt with applying currents to a patient. These studies investigated the best location to apply a current and whether AC or DC current was more effective.

Currents applied directly to the wound were found to cause faster healing, increased wound tensile strength, and increased inflammatory response [1]. Interestingly, it was noted that negative polarity current had an antimicrobial effect, whereas positive polarity currents did not and these wounds were likely to become infected. They noticed that exposing wounds to solely negative polarity current resulting in no infections but a slower healing process, while positive polarity had much faster healing but was liable to get infected [1]. They thus proposed periodically switching the polarity of the current to take advantage of both the speed and antimicrobial effects of the different polarities.

Low-frequency pulsed currents were applied in various locations of interest. Local application, spinal cord stimulation, and application at acupuncture points have all been tested [1]. Local application improved wound healing, consistent with previous findings using constant current. Spinal cord stimulation reduced pain and improved wound healing by stimulating blood flow to the wound. Most of the studies regarding acupuncture points were poorly designed or incomplete, but one good study found currents applied to acupuncture points also helped wound healing; however, more data is needed to make a definite conclusion.

High-voltage current pulses have also been tested and produced similar results, indicating accelerated wound healing when exposed to the current [1]. These results were observed even with short stimulation times.

A follow-up study to the above findings investigated whether AC or DC current was more effective at promoting and accelerating wound healing. They found that AC currents were more effective, but also noted that further investigation was needed before a definite conclusion could be made [7].

Pulsed Electromagnetic Fields and Wound Healing

The most research into the effects of electromagnetic fields on wound healing has been done using pulsed electromagnetic fields. Most of these studies have found similar results.

One of the most notable studies is Milgram et al. [2004] due to being one of the first well-designed studies to investigate the effects of pulsed electromagnetic fields on skin wound healing. The study found that rats exposed to pulsed electromagnetic fields showed increased epithelialization, which is an important part of the healing process [5]. They found no statistically significant healing rate increase, however.

Athanasiou et al. [2007] followed-up on the findings of Milgram et al. [2004]. They used the same setup as Milgram et al. [2004] except a lower pulse rate was used. They also found an increase in epithelialization, but in contrast, also observed a statistically significant acceleration in healing [8]. This acceleration was only found in early healing, about the first 10 days, and then healing rate slowed to match the control.

Another study by Saliev et al. [2014] also found that pulsed electromagnetic fields reduced healing time in ulcers. They found that pulsed electromagnetic fields also decreased pain intensity and reduced wound depth and size of ulcers. Their investigation found that electromagnetic fields affect stem cell differentiation and that the relationship is frequency-dependent [4].

Carruthers and Carruthers [2012] found that pulsed electromagnetic fields showed faster healing and reduced pain when used to treat ulcers, fractures, and whiplash. They also notably discussed how it is difficult to do bilateral studies, which produce data with more confidence, due to the closeness of body parts [9]. For example, exposing one eye may result in effectively exposing both eyes, just at different intensities.

Other Electromagnetic Fields or Radiation and Wound Healing

Many other electromagnetic fields, waves, or other radiation have been tested to determine their effects on wound healing. The most current findings are outlined below.

Extremely Low-Frequency Electromagnetic Fields

A study done just last year by Bai et al. [2017] tested how an extremely low-frequency electromagnetic field affects wound healing of mice skin wounds implanted with human epidermal stem cells. They found that the mice exposed to the electromagnetic field had the fastest healing, more mature new skin, more cell layers, and more continuity in the skin structure [10]. Their investigation found that electromagnetic waves promote the cell cycle and consequently epidermal stem cell proliferation and differentiation. The study

suggests that the mechanism behind these increases in healing is in part due to EMF-caused increased expression of β1 integrin, which is a compound that plays a role in the ERK healing pathway [10].

Another study from last year investigated the effects of extremely low-frequency electromagnetic fields on wound healing. They observed that cell cultures exposed to the ELF-EMF had a decreased cell-free area and reduction of inflammatory cytokines [11]. They also found an increase in MMP-9 (a chemical involved in keratinocyte migration) activity and expression when exposed to the ELF-EMF [11]. Thus, it would appear that extremely low-frequency electromagnetic waves promote the migration of keratinocytes, which play an important role in the epithelialization process of wound healing.

Electric Fields

Since natural electric fields created by injury currents affect wound healing, it makes sense that external electric fields would as well. Additionally, many of the mechanisms for natural electric field effects on healing were either discovered or confirmed by exposing cells or cell cultures to an external electric field.

Studies found that epidermal stem cell migration is affected by electric fields; without the field, migration is random, but with an external electric field, the stem cells migrate toward the cathode [3]. The epidermal stem cells sense the electric fields using the EGFR, ERK1/2, and PI3k/Akt pathways [3]. Electric fields have also been found to guide migration of keratinocytes and regulate migration and proliferation of epidermal cells, fibroblasts, and endothelial cells [3]. Endogenous electric fields serve as signaling cues for development and regeneration of biological systems [12].

Combined EM Radiation

A study investigating the effects of "combined" electromagnetic radiation, which consists of electromagnetic radiation of very different frequencies (infrared and microwave frequencies in this case), found that combined electromagnetic radiation had the greatest responses compared to non-combined radiation and control groups [13]. The combined electromagnetic radiation rats had wounds with the highest tensile strength, lowest tissue thickness, decreased leukocyte levels, and increased McFarlane flap survival [13]. Based on these results, it was proposed that combining the frequencies resulted in the benefits of each spectrum: increased oxygen due to infrared and enhanced immune response due to the microwave range.

