v. 3, n. 13 2023

International Journal of Health Science

EFFECTS OF PHOTOBIODULATION THERAPY IN PATIENTS WITH THIRD DEGREE BURNS

Carlos Alberto Ocon

Nina Pereira Aguiar
hpps://lattes.cnpq.br/9566276284335525

Aline da Silva
https://lattes.cnpq.br/4652697278989882

Marcelo Marreira
hpps://cnpq.br/ 1209250074846653

Renata Miniaci
hpps://cnpq.br/ 2051458165682353

Maria Cristina Chavants

Clinical, randomized, prospective study in patients who suffered burns and admitted to hospitals that are proven to be classified as references in the treatment of burns.

INTRODUCTION

Burns are the most traumatic injuries involving the skin, among which we can highlight third-degree burns, due to their devastating capacity, destroying the epidermis and dermis, contributing to increased morbidity and mortality. Some treatments such as resection and grafting are used in order to minimize these rates. However, the healing process resulting from this pathology is slow, providing an environment conducive to infections and greatly increasing the hospitalization rate. For the management of wound treatment, prompt recovery and complete healing are still a major challenge[1].

Burns are extensive forms of skin lesions and their consequences are devastating. Their scars, when they happen, become hypertrophic, and quinoid resulting in mental and emotional difficulties, due to physical modification [2]. The healing process is complex, as it involves many events, such as the coagulation cascade, inflammation, granulation, epithelialization, collagen synthesis and tissue remodeling. Several studies are being carried out in order to identify which factors may hinder or delay this process [3]. The most striking characteristic of severe burns is the catabolic dynamism triggered, this fact occurs because the body, in an attempt to repair the affected area, releases protein and fat stores. This release generates a hypermetabolic response, characterized by increased body temperature, glucose and oxygen consumption, resulting in increased $Co_{2\ formation,}$ glycogenolysis, lipolysis, and proteolysis.[5]

Medicine has always faced the extreme difficulty of definitively treating injuries caused by more extensive burns, even using various methods [2]. Photobiomodulation Therapy is a widely used technique for treatment and has the advantage of using Laser/Led light as equipment, thus not providing the possibility of infection by manipulation. [3,4] We can also highlight some properties of Photobiomodulation: ATP production, increased mitochondrial potential, stimulation of fibroblast proliferation, collagen synthesis, re-epithelialization, formation of granulation tissue, accelerating wound repair and increasing resistance to healing traction [5,]. Photobiomodulation has gradually been recommended for the treatment of burns, mainly those involving more extensive skin destruction, since it acts on cell proliferation, even though it is exhaustively discussed in the literature, its mechanisms are not well raised, generating a discordant understanding, since the dosimetric parameters are still incipient. [6]

JUSTIFICATION

The interest in the theme, the application of Photobiomodulation Therapy using low intensity laser in third degree burns. It arose due to the incipience of studies that deal with the case. Third-degree burns are extremely harmful, as observed in visits to the burn unit of a reference hospital. There is still a fragility of conventional treatment. Relatively effective, it is a lengthy process, leaving large burns exposed to a series of iatrogenic events. Therefore, a deepening is necessary so that we can find a more effective, fast and mainly less invasive way to be used in the treatment. This gives the patient a better quality of life. This fact reduces the risk of nosocomial infections, due to prolonged hospitalization. The results already achieved by the use of low-intensity laser (LLLT) in other situations are expected, so that, in the case of treatment of third-degree burns, this length of hospital stay and exposure to hospital infections will decrease considerably.

RELEVANCE

As burns are traumatic, coagulative, disabling and deadly injuries, the most

used treatments currently in burns prove to be efficient, but invasive and many treatments made unfeasible by the costs, have time-consuming results, increasing the hospitalization rate, increasing the possibility of infection. For this reason, the interest in the use of Photobiomodulation Therapy in the treatment of burns, as it is a painless, non-invasive method, consequently contributing to a reduction in the rate of infections. Laboratory studies on tissue injured by burns have shown considerable efficacy. Initially the investment would be reasonable, during the course of the treatment the cost would decrease significantly with the passage of time and number of treatments [8].

OBJECTIVES

GENERAL

Evaluation of Photobiomodulation-FBM Action in the treatment of patients affected by third-degree burns.

SPECIFICS

Define a dosimetry that is effective in the treatment of wounds caused by third-degree burns.

Develop a proposal for a protocol using low-intensity laser that fully meets the treatment of third-degree burns in humans.

To analyze the effectiveness of Photobiomodulation Therapy compared to conventional treatments.

To measure whether low-level laser therapy increases the rate of healing of third-degree burns in humans.

MATERIAL AND METHOD

Clinical, randomized, prospective study in patients who suffered burns and are hospitalized in hospitals that are proven to be classified as references in the treatment of burns.

Based on the problems raised, it is necessary to carry out a bibliographic survey to complement the pertinent information and concepts that will be used throughout the research.

