v. 3, n. 57, 2023

International Journal of Health Science

THE INFLUENCE OF LOW-FREQUENCY PULSED ELECTROMAGNETIC FIELDS ON HEALING OF CHRONIC WOUNDS AND THE RELATIONSHIP WITH KENKOBIO

Joselisa Grace Miranda Shinoda

Vinicius Alcântara Miranda Shinoda

Sônia Cristina Tinos Carroccine

Abstract: In Brazil, wounds constitute a serious public health problem, due to the large number of patients with alterations in the integrity of the skin. This condition affects about 3% of the Brazilian population, varying by sex, ethnicity and age, but the records of these treatments are still deficient. The high number of people with ulcers contributes to increasing public spending, in addition to interfering with the quality of life of the population. The lack of specialized professionals and the overload in the SUS contribute to inadequate wound management, with many patients opting for self-care at home, perpetuating the inflammatory cascade, exposing the injury to pathogens and hindering healing. The Kenkobio equipment is a PEMF device that is easy to use, portable and domestic, with more than 40 years being marketed to the population and the most widespread in the country. Although CEM therapy has been used since 4000 BC, the effectiveness of PEMF began to be studied around the 16th century. XX in several clinical applications and although its mechanisms of action need further investigation to clarify its process, it is believed that electromagnetic forces play a role in the repair of human tissues, improving blood circulation, tissue oxygenation and nutrition, shortening recovery, and for that reason, are widely studied for this capacity. This review seeks an outcome of the mechanism of action of PEMF therapy in chronic wounds to help refine the intervention, demonstrating its effectiveness in tissue regeneration, with the aim of justifying the use of Kenkobio in the home environment to stimulate future more targeted studies.

Keywords: chronic wounds; PEMF; Kenkobio; blood circulation.

INTRODUCTION

It is observed in everyday practice several difficulties in health care for people with chronic injuries. Currently, it appears that part of the care for people with wounds is assumed by family members and other informal caregivers, making the home management of chronic injuries more and more common (CARVALHO; SADIGURSKY; VIANA, 2006).

Inadequate physical infrastructure of basic health units stands out; lack of supplies for the treatment of wounds; health professionals who are unprepared or out of date to provide care empirically, meaning that the treatment does not follow and is not resolving; failures in referral and counter-referral, creating gaps in treatment and increasing the chance of recurrence. Thus, the prevalence of the biomedical model is identified, reducing the focus of care to the wound without an integral approach to the individual (FIGUEIREDO; ZUFFI, 2012).

Chronic wounds deserve special attention because they involve important aspects in an individual's life, as well as a burden on the health system (Ministry of health, 2008). As they are characterized by interruptions of the cutaneous integrity, they result in imbalances and health problems that can prevent or even hinder basic aspects of life, such as locomotion, coexistence and interpersonal relationships (DEALEY, 2008).

Wound healing is a coordinated, complex movement involving diverse cells, activation of chemical mediators and extracellular matrix, consisting of several overlapping dynamic processes. One of the underlying mechanisms responsible for disturbances in wound healing is an uncontrolled inflammatory response that can cause pathological consequences such as hypertrophic scarring, keloids or chronic wounds and ulcers. (PESCE, 2013)

The term "wound" is designed to

define the loss of the integument's means of continuity, evidenced by the rupture of skin layers or deeper structures. Tissue healing is a multifactorial and complex movement, composed of neurogenic (electrical and secretory), immune and endocrine elements; and by dynamic, interconnected and overlapping stages. The management of effective therapies depends on a systemic look, by trained professionals from multiple areas. (ALTOMRE, 2021)

Among the different types of injuries, the most frequently found in the services of the basic health network are venous, arterial, hypertensive, pressure and neurotrophic ulcers, usually with a long evolution and variable therapeutic response (BARROS, 2016). Among these, neurotrophic disorders stand out, common in some pathologies that affect the peripheral nervous system, such as leprosy, alcoholism and diabetes Mellitus; endemic diseases in Brazil.

Care involving chronic wounds, especially venous ulcers, requires a multidisciplinary approach due to its high complexity, its recurrence and the possibility of devastating morbidity. (White-Chu EF and Conner-Kerr T, 2014)

DEALEY (2008) characterized chronic wounds as those in which there is tissue deficiency as a result of lasting injury or injury or frequent recurrence, causing a lot of pain and discomfort to the bearer. Even with medical or nursing care, they do not heal easily, whether due to nutritional or emotional imbalance or even inefficient care with hygiene (LOPES et al., 2008).

Silva et al. (2007, p. 403) highlighted the importance of treatments for skin lesions that, since the dawn of civilization and with the unfolding of history and technological development, has gained a well-deserved scientific approach over the centuries in various professional health sectors.

