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Therapeutic Effects of Static Magnetic Fields for Diabetic Wound Healing: A Review of the Current Evidence

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Static magnetic fields (SMFs) have shown therapeutic outcomes for different wounds including diabetic chronic wounds. High penetration into the wound bed, highly steering and focusable and not approved harmful effects are the main advantages of SMF therapy for wounds. In addition to antimicrobial effects, triggering wound healing physiological mechanisms are among the mechanisms of action of SMF in wound healing. Despite of rigorous evidence on the therapeutic efficiency of SMFs in different chronic wounds particularly chronic wounds, no definite frequency-response existed on the clinical trials applications of this technique. This paper reviews the applications and therapeutic outcomes of SMFs on wound especially diabetic wounds.

Keywords: Static Magnetic Field, Diabetic wound, Wound Healing, Therapeutic effects

Static magnetic field (SMF) therapy, applied via a permanent magnet attached to the skin or hold above the targeted tissue is used worldwide for different healthcare purposes. As well as conventional medications, different more-recent techniques have been developed for the treatment of wounds such as pressure relieving beds, cushions, medicinal plants. They are generally used as measures for prevention and treatment of pressure wounds. High worldwide prevalence of wounds, high costs of traditional methods and elimination of reimbursement for various wounds like burns, venous leg ulcers or infections have boosted the rapid raising of alternative wound healing methods. During the last decade several methods for chronic and acute wounds treatment including laser, electricity, magnetic, light and electromagnetic that are being used for healing wounds and sores[1-21].

SMF based techniques have major advantages over the conventional as well as other alternative techniques. SMF can penetrate into the beyond of the wound bed and reach more deep-seated tissues compared with other methods. Furthermore, the SMF can be highly oriented and focused compared with other techniques. Studies on the interactions between SMF and living organs and tissues dated back seven decades. Various studies have shown that SMF has therapeutic potentials[22]. Since the discoveries of potential therapeutic effects of SMF, various SMF technologies have been used for treatment of several disorders including skin wounds, malignant tumors, bone fractures[22].

Advantages of SMF treatments have made them one of the most promising treatment options for the management of soft tissue injuries[14]. Many experimental studies have shown various physiological efficacies of SMF on living tissues[14, 22-33] and also vigorous evidence indicating the beneficial effects of these mechanical in the treatment of soft tissue disorders[22]. In clinical experiments, SMF have the agnostic values in different diseases.

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Chronic Wounds

Wounds are classified into two categories including acute and chronic. Majority of acute wounds can be healed by direct union while chronic wounds remain for an extended time. If a wound does not follow the normal model of healing which extends almost up to six weeks, it is considered a chronic wound[31]. All chronic wounds are infected by bacteria and wound healing occurs in the presence of bacteria. Certain bacteria appear to aid wound healing. It is not the presence of organisms but their interaction with the patient that determines their influence on wound healing.

Wound contamination: the presence of non-replicating organisms in the wound. All chronic wounds are infected .These infects come from the indigenous micro flora and/or the perimeter. Most contaminating organisms are not able to multiply in a wound.

Wound colonization: the presence of replicating microorganism adherent to the wound in the absence of injury to the host, this is also very common and most of these organisms are normal skin flora.

Ulcers infection: the presence of replicating microorganisms within a wound that cause host injury .Primarily pathogens are of concern. Examples include; Staphylococcus aureus, Beta-hemolytic Streptococcus.

Wound Healing Process

Whether ulcers are closed by primary animus, subject to delayed primary closure or left to heal by secondary intention, the wound healing process is a dynamic one which can be divided into three phases. It is critical to remember that wound healing is nonlinear and always wounds can progress both forwards and back through the phases depending upon intrinsic and extrinsic forces at work within the patient.

The phases of wound healing are inflammatory phase, proliferation phase, and maturation phase. The inflammatory phase is the body's natural response to injury. After initial wounding, the blood vessels in the wound bed contract and a clot is formed. Once hemostasis establishes, then blood vessels dilate to allow essential cells; antibodies, white blood cells, growth factors, enzymes and nutrients to reach the wounded area. This leads to a rise in exudate levels so the surrounding skin needs to be monitored for signs of maceration. It is at this stage that the characteristic signs of inflammation can be seen; erythema, heat, edema, pain and functional disturbance. The predominant cells at work here are the phagocytic cells; 'neutrophils and macrophages'; mounting a host response and autolysin any devitalized 'necrotic / sloughy' tissue.