The study will be submitted for approval by the Ethics Committee of Universidade Nove de Julho (UNINOVE) and the Hospital Ethics Committee regarding the study.

Each patient (if possible) will receive verbal explanations about the study and will only participate after free acceptance and signature of a free and informed consent form. TCLE

The study complies with the Declaration of Helsinki (2013) and will follow the regulations for research on human beings (resolution 466/12 of the National Health Council).

STUDY DESIGN

Randomized, controlled clinical trial with two parallel groups that will be designed according to the criteria of the CONSORT Statement (Schulz, 2010). The Project will be registered at www.clinicaltrial.gov

POPULATION AND SAMPLE

The sample will consist of patients with third-degree burns admitted to the burn treatment unit in a hospital that is proven to be a reference in the treatment.

20 patients will be submitted to the study

INCLUSION CRITERIA

The inclusion criteria for this study will be:

- Age equal to or greater than 18 years;
- Carrier of third degree burn;
- both genders;
- Who is hospitalized in the burn treatment sector at the Hospital...

EXCLUSION CRITERIA

The exclusion criteria will be:

- It is in a terminal state;
- Age under 18 years old;
- Current or having passed in the last 3

months for treatment Antineoplastic;
- pregnant or lactating women;
- Burns caused by electricity.

CURRENT TREATMENTS

Currently, some treatments are used for skin lesions caused by burns, among which we can highlight:

- Artificial skin, developed by the Massachusetts Institute of Technology (MIT), consisting of bovine collagen and protein extracted from shark cartilage, even though it was approved for use in Brazil by the Ministry of Health in 2001, costs are still factors that make its use unfeasible on a large scale in the country.
- Dermal matrices + vacuum, consisting of two layers, the first mimicking the dermis (collagen and Glycosaminoglycans) and the second composed of silicone (temporary epidermis)
- Natural Latex Biomembrane
- Hyperbaric oxygen therapy
- Nanomaterial, produced by the "Israeli Startup Nanomedic Technologies".
- Fish skin (tilapia)
- Silver Sulfadiazine ointment, widely used, in addition to its low cost, presents satisfactory results. [7]

LITERATURE REVIEW

SKIN

The skin is an organ of extreme complexity, and it covers the entire surface of the human body, it is composed of an extensive and complex structure, which at times is elastic and flexible, at times it is rigid. In addition to these presentations, the skin also plays a fundamental role in immunity and as a physical barrier [9].

The skin, as the largest organ in the body, accounts for around 16% of our entire body weight, its structure is divided into three layers, the most superficial of which is composed of dead cells called the Epidermis, below, the Dermis and just below the Hypodermis. [10]. This lining organ separates the organic content from the external environment, thus preventing the invasion of microorganisms and, consequently, infections, maintaining local hydroelectrolytic homeostasis [8].

Skin color is determined by some factors, which may be genetic, related to the amount of melanin produced by melanocytes, as well as the presence of a greater or lesser amount of blood volume. [11]

EPIDERMIS

The outermost layer of the skin, made up of cells that offer protection against toxins, bacteria and acts to prevent fluid loss. It is made up of five sublayers of cells called keratinocytes.

- Basal layer- the innermost layer responsible for the formation of keratinocytes.
- Spinous layer- in this layer keratin is produced
- Granular layer- keratinization transformation begins
- Lucid layer- where the cells are compressed and flat.
- Corneal layer- composed of several layers of dead cells, suffer frequent desquamation, in this, too, is located the pores of the sweat glands. [12]

DERMIS

Layer of the skin that is located just below the epidermis. This layer works as a nutritional support for the epidermis. It contains blood and lymphatic vessels, sweat and sebaceous glands. It also contains the sensitive nerves responsible for tactile sensations (heat, cold, pain, itching), while traction and resistance are given to elastic and collagen fibers

[12,13]. Body temperature regulation takes place in this layer through vasodilation and vasoconstriction [14].

This layer is made up of specific cells, such as:

- Fibroblast: Synthesis of collagen, reticulin, elastin, fibronectin, Glycosaminoglycans, Collagenase.
- Mobile mononuclear phagocyte: phagocytes and destroys bacteria, these also secrete cytokines lymphocyte immune surveillance.
- Langerhans cell: In transit between local lymph nodes and epidermis
- Dermal dendritic cells: Antigen presentation
- Mast cells: Stimulated by antigens, complements and other substances that release inflammatory mediators, such as histamine, heparin, prostaglandins,

Leukotrienes, tryptase, as well as chemotactic factors for eosinophils and neutrophils [15].

HYPODERMIS

Layer located just below the dermis, richly vascularized and innervated, due to its adipose constitution, it participates intensely in thermal insulation. Due to its deeper position in relation to the other layers, it provides support to the structures and because it is a looser tissue, it slides over the viscera and bones [1]. The connection between the dermis and hypodermis is carried out through elastin and collagen fibers, this layer works as a reservoir of energy, defense, physical shocks and fixation of the skin to adjacent structures, such as muscles and bones. The tissue that forms the hypodermis is the adipose tissue, where adipocytes are found, cells responsible for producing and storing fat.