Currently, the lack of specialized professionals and the overload of outpatient and hospital services contribute to many patients choosing to apply the dressing at home, without adequate assistance, in order not to expose themselves, increasing the time of injury and exposure to harmful microbial agents (DEALEY, 2008 and SILVA et al., 2007). Infected wounds also worry people due to the risk of amputation, which, in addition to severely affecting their self-image, makes it even more difficult to carry out daily and social activities(BRAZIL, Ministry of Health/2008 - Learning Notebook and Treatment in Leprosy), generating a strong psychic, social and economic impact, which, although there are no specific data, represent the second cause of absence from work in Brazil (Mandelbaum et al. (2003, p. 398) apud Ereno (2003)).

Severe sequelae are more frequent in the low-income population, which depends exclusively on the SUS for care.

Despite the advances made in recent decades, for various reasons it is still not possible to respond quickly to all demands. Thus, sometimes the patient has to wait months for a medical appointment, and the drugs, supplies and equipment necessary for their recovery are not always available. (BRAZIL, Ministry of Health/2008 - Prevention Notebook and Treatment in Leprosy)

Countries such as the United States, Japan, as well as the whole of Europe have adopted Pulsed Electromagnetic Fields (PEMF) as an adjuvant treatment, recognized by medicine, since the 21st century for being a non-invasive, natural option, with no side effects and systemic scope, which helps in the fight against several health problems. Europe has repeatedly shown benefits over the last 40 years with PEMF therapies in tissue regeneration and repair with reduced time and without adverse reactions.

Recent research has explored the beneficial therapeutic effect of PEMF on microvascularization and blood circulation. More recently, research interest has been the effect of PEMF on various targets, including peripheral vascular function and blood flow. It has been suggested that PEMF therapy increases the binding of free calcium (Ca2+) to calmodulin (CaM) and this phenomenon may improve tissue repair and pain. Furthermore, other studies have suggested an effect of PEMF on the Ca/CaM-dependent nitric oxide (NO) signaling pathway, which is one of the main components for the control of vascular tone and blood pressure. Researchers have recently demonstrated that in subjects with metabolic syndrome with hypertension, there was a tendency to reduce blood pressure and increase plasma levels of NO, as well as to improve flow-mediated dilation (*)

In a small pilot study in China, subjects with a history of diffuse coronary disease and evidence of myocardial ischemia underwent radionuclide SPECT before and after PEMF or control therapy. In this small pilot study, there was evidence of reduced ischemia in the treatment group versus a control group.

The Kenkobio electromagnetic device was designed and patented in Japan and emits low frequency pulsed electromagnetic fields associated with Photon Ion technology, bringing together three therapies in a single piece of equipment. There are several PEMF equipment being marketed in the world, with different frequencies and intensities, however, Kenkobio is the PEMF equipment most used in Brazil and South America and was chosen for the present study because its application is not restricted to health professionals and can be handled by lay people, under the guidance of a specialist, in a residential environment due to the practicality of applicability and the small size that allows it to be transported.

THE BIOLOGICAL MECHANISM OF HEALING

The skin represents 8 to 16% of the body mass and can reach up to $2m^2$ in extension in an adult individual, being considered the largest organ of the body. Its versatility, intrinsic functions and physiological interactions with other organs and systems make its restoration and integrity paramount and represent an evolutionary advantage and an important step towards survival (ALTOMARE, 2021).

In particular, injuries to the skin cause cell damage and damage to blood vessels. Damaged cells respond by activating various "stress signal" pathways within minutes (KOBAYASHI, 2003; YANO et al. 2004) and leaking endogenous molecules, including damage-associated molecular pattern molecules (DAMPs), which can act as stress signals. activation and/or chemotactic factors for other cells in the area (BIANCHI, 2007). The inflammatory response begins during the late phase of coagulation and begins immediately with passive leakage of circulating leukocytes (mainly neutrophils) from damaged blood vessels into the wound (KIM et al. 2008).

The inflammatory response continues with active recruitment of neutrophils and then macrophages from nearby vessels, which is orchestrated by serum growth factor signals (CHAI J, TAMAWSKI, 2002), release of platelet granules, activation of cells residing at the wound site, and presence of foreign epitopes from invading organisms.

Inflammation is mediated by a variety of soluble factors, including a group of secreted polypeptides known as cytokines. Inflammatory cytokines can be divided into two groups: those involved in acute inflammation and those responsible for chronic inflammation: some cytokines, such as IL-1, contribute significantly to acute inflammation and chronic inflammation. Cytokines play an important role in communication between cells. As intercellular mediators, they regulate survival, growth, differentiation, and effector functions.

Cytokines, along with other proteins, play regulatory roles in wound healing. As part of this process, inflammation involves platelet activation and the recruitment of neutrophils, macrophages, and fibroblasts to the wound site. Activated platelets release a wide range of biologically active mediators known to be key players in inflammation. Thrombin is another important and early coagulation mediator.

