CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF

PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Review Article

NON-MEDICATION TECHNIQUES FOR WOUND HEALING: CLINICAL CONSIDERATIONS

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Received: 26 March 2017 **Accepted:** 10 April 2017 **Published:** 18 April 2017

Abstract

Objective: *Several non-medication techniques have been proposed for the treatment of chronic wounds. Electric and magnetic fields, electromagnetic fields [EMFs], ultrasound [US], and photostimulation are some of these techniques with promising potentials. However, the clinical efficacy of these techniques for different chronic wounds is still not fully understood and standard guidelines on the allowed doses and possible side-effects should be determined. This paper aims to comprehensively review the therapeutic efficacies and clinical considerations of the main non-drug techniques for chronic wounds.*

Methods: *The databases of PubMed [1985-2016], EMBASE [1985-2016], Web of Sciences [1985-2016], and Google Scholar [1980-2016] were searched using the set terms of "non-medication" OR "non-drug treatment" AND "wound treatment". The obtained results were screened for the title and abstract by two authors and the relevant papers were reviewed for further details.*

Results: *Pulsed EMFs [PEMFs], non-contact low frequency US or MIST therapy, and Low Level Laser Therapy [LLLT] are the main non-drug techniques with promising effective outcomes for different wounds. PEMFs and MIST therapy have been used in some clinical studies with promising outcomes. In addition different lasers particularly HeNe lasers have shown therapeutic effect of superficial wounds. Despite of rigorous evidence on the therapeutic efficiency of these techniques, the main limit on developing approved clinical protocols of these techniques for wound treatment is the lack of definite dose-response on the clinical trials of these techniques.*

Conclusion: *The available data showed the therapeutic efficacy of PEMFs, MIST, and LLLT techniques for chronic wounds. Further in vitro and in vivo preclinical and clinical trials are needed to understand the mechanism of actions of these techniques for developing clinical protocols and guidelines of these techniques for treatment of different wounds.*

Key words: ***Non-medication, Wound, Clinical Considerations, Treatment***

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Please cite this article in press as Ali Yadollahpour et al, ***Non-Medication Techniques for Wound Healing: Clinical Considerations****, Indo Am. J. Pharm. Sci, 2017; 4(04).*

INTRODUCTION:

Wounds are among the most prevalent disorders with significant burden on healthcare systems worldwide. Despite of different medications for wound treatment, high costs of medications, resistant to conventional medications and high prevalence of chronic wounds have necessitated developing non-medication safe and feasible treatments. Nowadays, different non-medication techniques have been developed for the treatment of wounds that they are generally used for treatment and prevention of pressure wounds. Several methods such as light and photostimulation techniques [1-4], direct current [5], electric and magnetic fields [3, 6-9], and ultrasound [US] waves [10-15] have been shown promising therapeutic outcomes for different chronic and acute wounds.

Direct current and electric field, magnetic fields and electromagnetic field [EMFs] are among the first group of non-medication techniques developed for wound treatment. Several animal and human studies have shown that pulsed EMFs [PEMFs] can accelerate wound healing [16-20]. The results of these studies showed that PEMFs promote wound healing by up-regulation of FGF-2–mediated angiogenesis, nerve regeneration, alteration of the cell proliferation rate, changes in the levels of mRNA and protein synthesis, alteration of cellular membrane's permeability, and Ca^{2+}, Na^{+}, K^{+} ion transfer, effect on the production of melatonin and influence the expression of early-induced genes such as c-myc, c-fos, c-jun [16, 21-25].

Since the discoveries of potential therapeutic effects of US energy, various US technologies have been investigated for treatment of several disorders including skin wounds, malignant tumors, and bone fractures [26, 27]. Advantages of US treatments have made them one of the most promising treatment options for the management of soft tissue injuries [28]. Many experimental studies have shown various physiological efficacies of US on living tissues [12, 14, 29, 30] and also vigorous evidence indicating the beneficial effects of these mechanical waves in the treatment of disorders involving soft tissues [31-33].