BURNS

Burns are resulting injuries that affect the skin, such as: thermal, electrical, chemical, radiation energy, thus leading to cell death [16]. The striking feature of thermal injuries is the destruction of tissues that lead to catabolic dynamism. This fact occurs because, when the body tries to repair the affected area, protein and fat reserves are released, leading to a hypermetabolic response associated with increased consumption of energy and energy substrate during severe burns or even sepsis [5]. regeneration there is an occlusion of the surface, this happens by proliferation and migration of epidermal cells, sweat and sebaceous glands [16]. Burns are extremely invasive injuries and cause changes in quality of life. They are physical traumas, which cause permanent deformities, skin destruction and visual changes, incurring severe psychological damage [17]. Burns can be divided into stages related to depth, classified as first, second and third degree. The local reaction in the most affected region is called the central zone, where irreversible cellular destruction occurs, caused by the degradation of cellular proteins and also by coagulation [18]. The intermediate area undergoes profound changes in tissue blood perfusion. In addition, when the necessary treatment does not occur, it tends to evolve into necrosis. In the more peripheral area of the lesion, there is hyperemia resulting from greater vascularization, in this area there is no possibility of an evolution to necrosis [19].

BURN STATISTICS

Burns represent one of the biggest Public Health problems, accounting for 11 million cases worldwide, 2.9 million of which seek hospital help and 300,000 die according to Epidemiology of Burns Throughout the world (2011). Burns represent the fourth cause of death due to unidirectional injury. In Brazil there were 1,000,000 in 2017, of which 100,000 sought medical help, another

2,500 died. This way, a total of BRL 3,286.66 was spent, data from the unified health system (SUS), according to the Ministry of Health in 2017. The highest incidence occurs among children and low-income people, more frequently in the south, southeast and northeast of the country, with 70% of all cases occurring at home [20].

CLASSIFICATION OF BURNS

FIRST DEGREE BURNS

First-degree burns affect only the epidermis, are extremely painful, cause edema, a dry lesion, hardly require hospitalization, evolve quickly, cause skin desquamation, and do not cause sequelae [21].

SECOND DEGREE BURN

Second-degree burns are painful, cause phyctemas, and are wet in nature. It affects the epidermis in its entirety and part of the dermis, and scarring and dyschromia may occur. Neither does it require hospitalization, except in cases that progress to greater severity. [22]

THIRD DEGREE BURN

The third-degree burn is characterized by the total destruction of all layers of the skin. In the most severe cases, they can affect more internal structures, such as muscles, nerves and bones, causing an intense disturbance in the body [23]. Due to the degree of aggression, there is no re-epithelialization process. In these burns, nerve endings are destroyed, making it painless and also incurring loss of skin elasticity. This injury requires hospitalization, as it is extremely aggressive, negatively impacts all organic functioning, thus being more devastating. [24]

CHARACTERISTIC OF LOW INTENSITY LASER

The use of light as a therapeutic treatment dates back to antiquity, where reports mention that Indians, Chinese and Greeks used light from the sun. The Indians exposed herbs to sunlight, to later use them in the treatment of skin lesions, the Chinese macerated plants that, after being exposed to sunlight, were used to prevent the proliferation of contagious skin diseases and the Greeks believed that exposure to sunlight, it strengthened and healed [57].

Albert Einstein, in 1916, formulated the principles of light amplification by stimulated emission of radiation [32]. Laser is an acronym of the English words "Light Amplification by Stimulated Emission of Radiation". In the 60s, the first ruby laser was produced by Theodore Harold Maiman[30]. Becoming indispensable in the areas of telecommunications, art, cosmology, war industry, medicine and other areas [57].

The characteristics of the laser. It comes from the formation of light, which are particles of electromagnetic energy, known as photons. [25]

Electromagnetic waves have various wavelengths, ranging from 440 nm (violet) to 700 nm (red), only a fraction of this wave spectrum is visible to the human eye [25]. When the wavelength is greater than 700 nm we will have an infrared wave, which can be divided into short, medium and long radiation. Laser devices mostly offer wavelengths between 600 and 1000nm for therapeutic treatment. [51].

The continuous laser presents power variation, expressed in W/cm ^{2,} and radiant exposure, energy density, fluence or dose are measured in J/cm ^{2} [27]. Every laser device is an excellent source of radiation, with the ability to produce a very intense and precise electromagnetic field [26]. The laser differs from normal light as it is coherent, monochromatic and collimated. When this light reaches biological tissues, it produces a

physical effect of absorption, reflection and scattering [28]. The interaction with tissues is proportional to the wavelength used [30]. Low-intensity laser therapy (LTBI) is widely used by several health professionals, as several studies have shown that it improves the quality of healing, has regenerative, anti-inflammatory and analgesic effects. The energy produced and delivered by LLLT acts on revascularization directly on adenosine triphosphate (ATP), on fibroblast proliferation and inhibition of chemical mediators in the inflammatory process [31].