It is released by platelets and is a serine protease that mediates clot formation and plays a role in inflammation (He Zhu et al., 2010). Indeed, thrombin stimulates the release of pro-inflammatory cytokines such as MCP-1, IL-6 and IL-8 by endothelial cells, which induce neutrophil and monocyte chemotaxis (Marin V et al., 2001).

At the same time, there is activation of immune cells already resident in the tissue, such as mast cells (Noli C and Miolo A, 2001), T cells (Jameson JM, 2004) and Langerhans cells (Cumberbatch M, 2000), which, in turn, release a rapid pulse of chemokines and cytokines.

After injury, the remaining mast cells undergo degranulation within hours, contributing to neutrophil recruitment, vascular permeability, and wound closure rate (Weller K, 2006). Skin T cells are strictly limited in their distribution to the epidermis and are described as dendritic epidermal T cells (DETC).

Together, these signals trigger the "activation" of local endothelial cells and therefore the expression of selectins. These molecules control the rolling and then tethering of leukocytes to the vessel wall and subsequent crossing of the endothelial barrier (Yukami T et al., 2007). At this point, recruited and activated neutrophils initiate debridement of devitalized tissue and phagocytosis of infectious agents, using bursts of reactive oxygen species (ROS), release of cationic peptides and eicosanoids (Kim MH et al., 2008; Dovi JV, 2004)

Furthermore, an in vitro study demonstrated that neutrophils contribute to modulating the expression profile of macrophages in wound sites, regulating innate immunity in wound healing (Daley JM et al., 2005).

Macrophages appear in the wound 48-72 hours after injury (Mori R, 2008). Circulating monocytes mature into macrophages at the wound site and act with a specific expression profile according to their stimuli (Martinez FO, 2006). These cells clear the matrix and cellular debris, including apoptotic neutrophils (Diegelmann RF, 2004. Macrophages play a key role in the late phase of the inflammatory response, thereby releasing cytokines and growth factors that activate keratinocytes, fibroblasts, and endothelial cells (Diegelmann R.F., 2004).

Furthermore, these cells generate nitric oxide (NO) and large amounts of ROS (Schafer M, 2008), which are known to conducting the same aspects of the repair (Sem CK, 2008).

The inflammatory response ends when wound healing is complete and several mechanisms have been proposed to resolve this process. These mechanisms include drainage of inflammatory cells via lymphatic vessels (Cao C and Lawrence, 2005), downregulation of chemokine expression by anti-inflammatory cytokines such as IL-10 and TGF-α1 (Satoy, 1999; Werner F et al., 2000), upregulation of anti-inflammatory molecules (Schwab JM, 2007; Arend WP, 2000) and apoptosis (Grenhalgh DG, 1998).

An exaggerated and prolonged inflammatory response at the wound site is a key feature of non-healing and over-healing conditions (Loots MA, 1998).

DISORDERS IN THE HEALING MECHANISM

Healing time is categorical to indicate whether wounds are acute or chronic (Lazurus, 1994). Acute wounds repair and heal normally following the correct path and involve complex processes in the formation of distinct but overlapping phases such as hemostasis, inflammation, proliferation and remodeling (Enoch et al., 2006), as described previously.

Myofibroblasts play a key role in promoting wound remodeling (Hinz and Gabbiani, 2003; Baum and Arpey, 2005), enhancing tissue contraction to reduce the size of the edges. This produces new components of the extracellular matrix (Gabbiani, 2003; Desmouliere et al., 2005), contributes to the development of the vascular network (Mayrand et al., 2012) and, most importantly, the resolution of the inflammatory response.

One of the underlying mechanisms responsible for impaired wound healing is an out-of-control inflammatory response that can lead to consequences, including chronic ulcers. Altomare, 2021, described through his research and clinical practice, pathological scarring as the stagnation of the healing process, usually in the inflammatory phase, hindering normal cellular and molecular events, perpetuating the chronic process in a vicious cycle.

The factors that influence the healing process can be classified into local or systemic for Gray et al (2006), general and local for Rocha et al (2006) and Vowden et al (2008) divides them into four different categories that cover the wound, the individual, the health professional and the resources. For Rocha et al (2006), local factors are divided into: Chemical – are related to the characteristics that influence the ability of cells to perform normal biochemical reactions (pH of the medium); Physical – are related to properties that can be quantified and characterize the organism (temperature and humidity); Biological – are related to the factors that sustain life (presence of oxygen).

IMPORTANCE OF NITRIC OXIDE IN TISSUE REPAIR

Between 1984 and 1987, several studies demonstrated that NO is biosynthesized in various cells of the organism, being essential in numerous organic functions (Nelin, 1998; Mulsch, 1990; McCall, 1992; moncada, 1991).