Modulated Electromagnetic Fields

The effect of modulating electromagnetic fields has also been investigated. In both modulated and unmodulated fields, exposed animals showed an increased concentration of DNA, suggesting that the field increased cell proliferation [14]. The study found that

animals exposed to modulated electromagnetic fields had increased protein concentrations compared to those exposed to unmodulated electromagnetic fields [14].

Radiofrequency Electromagnetic Fields

A study done by Photiades and Osamo tested radio-frequency electromagnetic fields in wound healing and found that electromagnetic fields in this frequency range also facilitate and accelerate wound healing [15].

Magnetic Fields

Investigations into the effects of purely magnetic fields, both static and pulsed, have also been conducted.

Ekici et al. [2012] found that animals exposed to a bidirectional static magnetic field perpendicular to the wound had increased wound breaking strength [16].

Another study using pulsed magnetic fields similarly saw increased tensile strength in exposed rats, but observed other effects as well [17]. Rats exposed to the pulsed magnetic field has accelerated healing, and the increase in tensile strength was increased only earlier in the healing process, but stayed approximately the same later in the healing process to match the control. It was also concluded that the pulsed magnetic fields enhanced production of transforming growth factor-β (chemical involved in a healing pathway), increased endothelial cell proliferation, and could inhibit inflammatory responses by modulating lymphocyte receptors [17].

Low-Level Laser Therapy

In addition to electromagnetic fields, electromagnetic radiation in the form of low-level laser therapy has also demonstrated increased healing rates in exposed rats, as well as decreased mortality rates of rats exposed to low-level laser therapy or continuous and alternating electromagnetic fields compared to unexposed rats [18].

Influence of Diabetes

Diabetes has been found to have many negative effects of wound healing, including decreased fibroblast proliferation, delayed wound closure, decreased inflammatory response, and decreased collagen deposition [19]. Thus, it is important to investigate whether diabetes affects how electromagnetic fields improve wound healing.

Studies of wound healing in diabetic animals when exposed to pulsed electromagnetic fields have found very similar results to studies done on non-diabetic animals. Pulsed electromagnetic fields led to smaller wound area and a greater percentage of wound healing [21]. Similar to non-diabetic studies, it was found that pulsed electromagnetic fields accelerated early wound healing, but not as much in later wound healing [21]. Pulsed electromagnetic fields enhanced wound closure in diabetic animals with increased

tensile strength in early healing and increased wound thickness later in the healing process [6, 20, 21]. It was also found that pulsed electromagnetic fields promote collagen synthesis in the early stages of healing [19, 6]. Interestingly, however, studies have shown that pulsed electromagnetic fields both do and don't influence the alignment of collagen, so more investigation is needed for this mechanism [6, 19]. Animals exposed to pulsed electromagnetic fields also had more myofibroblasts, which is consistent with experiments on non-diabetic animals [19, 21]. Finally, intensity and exposure period (when in the healing process the exposure occurs) appear to be determining factors for what effects the pulsed electromagnetic fields have and the strength of those effects [20].

It was found that the pulsed electromagnetic fields had no effect on blood glucose levels [21]. This is interesting since blood glucose levels were previously thought to partially cause decreased healing in diabetic patients.

In all of the studies reviewed, there was no statistically significant difference in the effects of pulsed electromagnetic fields between diabetic and non-diabetic animals.

Other Applications of Electromagnetic Wound Healing

So far, all studies investigated wound healing of skin wounds or ulcers, but these are not the only wounds that could benefit from electromagnetic field exposure. Here, I briefly explore some of the other healing applications that are being investigated.

One unusual type of wound is frostbite. In frostbite, tissue dies due to prolonged exposure to the cold. The degree of severity of the frostbite determines whether the tissue can traditionally be saved; severe frostbite is completely dead and has to be amputated, while minor or moderate frostbite usually means that only a portion of the tissue is dead, and thus the rest can be saved and the dead tissue replaced. Notably, frostbite damages deep into tissue, so healing of frostbite can give some indication of healing other deep-tissue wounds.

It was found that pulsed electromagnetic fields can penetrate deep enough into tissue to help wound healing in plateau frostbite [22]. This is an exciting finding, since it means that pulsed electromagnetic fields could potentially be used to help in wound healing of deep-tissue wounds.

Another area that is being thoroughly investigated recently is electromagnetic fields in fracture and bone healing. Studies are showing promising results of electromagnetic fields promoting bone marrow growth and accelerating the healing of fractures [23]. One concern with healing fractures is if the electromagnetic radiation will negatively interact with metal plates that may be implanted to ensure bones heal in the correct position. Research has shown that low-dose microwave radiation does not

increase the temperature of metal plates, but does help the fracture heal [23].

Conclusions

In the majority of studies and articles reviewed, electromagnetic fields and radiation had a positive effect on wound healing. Electromagnetic radiation explored included direct and indirect current stimulation, pulsed electromagnetic fields, purely electric fields, purely magnetic fields, other electromagnetic fields of varying frequencies and modulations, and low-level laser therapy. The specific influences of the electromagnetic radiation varied, but the most common or noteworthy effects were accelerated wound healing, directing movement of cells used in epithelialization, activation or increase in concentration of chemical healing pathways, and increased tensile strength of the wound. As the specific mechanisms of the biochemical effects of electromagnetic waves are further investigated and elucidated, electromagnetic fields are becoming a more appealing, noninvasive method of treatment for a variety of wounds.

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