Low level laser therapy [LLLT] is an another technique that it has shown clinical efficacy for tissue healing by facilitates collagen synthesis, keratinocyte cell motility, and growth factor release and transforms fibroblasts to myofibroblasts [34-39].

However, the clinical efficacy of these techniques is still not fully understood and further studies are needed to determine the exact mechanism of action and also possible side-effects of these techniques on different chronic wounds.

METHOD:

The databases of PubMed [1985-2016], EMBASE [1985-2016], Web of Sciences [1985-2016], and Google Scholar [1980-2016] were searched using the set terms of "non-medication" OR "non-drug" AND "wound treatment". The obtained results were screened for the title and abstract by at least two authors and the relevant papers were reviewed for further details.

Animal and human studies in both in vivo and in vitro designs that evaluated the effects of any non-medication treatments in any type of wounds were included for further review. Due to the immense body of literature in this field, this study aims to provide a comprehensive and descriptive overview of the recent advances in applications of non-medication techniques for treatment of wounds as well as their clinical applications and perspectives. The initial review showed the most common and promising techniques were EMFs, LLLT, and US techniques. Therefore, these three techniques were reviewed in more details.

RESULTS:

Electromagnetic fields and wound

Chronic wounds are caused to high rate of morbidity and mortality and have a profound economic impact for human and health care systems [40-43]. The pathogenesis of wound healing is not completely understood. Evidence from in vitro and in vivo studies models is shown several abnormalities in different phases of the wound-healing process. In particular, in diabetic wound some mechanisms such as inflammatory response, angiogenesis, fibroplasias, defects in collagen deposition and differentiation of extracellular matrix are disturbed [44-47]. Results of several human clinical trials and animal studies have shown that electrical stimulation applied to full thickness excisional wounds produced a reduction in wound size and accelerates wound healing, probably with increasing the endogenous current induced by injury [48-52]. Direct current stimulation has the disadvantage of requiring electrode placement directly on or near the wound, whereas pulsed electromagnetic fields have an inherent advantage that the electromagnetic signal influences the dressing and tissue involved. The basic mechanisms of the clinical effects of pulsed electromagnetic fields are not clear. Based on the results, researchers suggested that PEMFs may cause to specific, measurable cellular responses such as DNA synthesis, transcription, and protein synthesis by altering or augmenting pre-existing endogenous electrical fields [8, 53]. Results of studies have reported that PEMF stimulation

induces differentiation of skin fibroblasts in culture and decreases the doubling time of fibroblasts and endothelial cells and as a result decreases wound-healing time and increases the tensile strength of scar tissue [54-56].
Previous studies showed that PEMFs may contribute to wound healing by increasing collagen synthesis, angiogenesis, and bacteriostasis [20, 54]. These specifications are appropriated PEMFs for delayed wound healing in diabetic patients and accelerating of wound healing and also PEMFs are able to prevent tissue necrosis in diabetic tissue after an ischemic insult [16, 18, 19, 57].

Ultrasound and wound

The current range of frequency and in therapeutic US is 0.75–3MHz. Low frequency US waves have more penetration depth and less focused. The frequencies is choose for deep injuries or superficial lesions based on the penetration depth. For example 1 MHz US has 3-5 cm penetration depth on tissues and is an ideal choice for deeper injuries or 3 MHz US has l–2 cm penetration depth on tissues and is applied for more superficial lesions [15, 58]. The US waves have high penetration on tissues with high-water content like fat because of its low absorption. Whereas tissues which are rich in protein like skeletal muscle have high US adsorption [59, 60]. With using pulsed waves and moving the transducer during the treatment process can avoid generating a standing wave and its side effects [15, 59, 61]. Low frequency US have shown effectiveness effects on accelerating the healing speed of open wounds and also an effective treatment for suspected deep-tissue injuries. However the results have shown therapeutic efficacies of US techniques in different wounds, there is not an exact dose-response for clinical applications of US treatments in different wounds. Therefore to reach a standard treatment, further studies are needed to demonstrate the exact mechanism of action and also to provide exact dose-response of therapeutic US for different wounds.