NO mediates several phenomena; and here we emphasize those related to blood circulation; as endothelium-dependent vessel relaxation (Ignarro, 1989; Ignarro 2002; Anggard, 1994), macrophage-mediated cytotoxicity, inhibition of platelet activation, adhesion and aggregation, as well as beneficial vasodilatory effects on the microvascular system (Cooke, JP).

In the immune system, macrophages, when stimulated, produce large amounts of NO, which works as a “killer” molecule, destroying target (cancerous) cells and microorganisms. A NO deficiency can promote vascular thrombosis, restenosis, atherogenesis and reperfusion injury (Chester et al.).

In chronic wounds, the inflammatory cycle is also supported by the generation of a pro-oxidant microenvironment.

PEMF IN INFLAMMATION AND TISSUE REPAIR

Articles were found referring to the application of PEMF in wounds, with different frequencies and intensities, in addition to varying application times, but with similar biological responses. Articles with frequencies closer to the equipment known as Kenkobio were sought for an analysis of the physiological effects in vitro and in vivo, in humans and in rats, as this equipment is the most popular and widespread in Brazil.

In one of the literature reviews, it was found that PEMFs can enhance the inflammatory response by improving the recruitment and activation of peripheral blood mononuclear cells (PBMCs), an important methodological approach to assess the status of the immune system at wound sites, in particular, increasing reactive oxygen species (ROS), nitric oxide (NO) and pro-inflammatory cytokines, increasing macrophage production. This event can be explained by the increase in NO bioavailability induced by exposure to PEMF, which at this level, and NO has the ability to activate guanylate cyclase (sGC) and adenylate cyclase (sAC), (Gualdi G et al. 2021)

In general, Electromagnetic Fields (EMFs) have been found to produce a variety of biological effects. Although the mechanism of interaction remains unclear, it has been demonstrated that PEMFs can cause changes in cell proliferation, cell differentiation, cell cycle, apoptosis, DNA replication and expression, and cytokine expression. The effects of EMF are quite heterogeneous with regard to the type of cell studied.

Stimulation of tissue repair is one of the best-documented biological effects of EMFs. Clinical studies in humans have highlighted that PEMFs act to reduce the healing time and the recurrence rate of venous leg ulcers (Stiller et al.). In particular, Stiller et al. observed that exposure to PEMFs induced a significant decrease in wound depth and pain intensity in patients with venous ulcers, and none of the treated patients exhibited worsening of the lesions. Furthermore, patients exposed to PEMFs showed a significantly higher rate of healing of venous ulcers and protection against ulcer recurrence when compared to the control group (Ieran et al., 1990). Canedo et al. reported that exposure to PEMF in ulcers of venous etiology reduced or eliminated pain and swelling within six weeks of starting therapy.

However, the worsening of lesions is present only in patients with ulcers associated with a concomitant cofactor, such as obesity or arterial occlusion (Canedo-Dorantes L et al., 2002).

Cossarizza et al described the effect of PEMFs on IL-2 and IL-2R expression in T lymphocytes in 1989. Their results suggested that PEMFs (50 Hz, 2.5 mT) do not increase IL-2 production after 24 h of exposure, but reported that the expression of IL 2R in the cell membranes of lymphocytes was markedly increased in cells exposed to PEMF, suggesting that field exposure could increase lymphocyte proliferation by increasing IL-2 utilization. For this purpose, Pessina and Aldinucci showed high levels of this cytokine in PBMCs exposed for longer periods (48 h) and stimulated with PHA. They proposed that proliferation rates also increased significantly as a consequence of IL-2 production at the same time as treatment with PEMFs, comparing biological activity with the presence of cytokine antigens.

The effects of EMF on cytokine expression were mainly investigated with in vivo and in vitro experiments on different types of cells involved in tissue repair. These reports contribute to the explanation of the positive effects of such a physical agent in clinical studies in humans and in studies with animal models.

Cytokines that affect different populations of target cells and are involved as regulators of immune and inflammatory reactions may represent an interesting therapy. The synthesis of different cytokines, induced by different stimuli, is responsible for activating different immunological mechanisms. The outcome of the interaction between the stimulus and the tissues depends on the specific cytokine response. There are several reports investigating the effect of EMFs/PEMFs on the regulation of cytokine expression (Liburd et al.).

The increased population of myofibroblasts observed in a study with diabetic wounds induced in rats is solid evidence of the interaction of PEMF with the ulcer bed, effectively showing tissue healing through collagen deposition in the early phase of repair (PEMF Promote Early Wound Healing and Myofibroblast Proliferation in Diabetic Rats, 2014). Another study corroborated to justify the acceleration of healing in rats through planimetry, which showed statistical significance in accelerating the healing rate in the first 9 days, and by histological exam, which demonstrated progress at all time points compared to the control group (Bioelectromagnetism 2006, Wiley-Liss, Inc.).

PEMF can significantly increase collagen fiber in the early healing phase of diabetic wounds, which is associated with increased myofibroblast population (CHOI et al. 2016).