According to (Veles et al 1987). In low power laser treatment, important therapeutic effects such as edema reduction, anti-inflammatory action and wound recovery are clinically observed. The normalization of metabolic processes takes place by converting light energy and biochemical energy, inhibiting or stimulating the regeneration process.

LASER PERFORMANCE IN BURNS

Photobiomodulation Therapy (TFBM) is a promising treatment with regard to re-epithelialization, its use accelerates the healing process, acts to reduce pain, stimulating the proliferative phase and decreasing the inflammatory phase. [37]

Studies reveal that the epidermis and the dermis present an improvement in the organization and restoration of the fibers, when treated with low-intensity laser at 660 nm at 20J/cm ^{2} due to the formation of granulation tissues and neoangiogenesis. [36, 37, 38,] LTBI has the ability, through its light radiation, to change all cellular behavior without generating heat [39]. the physical-chemical process, also acting in the organization of the healing process promoting a facilitating effect on the scar [35]. [40]. According to Fiorio (2009) doses of 3J and 4J/cm ^{2} promoted collagen deposition, improving healing, reducing the inflammatory process. [37,44]. An AlGalnP laser was used, which demonstrated effectiveness when used at 3J/cm ^{2,} mainly in the initial phase of tissue repair, with a decrease in necrosis. in the final stage of healing. [45]. According to BOSINI et al (2013), related the improvement in the healing condition to a laser dose of 6 to 8J/cm ^{2,} acting in the regulation of cell metabolism. In this study, they demonstrated the antioxidant effect by increasing radicals due to the enzyme superoxide dismutase. Irradiation in a third-degree burn wound by 890 nm pulsed laser, with an energy density of 11.7 J/cm 2, provided an increase in the wound contraction rate, however its inhibitory effect on the microbial flora was minimal [60,62]. In a study with pulsed infrared diode laser at 8J/cm ^{2,} there was a total decrease in mast cells during the wound proliferation and maturation phases, caused by third-degree burns [15]. A study carried out with two different laser application modes showed that in the scanning mode in a third-degree burn wound, it closed completely in 14 days, and in the punctual mode, this closure did not occur at the same speed. [10]

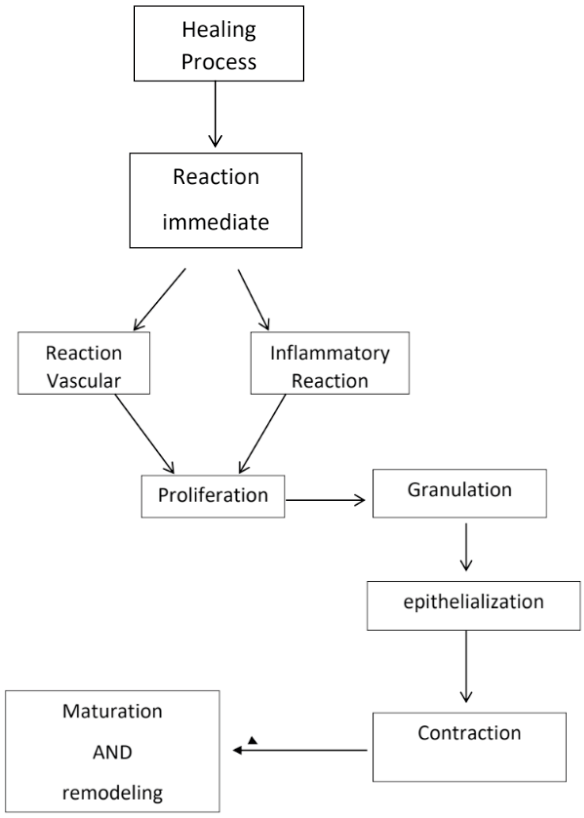
Studies indicate that the laser stabilizes the release of cytokines, which are responsible for the increase of fibroblasts in collagen synthesis and, consequently, improves the organization of architectural collagen [63,64]. The energy released from the low-intensity laser causes an inhibition in the release of Prostaglandin, causing the inflammatory synthesis to also decrease, directly influencing the extracellular matrix in healing. [65.66]

Photobiomodulation Therapy proved to be relevant, as it provides leukocyte migration to the wound site, leading to angiogenesis [67]. A study has shown that laser therapy, with a wavelength of 830nm and an energy density of 3J/cm ^{2,} compared to other wavelengths, promotes effective formation of microvascularization, anticipates the

proliferative phase and promotes rapid contraction. [68]

HEALING PROCESS

Healing is a complex, potent and biochemical process. Some factors may contribute to the delay in repair. Extrinsic factors: age, pre-existing diseases, medications, nutritional, immunological status. Intrinsic factors: infections, necrosis, low oxygenation rate, hemorrhage and presence of a foreign body at the site [37]. During healing, there is intense platelet activity and formation of the coagulation cascade [38]. According to IRION (2005), a primary cover is formed over the wound bed consisting of fibrin, providing a favorable environment for platelets to secrete growth factors (FCs) [39]. The formation of clots acts directly on the edges of the wound, minimizing blood loss, fluids, preventing the penetration of exogenous agents, providing a provisional matrix, where the organization of the wound begins [40]. Neutrophils and macrophages are recruited by inflammatory mediators, as they secrete several specific factors that coordinate the following phases of tissue repair [41].