During proliferation, the wound is 'rebuilt' with new granulation tissue which is comprised of collagen and extracellular matrix and into which a new network of blood vessels develop, a process known as 'angiogenesis'. Healthy granulation tissue is dependent upon the fibroblast receiving sufficient levels of oxygen and nutrients supplied by the blood vessels. Healthy granulation tissue is granular and uneven in texture; it does not bleed easily and is pink / red in color. The color and condition of the granulation tissue is often an indicator of how the wound is healing. Dark granulation tissue can be indicative of poor perfusion, ischemia, and / or infection. Epithelial cells finally resurface the wound, a process known as 'epithelialization'.

Maturation is the final phase and occurs once the wound has closed. This phase involves remodeling of collagen from type III to type I. Cellular activity reduces and the number of blood vessels in the wounded area regress and decree. In the field of wound healing, most of the emphasis has been on the mechanisms underlying the normal repair process. Much has been learned about wound healing even in the last few years, given the technical opportunities brought about by molecular science. For example, numerous growth factors, thought to play a role in wound healing ,have been isolated, cloned, produced as recombinant molecules, and tested for their ability to accelerate wound closure (34, 35). Another dramatic example is our ability to grow cells in vitro, including what were previously rather fastidious cells such as keratinocytes and microvascular endothelial cells(36, 37). These tissue culture techniques, together with increased understanding and more effective manipulation of extracellular matrix components, have helped spawn the field of tissue engineering in wound repair (33,34). We have also learned some important lessons from fetal wound healing, where scarring is noticeably down regulated or absent. In addition, our understanding of the mechanisms underlying tissue repair is benefiting from transgenic and knockout animal models, which are beginning to point to particular proteins that are critical to healing[38]. The above advances have also brought to the field a rather sophisticated array of new therapeutic products. However, in chronic wounds, the efficacy of many advanced therapeutic agents has been less than what had been predicted from in vitro studies or from animal models and human acute wounds.

Wound Treatment

During recent years different techniques have been developed for the treatment of chronic wounds. Bio-engineered tissue substitutes, hyperbaric oxygen therapy, negative pressure wound therapy, ultrasound treatment, electric stimulation, laser therapy, magnetic stimulation, and pulsed electromagnetic field stimulation

The foundation for electrostimulation in wound healing began in 1860 when DuBois-Reymond described the electrical currents within a human skin wound(39). Herlitzka (1910) measured this current as approximately 1ìA(39). Cunliffe and Barnes (1945) discovered that wounds had a positive potential compared to the surrounding intact skin.(40) In 1980, Illingworth and Barker found that a peak current of 22 ìA cm –2 could be measured in the fingertips of children who had undergone accidental amputation[41]. Barker presented a map of human "skin battery" voltages in 1982[41]. He measured transcutaneous voltages up to 40mV and also noted that the skin surface was always negatively charged when compared with the deeper skin layers[42]. These findings have lead researchers and clinicians to examine the use of various forms of electrostimulation in chronic wound healing. Currently, there are four primary types of stimulation used: direct current, low-frequency pulsed current, high-voltage pulsed current and pulsed electromagnetic fields.

EMF based techniques for Wound Healing

Remedial approaches using ET (direct skin contact using electrodes) and EMFT (non-contact) may be divided into two broad categories; (a) those applied at the wound site and (b) those applied remote from the wound site. Included in category (a) are electric currents and fields, generated in variety of ways, with a range of excitation patterns, in which the wound itself is directly exposed to the currents or fields. In the case of ET, an electrode may be placed directly in the wound bed or the wound may be in the path of electrode pairs that straddle the wound. Included in category (b) is electrostimulation (ET or EMFT) of either nerves or tissue regions that functionally connect with, and potentially alter, wound site processes, either directly or via reflex effects. Both categories have been reviewed as they relate to different wound conditions[43, 44].