CONSIDERATIONS ON PEMF AND KENKOBIO

The Doctor Pawluk reports on his knowledge in the field of chronic wound care and makes an interesting comparison between patients who have been in wound centers or wards for months, using only conventional and local treatments, and studies with PEMF in wounds and their control groups.

He states that one cannot force tissue to regenerate beyond its optimal capacity. However, PEMFs can stimulate damaged tissue to heal beyond what is considered normal without stimulation. In other words, PEMFs may set new standards for tissue healing. These processes require electrical energy or load. Since magnetic fields interact and increase natural electrical charges and ATP, PEMF therapy can help transfer information.

To seek a theory based on the Laws of Physics, Tiago Arruda explains that matter is essentially composed of elementary particles (discrete electrical charges), namely, electrons and protons. Classically, if an obstacle, which could be an electron, an atom, a molecule, a solid or liquid particle, is irradiated by an electromagnetic wave, the electric charges present in that obstacle are led to perform an oscillation movement due to the electric field of the incident wave.

These accelerated electrical charges radiate electromagnetic energy in all directions, and it is precisely this secondary radiation that we call radiation scattering by the obstacle. In addition to this secondary radiation of electromagnetic energy, excited elementary charges can transform part of this incident energy into other forms of energy, such as thermal energy, for example, in a process called absorption (USP Thesis, Tiago Arruda - Chapter 2, p. 25) and this movement of energies can be an explanation for the activation of chemical mediators of inflammation that accelerate tissue regeneration.

The Kenkobio electromagnetic device is a PEMF system, with a frequency of 60 Hz, sine wave and magnetic concentration of 0.055 mT associated with Photon (Long Infrared) and negative ion technology that together form a complementary treatment system with high tissue regenerative power (Nikken from Brazil).

It is articulated equipment, made up of 5 pairs of coils that generate alternating electromagnetic currents, with instantaneous polarity changes (positive and negative) 60 times per second. It weighs an average of 2,600g and measures approximately 43cm, easy to transport and can be used at home by the patient or family member under the guidance of the manufacturer or a professional.

Due to its versatile characteristic, it is marketed by its manufacturer to the final consumer and its distributors (as the company's sales representatives are called) are trained to apply and accompany their customers in the evolution of the given treatment.

FINAL CONSIDERATIONS

In this review, we report a brief summary of works available in the literature that describe the effects of PEMFs in regulating the expression and modulation of inflammation in relation to pathological conditions, particularly in chronic wound healing.

The intensity of a magnetic field is responsible for the amount of 'charge' induced in the stimulated tissues and different frequencies have been tested in research to treat chronic wounds. Frequencies below 100Hz were considered effective and statistically relevant for interfering with cell biology, which points positively to us as a coadjuvant to accelerate tissue healing, consequently, the reduction of public health expenditures for this patient and the quick return to routine activities, and even, to work.

Some manufacturers have documented circulation improvements with their specific devices, which doesn't mean others won't have the same action and benefit. These improvements also need to be put into perspective, given all the actions and benefits of PEMFs, and must be considered as one of the components responsible for accelerating healing.

Ultimately, it is the body that chemically responds to incoming energy, transforming the magnetic field into electrical energy, activating chemical mediators and restoring the inflammatory cascade.

Of course, all PEMFs improve blood circulation, however the differential of the Kenkobio equipment, in addition to the possibility of using it at home, is the action of Photontherapy, which acts on molecular vibration and rotation, promoting the rupture of agglomerates of water molecules, complexes and dynamic, called clusters, with a tendency to growth and direct action on chemical reactions by trapping ions.

In addition to this property, this nanotechnology is composed of colloidal silver, with proven effects on the pathogenic microbiology, colloidal gold, an anticoagulant structure and negative ions, also called "vitamin of the air".

These three technologies united in a single device, applied at specific points in the body, have a systemic effect that promotes biochemical homeostasis.

As the prevalence of chronic wounds increases with age, and with the progressive aging of the population, the number of patients with chronic wounds has increased, leading to increasing efforts to address the problem.

A study on the epidemiology of wounds found that at least 10% of the population will develop a chronic wound during their lifetime, and the mortality rate related to these injuries is 2.5%. As mentioned above, these wounds are chronic: only 20% heal in less than 3 months, 50% take more than 1 year to heal, 20% take more than 2 years and the remaining 10% do not have a good prognosis. This chronicity entails high costs for society and the health system, while the patients' quality of life is affected; the problem is therefore more than merely economic.

And as noted, the portion of care offered to people with chronic wounds is adopted by family members and informal caregivers, making the home management of chronic injuries situations increasingly common (Sadigursky and Viana, 2006). Scientific research by Chayamiti and Caliri (2010) point out that the main caregiver is the husband and son, also for Bezerra et al. (2013) it is the informal caregiver who changes the dressings (56.5%).