Healing process diagram

Source Brazil 2002

INFLAMMATORY PHASE

Tissue injury causes a release of histamine and bradykinin, leading to local vasodilation, consequently inflammatory signs such as heat and flushing. Increased capillary permeability, and extravasation of fluid into the extracellular space leading to edema [45]. This phase is characterized by the presence of several cells of the immune system, which participate in the inflammatory process, (lymphocytes, macrophages and neutrophils) next to the scar tissue [42]. process of hemostasis through platelet aggregation and release of chemical mediators. Subsequently, vasodilation provides greater migration of polymorphonuclear cells, especially macrophages [43]. The extravasation of serum molecules, antibodies and proteins through capillaries is controlled by permeability and increased local blood flow [44]. The

predominance of polymorphonuclear leukocytes in the wound is brief and varies from three to five days, acting directly phagocytizing bacteria [42]. After the period of leukocyte presence has elapsed, macrophages predominate, in addition to continuing the phagocytosis process, they act as sources of growth factors, present antibody cells and chemical mediators, thus constituting the support of the healing process [45]. It also acts by removing phagocytes, synthesizing proteases, removing devitalized collagen, fibrin clots, evidencing mitogenic factors and cytokinins [42].

PROLIFERATIVE PHASE

In this phase, there is a period of intense activity, with emphasis on neoangiogenesis. It starts around the third day after the tissue injury, remaining active until approximately the third week. This is characterized by the formation of granulation tissue, consisting of vast beds of capillaries, macrophages, fibroblasts, loose collagen arrangement, fibronectin and hyaluronic acid. This phase serves as the initial matrix for scar formation [46].

REMODELING PHASE

In this phase, the healing process is marked by the maturation of the elements, transformation of the provisional cell matrix into a definitive one, where the fibroblasts of the granulation tissue are transformed into myofibroblasts, acquiring the contractile function, the proteoglycan and collagen deposits are sedimented [53]. In the course of the remodeling process, fibroblasts and inflammatory cells undergo emigration or apoptosis. This fact leads to homogeneous healing, but if cellular decrease does not occur, a hypertrophic or keloid scar will form [54]. The cytokines involved in this phase are: tumor necrosis factor (TNFα), interleukin (IL-1), PDGF and TGFβ produced by fibroblasts, EGF and TGF-b factors are produced by epithelial cells [55]. Gradually, the bundles of collagen fibers become thicker and more regular, this regularity of the fibers is directly related to the area and the mechanical forces performed in normal activities [56].

NEOANGIOGENESIS

Angiogenesis constitutes the formation of new blood vessels, from the existing ones [47], they are extremely important, since they provide oxygen and essential nutrients for the formation of new granulation tissues [48]. According to Risau (1997), the supply of oxygen and nutrients act in the first stages of vascular development, where the predecessor cells of the vascular endothelium undergo differentiation, expansion and coalescence to form the primitive tubules of the organism [49]. The induction of angiogenesis is initially attributed to (fibrobastic growth factor), acidic FGF. Angiogenic molecules, VEGF, TGFβ, angiogenin, angiotropin and angiopoietin-1 are also included as induction factors[50]. Indirectly, angiogenesis can be stimulated by low oxygenation rates, high levels of lactic acid and bioactive amines [51,52].

ANNEX I

TCLE - Term of Consent for Participation in Clinical Research:

Volunteer's name _____

Address:_____

Telephone:_____City:_____ZIP Code:_____

E-mail: _____

1.Title of the Paper:– EFFECTS OF PHOTOBIOMODULATION THERAPY IN PATIENTS WITH THIRD-DEGREE BURNSrandomized trial

2.Objective: Evaluation of the Action of Photobiomodulation-FBM in the treatment of patients affected by third-degree burns.

3. Justification: Biophotomodulation promotes the healing of third-degree burns faster than conventional treatments.

4 Procedures of the Experimental Phase: Biophotomodulation will be applied in the third-degree burn area, after carrying out local cleaning with 0.9% saline solution. After application, the lesions will be covered with Rayon soaked in age or (substances for protocol use at the hospital), receiving a secondary dressing with gauze and closure with a crepe bandage (if institutional protocol).

The treatment will be carried out daily.

5.Benefits, Discomfort or Expected Risks: as benefits, the patient will be guaranteed daily follow-up by the multidisciplinary team, which helps to promote the closure of the lesion. Additionally, the results of this study will prove whether phototherapy is a tool that can help close wounds in a shorter time and at a lower cost.