In the electromagnetic devices for wound healing, no electrodes are needed and target tissues are exposed to electric and magnetic fields and their associated induced currents. Among electromagnetic devices, all use time varying or pulsed excitation, some of which modulate a carrier frequency, commonly 27.12 MHz. A further distinction among pulsed radio frequency devices is made with respect to their potential tissue heating effects which are related to the energy they deliver to the tissue. Commercially available EMF devices usually specify device average or peak power but these do not specify the energy or field strengths delivered to target tissues. Pulse width and shape generated by most commercial devices is fixed (65-95 ¼sec), with the power per pulse usually controlled by varying pulse amplitude. Total power is adjusted by varying the pulse repetition frequency, which, for "no thermal" devices, typically ranges between 80 and 600 pps (Diapulse and Sofpulse). Device with non-thermal and thermal effects may allow the both pulse width and rates (Magnatherm, 700—7000 pps), whereas other devices provide no control features (Regenesis). Tissue thermal effects are thought to be minimized by use of low duty cycles, on the assumption that heating due to high power single, short pulses, will be dissipated during a much longer off-time between successive pulses. In general, for ET or EMFT, the parameter variants include generated power, excitation frequency, pulse width, repetition rate and duty cycle, carrier frequency, current magnitude, and magnetic field intensity. In addition there are variants with respect to specific features of the excitation patterns, i.e., whether stimulation is continuous or pulsed, galvanic or frequency modulated, biphasic or monophasic, symmetrical or asymmetrical, sinusoidal or not, and whether high voltage or low voltage stimulation is applied (43-45). It is partly because of this wide range of physical excitation parameters that it has been impossible to correlate specific features with wound healing efficacy. However, it has been argued that the use of pulse radio frequency EMF (PREMF), with its inductive coupling to tissue, provides for a more uniform and predictable electromagnetic field signal in the target tissue than is currently achieved with surface contact electrodes[46]. Therefore, the tissue dose is more reliably characterized. It has also been argued that, because of the large spectral range of PREMF, there are more possibilities for coupling of the field to produce effects in a wider range of possible (but as yet unspecified) biological processes. More detailed technical descriptions may be found in several sources[11, 34, 46,46, 47].

In a randomized, double-blinded study, Czyz et al. (2012) investigated the benefits of electromagnetic energy in eyelid wound healing in 57 patients who underwent upper blepharoplasty. There was no difference in patient pain rating when comparing placebo with the electromagnetic energy patch. Patients reported 6% less edema and 10% less ecchymosis with the active patch eye than in control eye. The authors concluded that the use of pulsed electromagnetic energy did not have an effect on postoperative pain, edema, or ecchymosis as rated by patients and physicians. The authors noted that there was a statistically significant reduction in physician-graded erythema for active patch eyes versus placebo. The significance of these results is limited by an extremely small sample size. These findings require confirmation in a larger study. Findings reported in earlier randomized controlled trials suggest that pulsed electromagnetic therapy may improve healing rates in venous or pressure ulcers and in the donor site following skin grafting, compared with standard wound care (Kenkre et al., 1996; Salzberg et al., 1995). Another earlier randomized controlled trial failed to find a significant treatment effect of electromagnetic therapy for patients with chronic venous ulcers, although there was a trend toward improved healing in the intervention group (Todd et al., 1991). Several earlier randomized controlled studies examined pulsed electromagnetic energy therapy for management of disparate types of soft tissue injuries, including whiplash, ankle sprains, and hand/finger lacerations. (Foley-Nolan et al., 1992; Pennington et al., 1993) In these studies, trends were found toward significant benefit to the intervention groups with respect to swelling, pain, and mobility, particularly when treatment was applied in the acute phase (within 3 to 4 days of injury).

However, the studies differed substantially in type of injury and treatment protocol that no overall conclusions regarding the efficacy of PEMF therapy can be made. Gupta et al. (2009) assessed the effectiveness of pulsed electromagnetic field therapy (PEMF) in the healing of pressure ulcers in patients with neurological disorders in a randomized double blind control trial. The study included 12 patients with pressure ulcers who were 12-50 years of age. Six patients with 13 ulcers received PEMF therapy and the remaining 6 patients with 11 ulcers received sham treatment, for 30 sessions (45 minutes each) using the equipment 'Pulsatron'. The frequency of PEMF was set at 1 Hz with sine waves and current intensity of 30 mA. Whole body exposure was given in both the groups. Bates-Jensen wound assessment tool (BJWAT) score was used as the main outcome measure and scores at the end of session were compared with initial scores and analyzed.

Similarly, National Pressure Ulcer Advisory Panel (NPUAP) scores were compared and analyzed as secondary outcome measure. Thirteen ulcers were in stage IV and 11 in stage III at the start of the study. Significant healing of ulcers was noted, BJWAT scores, in both the treatment and sham groups at the completion of the study. However, when comparing between the groups, healing was not significant. A similar trend was noted with NPUAP scores with no significant difference between the treatment and sham groups at the completion of study. The investigators concluded that no significant difference in pressure ulcer healing was observed between PEMF treatment and sham group in this study. Junger et al. (2008) investigated 39 patients in a prospective, placebo-controlled, double blind study on the effect of low-frequency pulsed current on healing in chronic venous ulcers. The patients were treated with the Dermapulse or a placebo for 4 months. Ulcer area decreased in both groups, but pain reduction was better in the treated group. These findings require confirmation in a larger study.