Therefore, the use of PEMF is an effective alternative, which tends to restore the integrity of the skin, and which, in the case of the Kenkobio equipment, can be used by the patient himself at home as an individual therapeutic resource or as an adjunct to other therapies, as it is a Portable design, small and easy to apply.

The action of Photon and the negative ion will be discussed in a future article, but beforehand it is noted that their effects associated with PEMF enhance its regenerative and antibiotic action, the nutritional quality of the cell environment, in addition to preventing platelet aggregation responsible for thrombus.

Another positive point to emphasize is the fact that the equipment has high durability, even in falls or in electrical networks different from its voltage. It is an equipment that does not need frequent revision and its maintenance has a low cost.

This work opens up a prerogative for the development of experimental research with the Kenkobio equipment in the home environment in chronic wounds to analyze the effects of PEMF applied by lay individuals.

REFERENCES

ALTOMARE, Mariane. Livro: Fisioterapia em tecidos cicatriciais, Editora Dilivros. Ed. 1. 2021

AREND WP, Guthridge CJ. Biological role of interleukin 1 receptor antagonist isoforms. Ann Rheum Dis 2000; 59(Suppl 1): i60-4.

ATHANASIOU, Athanasios *et al.* The Effect of Pulsed Electromagnetic Fields on Secondary SkinWound Healing: An Experimental Study. **Bioeletromagnetics**, v. 28, n. 5, jul. 2007, p. 362-368. Disponível em: https://pubmed.ncbi.nlm.nih.gov/17486634/. Acesso em maio 2022.

BARROS, M. P. L. et al. Caracterização de feridas crônicas de um grupo de pacientes acompanhados no domicílio R. Interd. v. 9, n. 3, p. 1-11, jul. ago. set. 2016

BASSETT CA, Pawluk RJ, Pilla AA. Augmentation of bone repair by inductively coupled electromagnetic fields. Science 1974; 184: 575- 7.

BAUM CL, ARPEY CJ. Normal cutaneous wound healing: clinical correlation with cellular and molecular events. Dermatol Surg. 2005 Jun;31(6):674-86; discussion 686. doi: 10.1111/j.1524-4725.2005.31612. PMID: 15996419.

BIANCHI ME. DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol 2007; 81: 1-5.

BERENGUER Pérez M, López-Casanova P, Sarabia Lavín R, González de la Torre H, Verdú-Soriano J. Epidemiology of venous leg ulcers in primary health care: Incidence and prevalence in a health centre-A time series study (2010-2014). Int Wound J. 2019 Feb;16(1):256-265. doi: 10.1111/iwj.13026. Epub 2018 Nov 4. PMID: 30393963; PMCID: PMC7949455.

BEZERRA, S. M. G. et al. A. Caracterização de feridas em pacientes acamados assistidos pela Estratégia Saúde da Família. Rev. Interdisciplinar, Teresina, v. 6, n. 3, p.105-114, jul./set. 2013. Disponível em: Acesso em jun. 2023

BRASIL. Ministério da Saúde. Secretaria de Políticas de Saúde. Departamento de Atenção Básica. **Manual de condutas para úlceras neurotróficas e traumáticas.** Brasília: Ministério da Saúde, 2002.

BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. **Manual de condutas para tratamento de úlceras em hanseníase e diabetes** / Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância Epidemiológica. – 2. ed., rev. e ampl. – Brasília: Ministério da Saúde, 2008. 92 p.

CANEDO-DORANTES L, Garcia-Cantù R, Barrera R, et al. Healing of chronic arterial and venous leg ulcers through systemic electromagnetic fields. Arch Med Res 2002; 33: 281-9.

CAO C, Lawrence DA, Strickland DK, Zhang L. A specific role of integrin Mac-1 in accelerated macrophage efflux to the lymphatics. Blood 2005; 106: 3234-41.

CARVALHO, E. S.; SADIGURSKY D.; VIANA. R. O significado da ferida para as pessoas que a vivenciam. Revista Estima, v.4, n. 2, p. 26-32, 2006. Disponível em: Acesso em 04 jan. 2023.

CHAI J, Tarnawski AS. Serum response factor: discovery, biochemistry, biological roles and implications for tissue injury healing. J Physiol Pharmacol 2002; 53: 147-57.

CHAYAMITI, E. M. P. C.; CALIRI, M. H. L. Úlcera por pressão em pacientes sob assistência domiciliária. Acta paul. Enferm, São Paulo, v. 23, n. 1, p. 29-34, 2010. Disponível em:< http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0103-21002010000100005>. Acesso jun. 2023

CHEING, Gladys Lai-Ying *et al.* Pulsed Electromagnetic Fields (PEMF) Promote Early Wound Healing and Myofibroblast Proliferation in Diabetic Rats. **Bioelectromagnetics,** v. 35, 2014, p. 161-169.