To change dressings and applying the laser can cause mild discomfort due to manipulation. So that the patient does not know in which group he is allocated, personal protective equipment (goggles) will be made available during the application of the light.

There is no risk for the patient.

6. Existing Alternative Methods: There are no alternative methods.

7.Withdrawal of Consent: You will be informed about the research in any aspect you wish. You are free to refuse to participate, withdraw your consent or discontinue participation at any time. Your participation is voluntary, there will be no payment in any way for your participation in the work. Refusal to participate will not result in any penalty or damage to the assistance you have been receiving.

The researcher(s) will treat your identity with professional standards of confidentiality. The results will be made available to you and will remain confidential. Your name or material indicating your participation will not be released without your permission. You will not be identified in any publication that may result from this study. A copy of this informed consent will be kept on file at the Graduate Course in Applied Biophotonics

to the Health Sciences of ''Universidade Nove de Julho" (UNINOVE) and another one will be provided to you.

8. Confidentiality Guarantee: Your privacy will be respected, that is, your name or any other data or element that may, in any way identify you, will be kept confidential.

9. Research Location:

10. Research Ethics Committee: it is an interdisciplinary and independent collegiate, with a "public role", which must exist in institutions that carry out research involving human beings

in Brazil, created to defend the interests of research participants without their integrity and dignity and to contribute to the development of research within ethical standards (Norms and Regulatory Guidelines for Research Involving Human Beings – Resolution number: 466/12). The Ethics Committee is responsible for evaluating and monitoring the research protocols in terms of ethical aspects.

Uninove Ethics Committee address: Rua. Vergueiro nº 235/249 – 3rd basement - Liberdade – São Paulo – SP - Zip code: 01504-001 Telephone: 3385-9197

comitedeetica@uninove.br

11. Full name and telephone numbers of the Researchers (Advisor and Students) for Contact:

12. Eventual intercurrences that may arise during the research can be discussed by the proper means.

I,_____was informed of the above research objectives in a clear and detailed manner and clarified my doubts. At any time I can request new information and motivate my decision if I so wish.

I declare that I agree to participate in this study. I received a copy of this informed consent form and was given the opportunity to read it and clarify my doubts.

Name - Signature of Participant- Date

_____

Name - Researcher Signature - Date

_____

Name - Signature of Witness - Date

_____

REFERENCES:

1. Ocon CA, Santos SA, Caires JR, Oliveira MFD, Serra AJ, Junior ECL, Carvalho PTC -Effects and parameters of the photobiomodulation in experimental models of third-degree burn: systematic review

2.Oryan A, Alemzadeh E, Moshiri A. Burn wound healing: present concepts, treatment strategies and future directions. J Wound Care. 2017 Jan 2; 26(1):5-19. doi: 10.12968/jowc.2017.26.1.5.

3.Fiorio FB, Dos Santos SA, de Melo Rambo CS, Dalbosco CG, Serra AJ, de Melo BL, Leal-Junior ECP, de Carvalho PTC. Photobiomodulation therapy action in wound repair skin induced in aged rats old: time course of biomarkers inflammatory and repair. Lasers Med Sci. 2017 Nov; 32(8):1769-1782. doi: 10.1007/s10103-017-2254-2.

4.Avci, P., Gupta, A., Sadasivam, M., Vecchio, D., Pam, Z., Pam, N., & Hamblin, M. R. (2013). Low-level laser (light) therapy (LLLT) in skin: stimulating, healing, restoring. Seminars in Cutaneous Medicine and Surgery, 32(1), 41–52.

5.Bayat M, Vasheghani MM, Razavi N, Taheri S, Rakhshan M. Effect of low-level laser therapy on the healing of second-degree burns in rats:a histologicaland microbiological study.J Photochem Photobiol B. 2005 Feb 1;78(2):171-7.

6.Vasheghani MM, Bayat M, Rezaei F, Bayat A, Karimipour M. Effect of low-level laser therapy on mast cells in second-degree burns in rats.Photomed Laser Surg. 2008 Feb; 26(1):1-5. doi: 10.1089/pho.2007.2103

7.Coutinho BBA, Balbuena MB, Anbar RA, Anbar RA, Almeida KG, Almeida PYNG. Perfil epidemiológico de pacientes internados na enfermaria de queimados da Associação Beneficente de Campo Grande Santa Casa/ MS. Rev Bras Queimaduras. 2010;9(2):50-3.

8. Mello PB, Sampedro RMF, Piccinini AM. Efeitos do laser HeNe e do ododе aplicação no processo de cicatrização de queimaduras em ratos.Fisioter Pesqui. 2007;14(2):6-13.

9. Woo K,Ayello A, Sibbald R (2009)the skin and periwound skin disorders and management. Wound Healing Southern Africa 2(2): 1–6

10. VAN DE GRAAFF,K.M. Anatomia Humana. Barueri: Manole 2003

11. Zhu, L.; Yang, H. Bin; ZHONG, C.; LI, C. M. Rational design of triphenylamine dyes forhighly efficient p-type dye sensitized solar cells. Dyes and Pigments, v. 105, p. 97–104,2014.