In a Cochrane review, Aziz et al. (2011) assessed the effects of electromagnetic therapy (EMT) on the healing of venous leg ulcers. Three randomized controlled trials (RCTs) of variable quality involving 94 people were included in the review. All the trials compared the use of EMT with sham-EMT. In the two experiments that reported healing rates; one small trial (44 participants) reported that significantly more ulcers healed in the EMT group than the sham-EMT group however this result was not robust to different assumptions about the outcomes of participants who were lost to follow up. The second trial that reported numbers of ulcers healed found no significant difference in healing. The third experiment was also small (31 participants) and reported significantly greater reductions in wound size in the EMT group however this result may have been influenced by differences in the prognostic profiles of the treatment groups. The authors concluded that there is low quality evidence that electromagnetic therapy increases the rate of healing of venous leg ulcers, and further research is needed.

Static magnetic fields in wound healing

SMFs are reportedly effective in wound healing despite a paucity of scientific evidence[24].

Static magnetic field increases the rate of cutaneous wound healing by secondary interaction and provides further testimony to the notion that magnetic fields can influence the physiology of the human body. However, the precise mechanism and clinical applicability of this effect are still poorly defined. The earliest reported use of magnetic therapy to aid wound healing dates to the 1600s, when electrically charged gold leaf was applied to smallpox lesions in an attempt to prevent scarring(24). Throughout the following centuries magnetic energy was propounded as a treatment for innumerable ailments and conditions, usually without substantiation of any kind. Today, however, at least 1 application, the promotion of bone healing has garnered strong scientific support and widespread clinical acceptance.

The genesis of this application began in the 1950s, when Fukuda and Yasuda in Japan described the piezoelectric effect of bone, in which an electrical potential is produced as a response to mechanical stress[48]. Subsequent investigations elucidated the numerous actions of electromagnetic energy on bone including effects on cellular calcium and calcification(49),(50) collagen and proteoglycans(51),(52) and angiogenesis(53). Clinical investigations proved the benefit of electromagnetic therapy in the treatment of delayed unions(54-57) difficult fractures,(58) and osteotomies(59, 60).The electrical current and electromagnetic field produced by a bone stimulator is a common application of this concept. Although there is ample experimental and clinical evidence supporting the use of magnetic fields to aid bone healing, its application for soft tissue healing, including skin and tendons, is still ambiguous. Promising research along these lines was first produced in the 1960s by Becker. Studying amphibians, he described the presence of an electromagnetic skin circuit, alterations which accompanied limb regeneration[60]. Borgens et al confirmed that this current is essential for amphibian limb regeneration and that its reversal induces limb degeneration[61, 62].

In one study involving organ amputations in frogs, a species that does not naturally produce this current and that is normally incapable of limb regeneration, induction of this current stimulated the regeneration of a rudimentary limb that included cartilage, nerve, and skin tissues[62]. These skin circuits have been identified in humans and are similar in magnitude to those demonstrated in amphibians[63]. Given this fact, it is plausible that external magnetic therapy could influence soft tissue healing in humans as well. Several in vivo studies support this theory and most implicate a vascular mechanism of action. Such as, Tepper et al used pulsed electromagnetic energy to endothelial cell cultures and demonstrated a marked rise in proliferation and tubulization.

Mechanism of actions of SMF

There is substantial evidence indicating that moderate-intensity SMFs are capable of influencing a number of biological systems, particularly those whose function is closely linked to the properties of membrane channels. Most of the reported moderate SMF effects may be explained based on alterations in membrane calcium ion flux. The mechanism indicated to explain these effects is based on the diamagnetic anisotropic properties of membrane phospholipids. It is proposed that reorientation of these molecules during moderate SMF exposure will result in the deformation of imbedded ion channels, thereby altering their activation kinetics. Patch-clamp studies of calcium channels have supported this hypothesis, as well as indicating a temperature dependency that is understandable on the basis of the membrane thermo tropic phase transition[64]. Additional studies have demonstrated that sodium channels are similarly affected by SMFs, although to a lesser degree. These findings support the view that moderate SMF effects on biological membranes represent a general phenomenon, by some channels being more susceptible than others to membrane deformation.

CONCLUSION

Review of the literature reveals effectiveness of SMFs for the treatment of chronic wounds, however the evidence is limited. Recent laboratory and animal studies indicating a vascular and likely a calcium-based, mechanism of actions of SMFs in wound healing. There are few studies with level I evidence on SMFs and wound healing which necessitates conducting further controlled trials on the effects of these fields on different chronic wounds.

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