CHOI, Ming-Chun *et al*. Pulsed electromagnetic field (PEMF) promotes collagen fibre deposition associated with increased myofibroblast population in the early healing phase of diabetic wound. **Arch Dermatol Res**, v. 308, 2016, p. 21–29.

CHOI HMC, Cheung AKK, Ng GYF, Cheing GLY. Effects of pulsed electromagnetic field (PEMF) on the tensile biomechanical properties of diabetic wounds at different phases of healing. PLoS One. 2018 Jan 11;13(1):e0191074. doi: 10.1371/journal.pone.0191074. Erratum in: PLoS One. 2018 Nov 28;13(11):e0208475. PMID: 29324868; PMCID: PMC5764361.

CUMBERBATCH M, Dearman RJ, Griffiths CE, Kimber I. Langerhans cell igration. Clin Exp Dermatol 2000; 25: 413-8.

DALEY JM, Reichner JS, Mahoney EJ, et al. Modulation of macrophage phenotype by soluble products released form neutrophils. J Immunol 2005; 174: 2265-72.

DIEGELMANN RF, Evans MC. Wound healing: an overview of acute, fibrotic and delayed healing. Front Biosci 2004; 1: 283-9.

DOVI JV, Szpaderska AM, Di Pietro LA. Neutrophil function in the healing wound: adding insult to injury? Thromb Haemost 2004; 92: 275-80.

ENOCH, S., Harding, K. (2003). Wound Bed Preparation: The Science Behind the Removal of Barriers to Healing. Wounds, 15(7), pp. 213-229

FELIPPE JUNIOR, José. Bio-eletromagnetismo: Medicina com Base na Biofísica. **Revista de Medicina Complementar**. Órgão Científico Oficial da Associação Brasileira de Medicina Complementar. V. 7, N. 1. Maio-Ago. 2001, P. 14.

FIGUEIREDO, M.L.; ZUFFI, F.B. Cuidados aos portadores de úlcera venosa: percepção dos enfermeiros da Estratégia de Saúde da Família. Enfermería Global, v. 11, n. 28, p. 147-158, 2012.

GUALDI G, Costantini E, Reale M, Amerio P. Wound Repair and Extremely Low Frequency-Electromagnetic Field: Insight from In Vitro Study and Potential Clinical Application. Int J Mol Sci. 2021 May 10;22(9):5037. doi: 10.3390/ijms22095037. PMID: 34068809; PMCID: PMC8126245.

GREENHALGH DG. The role of apoptosis in wound healing. Int J Biochem Cell Biol 1998; 30: 1019-30.

GREY, J., Enoch, S., Harding, K. (2006). Wound Assessment. ABC of Wound Healing, 332, pp. 285-288.

GROSE R, Harris B, Cooper L, Topilko P, Martin P. The immediate early genes krox-24 and krox-20 are rapidly upregulated following wounding in the embryonic and adult mouse. Dev Dynamics 2002; 223: 371-8.

HE ZHU, Hoppensteadt D, Cunanan J, Fareed J. Cross-reactivity of rabbit anti-bovine thrombin IgGs with human alpha-thrombin and a recombinant version of human thrombin (Recothrom). Clin Appl Thromb Hemost 2010; 16(3): 273-80.

HINZ B, GABBIANI G. Mechanisms of force generation and transmission by myofibroblasts. Curr Opin Biotechnol. 2003; 14: 538-46.

IERAN M, Zaffuto M, Bagnacani M, et al. Effect of low frequency pulsing electromagnetic fields on skin ulcers of venous origin in human: a double-blind study. J Orthopedic Res 1990; 8: 276-82.

JAMESON JM, Sharp LL, Witherden DA, Havran WL. Regulation of skin cell homeostasis by gamma delta T cells. Front Biosci 2004; 9: 2640-51.

JERABECK, J; PAWLUK, W (1998). Terapia magnética na Europa Oriental: uma revisão de 30 anos de pesquisa. **American Journal of Computational Mathematics**. V. 8, n. 1, mar. 2018, p. 78-95.

KIM MH, Liu W, Borjesson DL, et al. Dynamics of neutrophil infiltration during cutaneous wound healing and infection using fluorescence imaging. J Invest Dermatol 2008; 128: 1812-20.

KOBAYASHI H, Aiba S, Yoshino Y, Tagami H. Acute cutaneous barrier disruption activates epidermal p44/42 and p38 mitogenactivated protein kinases in human and hairless guinea pig skin. Exp Dermatol 2003; 12: 734-46.

KWAN RL, Wong WC, Yip SL, Chan KL, Zheng YP, Cheing GL. A terapia de campo eletromagnético pulsado promove a cicatrização e a microcirculação de úlceras crônicas do pé diabético: um estudo piloto. *Adv Tratamento de Feridas de Pele*. 2015; 28 (5): 212–219. doi: 10.1097/01.ASW.0000462012.58911.53 [PubMed] [Google Scholar]

LAZURUS GS, Cooper DM, Knighton DR, et al. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Dermatol 1994; 130: 489-93

LOOTS MA, Lamme EN, Zeegelaar J, Mekkes JR, Bos JD, Middelkoop E. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous ulcers versus acute wounds. J Invest Deramtol 1998; 111: 850-7.