12. Brenner M, Hearing VJ. The protective role of melanin against UV damage in human skin. Photochem Photobiol. 2008;84(3): 539–549. PMID: 18435612

13. Turkington C, Dover JS (2007) Skin Deep. third edition. checkmark books, NewYork NY.

14. Tortora GJ, Derrickson BH (2009a) principles of anatomy and physiology: organisation, support and movement and control systems of the human body. Volume 1. Twelfth edition. John Wiley and Sons, Hoboken NJ.

15. DANGELO, J. G.; FATTINI, C. A. Anatomia humana sistêmica e segmentar. 3. ed.São Paulo: Atheneu, 2007. 732 p.

16.Ministério da Saúde-cartilha para tratamento de emergência da queimadura, 2012

17. Peck, M.D. Epidemiology of burns throughout the world. Part I: distribution and risk factors. Burns, v. 37, n. 7, p. 1087-100, 2011.

18. Teot, L. et al. Burn wound healing: Pathophysiology. In: Kamolz, L.P., et al. andbook of Burns Reconstruction and Rehabilitation. Germany: SpringerWienNewYork, 2012. p. 47-53.

19. Borges, E.L. Evolução da cicatrização. In: Borges, E.L.; SAAR, S.R.C.;Magalhães, M.B.B.; Gomes, F.S.L.; Lima, V.L.A.N. Feridas: como como tratar.2.ed. Belo Horizonte, Coopmed, 2008. 246p. cap.3, p.31-43.

20. Revista Brasielira de Queimaduras-novembro 2017.

21. C. S. Enwemeka, J. C. Parker, D. S. Dowdy et al., "The efficacy of low-power lasers in tissue repair and pain control: a meta-analysis study," Photomed Laser Surg, vol. 22, no. 4, pp. 323-329, 2004.

22. Toussaint, J., & Singer, A. J. (2014). The evaluation and management of thermal injuries: 2014 update. Clinical and Experimental Emergency Medicine, 1(1), 8–18. http://doi.org/10.15441/ceem.14.029

23. Barreto, M.G.P. et al. Estudo epidemiológico de pacientes queimados em Fortaleza, CE: revisão de 1997 a 2001. Rev Pediatr v.9, n. 1, p. 23-9, 2008.

24. Rushton, I. Understanding the role of proteases and pH in wound healing. Nursing Standart, v.21, n.32, p.68-74, Apr. 2007

25. Differy, B. L.; Kochevar, I. E. Basic principles of photobiology. In: Lim,H. W.; Hönigsmann, H.; Hawk, J. L. M. Photodermatology. 1.ed. New York: Informa Healthcare, 2007. p. 15-28.

26. Lizarelli RFZ (2010). Protocolos clínicos odontológicos. [(S.l.: s.n.] Uso do laser de baixa intensidade)

27. Mikail, S. Laser terapêutico. IN: MIKAIL, S.; PEDRO, C. R. Fisioterapia veterinária. 2.ed. São Paulo: Editora Manole, 2009. p. 81-90.

28.R. Hamblin, Michael; Victor,, Pires de Sousa, Marcelo; Tanupriya,, Agrawal,. Handbook of low-level laser therapy. Singapore: [s.n.] ISBN 9789814669610. OCLC 960707689

29. Millis, D. L.; Franvis, D.; Adamson, C. Novas modalidades terapêuticasna reabilitação veterinária. In: Levine, D.; Millis, D. L.; Marcellinlitlle,D. J.; Taylor, R. Reabilitação e fisioterapia na prática depequenos animais. São Paulo: Editora Roca, 2008. p. 95-117.

30. Karu, Tina. «Mitochondrial Signaling in Mammalian Cells Activated by Red and Near-IR Radiation». Photochemistry and Photobiology. 2008.

31. BUSNARDO, Viviane L. e BIONDO-SIMOES, Maria L. P.. Os efeitos do laser hélio-neônio de baixaintensidade na cicatrização de lesões cutâneas induzidas em ratos. Rev. bras. fisioter. [online]. 2010, vol.14,n.1, pp. 45-51. ISSN 1413-3555. Disponível em: < http://dx.doi.org/10.1590/S1413-35552010000100008>.Acesso em 21 Nov 2012.

32.Evers,LH.,Bhavsar.D.Mailander,P.2010 The biology of burn injury,Experimental Dermatology 19.777-783.