Non-contact low frequency US

Non-contact low frequency ultrasound [NCLF-US] devices have been used to treat of some kinds of wounds. Results of several studies have shown that ultrasound has an effect on decreasing the bacterial count in wounds, inflammatory cytokines and pain [13, 62, 63]. Yao et al. [2014] in a pilot study evaluated effects of non-contact low-frequency ultrasound and its molecular mechanism on diabetic foot ulcers [DFUs]. One of the aims of their study was to evaluate and explore the correlation between wound healing and change of cytokine, proteinase and growth factor profile. Results showed reduction on pro-inflammatory cytokines [IL-6, IL-8, IL-1β, TNF-α, and GM-CSF], matrix metalloproteinase-9 [MMP-9], vascular endothelial growth factor [VEGF] and macrophages in treatment group compared with control group. The results demonstrated that NCLF-US is effective in treating neuropathic diabetic foot ulcers with inhibiting pro-inflammatory cytokines in chronic wound and improving tissue regeneration [63]. Honaker et al. [2013] in a retrospective analysis study evaluated the effectiveness of non-contact low-frequency ultrasound on the healing of suspected deep tissue injury [SDTI]. They measured surface area, wound colour/tissue assessment, and skin integrity with potential scores of 3 to 18 [higher scores indicate greater severity] before and after treatment in patients. The results showed reduction in wound severity for the intervention group [1.45] and increase in the non-intervention group [1.06]. They suggested that non-contact low frequency ultrasound is effectiveness on healing of SDTI [13].

Low level laser and wound

Low level laser therapy [LLLT] has been shown beneficial effects on tissue healing and pain relief. However, the results of in vitro and in vivo studies have shown varies reported [1, 35, 64]. Results of several studies have reported the effectiveness of using the helium neon [HeNe] and gallium arsenide lasers in cell proliferation and collagen production [1]. They suggested that the effectiveness of laser therapy may be related to photothermal, photochemical, or photomechanical effects but the exact mechanism is not yet clear [1, 35, 64]. Although the conflicting results have limited and disputed using low level laser therapy but it is widespread used clinically in the treatment of various neurologic, chiropractic, dental, and dermatologic disorders [35, 65-67]. The low level laser therapy [LLLT] has been also used in Dentistry to improve wound healing. Lopes et al. [2001] in a study investigated the effect of LLLT on the in vitro proliferation of gingival fibroblasts. The results of their study showed that a smaller laser exposure time results in higher proliferation and improve the fibroblast proliferation [67]. Medrado et al. [2003] evaluated the effects of low level laser therapy on wound healing and its biological action upon myofibroblasts. Before and after treatment, the tissues were assessed by histology, immunohistochemistry, and electron microscopy. The results showed that low level laser therapy induced increased collagen deposition, reduced the inflammatory reaction, and a greater proliferation of myofibroblasts [64]. Further studies with controlled dose-response design are needed for better understanding of the mechanisms of action of LLLT to develop clinical applications of the technique.

CONCLUSION:

Several techniques with diverse mechanisms have been suggested for treatment of different types of wound [35]. PEMFs have shown beneficial effects on wound healing through the production of small quantities of free radicals within cells, DNA synthesis, transcription, protein synthesis and other several mechanisms [16-19]. US particularly the NCLFUS or MIST therapy is a relatively new technique with promising clinical outcomes in superficial and even deep seated soft injuries. The most US machines are set at the frequency of 1 or 3 MHz. Low frequency US and NCLFUS have shown therapeutic effects on periodic wound debridement and bacterial biofilm destruction that indicated their bright perspectives as adjunctive or alternative wound treatment [15, 60, 61]. These techniques because of their capability for focusable and steerable penetration can be used for deep seated or superficial injuries. LLLTs have been reportedly as effective treatments for different wounds and their main mechanism of actions are reducing the inflammatory reaction, enhancing collagen deposition and pain relieving [35, 64, 65]. Considering the different mechanism of action of the above mentioned techniques, using combined approaches of these techniques has been recently developed and seems using appropriate combinations of the techniques can result in more effective treatment with synergistic therapeutic effects. Further controlled studies in this regard should be conducted to develop such combined techniques.

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