MARIN V, Montero-Julian FA, Grès S, et al. The IL-6-soluble IL6Ralpha autocrine loop of endothelial activation as an intermediate between acute and chronic inflammation: an experimental model involving thrombin. J Immunol 2001; 167(6): 3435-42.

MARKOV, Marko S. Expansão do uso de terapias de campo eletromagnético pulsado. **Biologia e medicina eletromagnética**. v. 26, n. 3, 2007, p. 257–274.

MARTINEZ FO, Gordon S, Locati M, Mantovani A. Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression. J Immunol 2006; 177: 7303-11.

MATHIAS JR, Perrin BJ, Liu TX, Kanki J, Look AT, Huttenlocher A. Resolution of inflammation by retrograde chemotaxis of neutrophils in transgenic zebrafish. J Leukoc Biol 2006; 80: 1281-8.

MCGAUGHEY H, Dhamija S, Oliver L, Porter-Armstrong A, McDonough S. Energia eletromagnética pulsada no tratamento de feridas crônicas: uma revisão sistemática. *Phys Ther* Rev. 2009; 14 (2): 132–146. [Google Acadêmico]

MORI R, Shaw TJ, Martin P. Molecular mechanisms linking wound inflammation and fibrosis: knockdown of osteopontin leads to rapid repair and reduced scarring. J Exp Med 2008; 205: 43-51.

NOLI C, MIOLO A. The mast cell in wound healing. Vet Dermatol 2001; 12: 303-13.

PAWLUK, William; LAYNE, Caitlin. **Power Tools for Health:** How pulsed magnetic fields (PEMFs) help you. p. 66-69. [S.l.]: FriesenPress. Edição do Kindle.

PERRETTI M, Gavins FN. Annexin 1, an endogenous antiinflammatory protein. News Physiol Sci 2003; 18: 60-4.

PESCE, Mirko et al. Extremely low frequency electromagnetic field and wound healing: implication of cytokines as biological mediators. **Eur Cytokine Netw**, v. 24, n. 1, p. 1-10, 2013.

WHITE-CHU EF, Conner-Kerr T. Visão geral das diretrizes para a prevenção e tratamento de úlceras 121venosas de perna: uma perspectiva dos EUA. *J Saúde Multidisciplinar c*. 2014; 7:111-117 https://doi.org/10.2147/JMDH.S38616

https://clinicaltrials.gov/show/NCT05111288, 2021 | adicionado à CENTRAL: 31 de dezembro de 2021 | 2021 Edição 12

RAMASASTRY SS. Acute wounds. Clin Plast Surg 2005; 32: 195-208.

RYABY JT. Clinical effects of electromagnetic and electric fields on fracture healing. Clin Orthop 1998; 355S: S205-15.

ROCHA, M., et alii. (2006). Feridas Uma Arte Secular. Avanços tecnológicos no tratamento de feridas. Coimbra, MinervaCoimbra.

SATO Y, Ohshima T, Kondo T. Regulatory role of endogenous IL10 in cutaneous inflammatory response of murine wound healing. Biochem Biophys Res Comm 1999; 265: 194-9.

SCHAFER M, Werner S. Oxidative stress in normal and impaired wound repair. Pharmacol Res 2008; 58: 165-71.

SCHWAB JM, Chiang N, Arita M, Serhan CN. Resolvin E1 and protectin D1 activate inflammation-resolution programmes. Nature 2007; 447: 869-74.

SEN CK, Roy S. Redox signals in wound healing. Biochim Biophys Acta 2008; 1780: 1348-61.

VOWDEN, P., Cooper, R. (2006). An Integrated Approach to Managing Wound Infection. Management of Wound Infection EWMA Position Document. London, Medical Education Partnership LTD.

WELLER K, Foitzik K, Paus R, Syska W, Maurer M. Mast cells are required for normal wound healing of skin wound in mice. FASEB J 2006; 20: 2366-8.

WERNER F, Jain MK, Feinberg MW, et al. TGF-b1 inhibition of macrophage activation is mediated via Smad3. J Biol Chem 2000; 275: 36653-8.

YANO S, Komine M, Fujimoto M, Okochi H, Tamaki K. Mechanical stretching in vitro regulates signal transduction pathways and cellular proliferation in human epidermal keratinocytes. J Invest Dermatol 2004; 122: 783-90.

YUKAMI T, Hasegawa M, Matsushita Y, et al. Endothelial selectins regulate skin wound healing in cooperation with L-selectin and ICAM-1. J Leukoc Biol 2007; 82: 519-31.