33.Corazza AV, Jorge J, Kurachi C, Bagnato VS. 2007. Photobiomodulationon the angiogenesis of skin wounds in rats using different lightsources. Photomed Laser Surg 25:102–106

34.Janis, JE; harrison, B. Wound Healing: Part I. Basic Science. Plastic and Reconstructive Surgery, v. 133, n. 2, 2014, pp. 199-207

35.Sánchez, M. E. C. El láser de media potencia y sus aplicaciones em medicina.Plasticidad e Restauración Neurológica, Distrito Federal do México, v. 6, n. 1, p. 45-53, 2007

36. Lui, H.; Anderson, R. R. Radiation source and interaction with skin. In: Lim,H. W.; Hönigsmann, H.; Hawk, J. L. M. Photodermatology. 1.ed. NewYork: Informa Healthcare, 2007. p. 29-40

37.Fiório FB, Albertini R, Leal-Junior EC, de Carvalho Pde T. Effect of low-level laser therapy on types I and III collagen and inflammatory cells in rats with induced Lasers Med Sci.2014 Jan;29(1):313-9.doi:10.1007/s10103-013-1341-2.

Carvalho F.A.D.; AFONSO C.L, treatment physical therapy ambulatory of injuries for burning using laser deservice low power,Burns v.35 S,p; S172-2009

38. Kumar V, Abbas AK, Fausto N. 2005. Robbins e Cotran –Patologia: bases patologicas das doencas. 7a ed. Elsevier, Rio de Janeiro.

39. Dário G.M. 2008. Avaliação da atividade cicatrizante deformulação contendo argila medicinal sobre feridas cutâneas emratos. Dissertação de mestrado, Universidade do Extremo SulCatarinense, Criciúma, 78p.

40.Barbul A. 2006. History of wounds healing, p.25-78. In:Brunicardi F.C., Seymour I., Schwarts D.L., Dun D.K. &Andersen R.E. Schwartz's Surgery. Companion handbook,Ontario.

41.Santoro, M.M. & Gaudino G. 2005. Cellular and molecular facetsof keratinocyte reepithelization during wound healing. Experimental Cell Research. 304:274-286.

42. Neto J.C.L. Considerações sobre a cicatrização e o tratamentode feridas cutâneas em equinos em 2003. Online. Disponível nainternet http://br.merial.com/pdf/arquivo8.pdf

43. 48. Metcalfe, A.D.; Ferguson, M.W.J. Tissue engineering of replacement skin:the crossroads of biomaterials, wound healing, embryonic development, stem cells and regeneration. J R Soc Interface, v.4, n.14, p.413-437, Jun. 2007

44. Carvalho P.T.C. 2002. Análise da cicatrização de lesõescutâneas através de espectrofotometria: estudo experimental emratos diabéticos. Dissertação de mestrado, Universidade de SãoPaulo, São Carlos. 72p.

45.Mandelbaum S.H., Di Santis E.P. & Mandelbaum M.H.S. 2003.Cicatrização: conceitos atuais e recursos auxiliares – Parte 1. Na Bras de Dermatol. Jul./ago., Rio de Janeiro, RJ. 78(4):393-410

46. Tazima MFGS, Vicente YAMVA, Moriya T. Biologia da ferida e cicatrização. Medicina (Ribeirão Preto) 2008; 41(3): 259-64.

47. Folkman J, Shing Y. Angiogenesis. J Biol Chem.1992;267:10931-4

48. Li J, Foitzik K, Calautti E, Baden H, Doetschman T,Dotto GP. TGF-beta3, but not TGF-beta1, protectskeratinocytes against 12-O-tetradecanoylphorbol13-acetate-induced cell death in vitro and in vivo. J BiolChem. 1999;274:4213-9.

49. Risau W. Mechanisms of angiogenesis. Nature.1997;386:671-4.

50. Folkman J, D'Amore PA. Blood vessel formation: what isits molecular basis? Cell. 1996;87:1153-5

51 Detmar M, Brown LF, Berse B, Jackman RW, Elicker BM,Dvorak HF, et al. Hypoxia regulates the expression ofvascular permeability factor/vascular endothelialgrowth factor (VPF/VEGF) and its receptors in humanskin. J Invest Dermatol. 1997;108:263-8.

52. Remensnyder JP, Majno G. Oxygen gradients in healingwounds. Am J Pathol. 1968;52:301-23

53. Gabbiani G, Hirschel BJ, Ryan GB, Statkov PR, Majno G.Granulation tissue as a contractile organ. A study ofstructure and function. J Exp Med. 1972;135:719-34.

54. Arnold F, West DC. Angiogenesis in wound healing.Pharmacol Ther. 1991;52:407-22.

55. Karukonda SR, Flynn TC, Boh EE, McBurney EI, RussoGG, Millikan LE. The effects of drugs on woundhealing--part II. Specific classes of drugs and their effecton healing wounds. International journal of dermatology.2000;39:321-33

56. Oliveira A.F. 2008. Avaliação da atividade cicatrizante daCaesalpinia ferrea (tul.) Martius (Jucá) em lesões cutâneas decaprinos. Dissertação de mestrado, Universidade Federal Ruraldo Semiárido, Mossoró, Rio grande do Norte, 65p.

57. Chavantes, MC. Laser em bio-medicina: principios e prática. São Paulo: EditoraAtheneu, 2009.