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ILIB LASERTHERAPY AND ITS SYSTEMIC EFFECT MARKERS: INTEGRATIVE REVIEW

Rebeca Góes Gonçalves[1], Ana Vitoria Gonçalves de Oliveira Cruz[2], Lucas dos Santos Nunes[3], Larissa Duarte Ferreira[4], Danyela Darienso[5], Ester Suane Lima Monteiro[6], Emily Dhara dos Santos Ferreira[7],ÍtaloSoares Eneias[8], Pedro Guilherme CastilhoCosta[9], Taynara Camille Guilherme Lima[10], Erick Souza Neri[11], João Douglas Quaresma de Oliveira[12]and Ana Rita Pinheiro Barcessat[13]

[1]Graduanda de Bacharelado em Enfermagem pela Universidade Federal do Amapá (UNIFAP); [2] Graduanda de Bacharelado em Enfermagem pelaUNIFAP; [3] Graduandode Bacharelado em Enfermagem pela UNIFAP;[4]Enfermeira, Mestra em Ciências da Saúde pela UNIFAP; [5]Odontóloga, Mestranda em Ciências da Saúde pela UNIFAP; [6]Graduanda de Bacharelado em Enfermagem pela UNIFAP; [7]Graduanda de Bacharelado em Enfermagem pela UNIFAP;[8] Graduando de Bacharelado em Medicina pela UNIFAP; [9]Graduando em Bacharelado de Enfermagem pela UNIFAP;[10] Enfermeira, Mestranda em Ciências da Saúde pela UNIFAP; [11]Enfermeiro, Residente em Infectologia pela Universidade Estadual de Londrina (UEL); [12]Graduandode Bacharelado em Enfermagem pela UNIFAP;[13] Doutoranda em Genética Médica pela Universidade de Sassari – Itália, Docente do curso de Bacharelado em Enfermagem na UNIFAP

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Corresponding author:
Rebeca Góes Gonçalves

ABSTRACT

Intravascular laser Irradiation of Blood (ILIB) consists of transcunaneos blood irradiation by low-power laser capable of generating a biological response to the photostimulation cell. From the range of applications described in the scientific literature, this research aims to review and describe the main effects of ILIB therapy. It’s an integrative literature review, in order to answer the question: “What’s the evidence that the use of ILIB therapy impacts the clinical condition of patients at a systemic level?”. From the data collection on the platforms PubMed, VHL, Web of Science and Scopus, 7 articles were selected to compose the review. It was then observed the description of effects on inflammatory interleukins, erythrocyte viscosity, glucose, HDL, LDL, mitochondrial DNA, immunoglobulins, CuZn Superoxide Dismutase (SOD) enzyme and on the immune system. The effects anti-inflammatory, immunological and antioxidants were the most predominant, capable of improving the general condition of patients by stimulating circulating cells in the short term. Therefore, ILIB presents itself as promising therapeutics with a supporting and complementary character in several clinical situations, in order to improve the quality of life of people and their affections.

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INTRODUCTION

Although the term ILIB is an acronym for the word in English “Intravascular Laser irradiation of blood”, the technique consists of transcutaneous or transmucosal and non-intravascular irradiation of a measurable pulse artery , predominantly used in the radial artery through a bracelet-type device, by low-intensity red or infrared laser. It’s a painless technique, without side effects and non-invasive, performed with a specific wristband with continuous irradiation (Gomes; Schapochnik, 2017; Nuñez, 2018). ILIB therapy began to be studied in 1981 in the former Soviet Union and, three decades later, has been clinically applied in the treatment of several pathologies such as arterial hypertension, diabetes mellitus, vascular diseases, pneumonia, tissue repair, endometriosis and autoimmune diseases, in addition to used in aesthetic treatment clinics with the aim of stimulating collagen production for the purpose of skin rejuvenation and scar improvement. Futhermore, several areas of health sciences are appropriating its use, such as medicine, dentistry, nursing and physiotherapy, in order to impact patients' quality of life indices. (Isabella *et al.,* 2019; Gomes; Schapochnik, 2017; Huang *et al.*, 2012). The photobiomodulation through ILIB occurs by the biological response to irradiation by cells, stimulating mitochondria and cell membrane. This stimulation, through the Cytochrome C photoreceptor, activates the production of Adenosine triphosphate (ATP), decreases the production of free radicals and alters the sodium and potassium pumps and calcium channels, which improves the flow of electrons in the respiratory chain, thus generating biological effects on a systemic scale (Huang *et al.* , 2012; Yang *et al.* , 2017; Isabella *et al.*, 2019; Da Silva Leal *et al.* 2020). Even though the use of ILIB technology has grown over the years, the evidence needs to be systematized in order to speak of evidence-based practice. Therefore, this research aims to review and describe the main markers of the systemic therapeutic effects of ILIB found in the literature.

METHOD

This is an integrative review of the constructed literature from six fundamental steps: elaboration of the guiding question; search or sampling in the literature; data collect; critical analysis of selected studies; discussion of results; review presentation (Souza *et al.*, 2010). The guiding question was based on the PICO strategy, an acronym for P: population/patients (Patients with chronic or acute conditions); I: intervention (ILIB therapy); C: comparison/control (non-intervention); O: outcome (improvement of the clinical picture), and was consolidated in: What's the scientific evidence that the use of technology Intravascular Laser Irradiation of Bloodimpact the clinical condition of patients at the systemic level? In the direction of data collectionthe descriptors found on the platform Health Sciences Descriptors (DeCS) were used: Low Intensity Light Therapy, Laser Biostimulation. In addition, keywords were also used: "Intravascular Laser irradiation of blood ", "ILIB", "Laser therapy ", "Blood irradiation" and " Low-level light therapy ". Likewise, the Boolean operators " *AND*" and " *OR* " in search strategies. Data collection was carried out in January of 2022, in which the electronic databases consulted were: MedLine(National Library of Medicine- PubMed), MedLine (Virtual Health Library - VHL), SciELO (Web of Science) and Elsevier (Scopus).

At strategies in search used were: (intravascular laser irradiation of blood) AND (low level light therapy) AND (laser biostimulation) for PubMed; (intravascular laser irradiation of blood) OR (ilib) AND (terapia com luz de baixaintensidade) OR (low level light therapy) AND (bioestimulação a laser) OR (laser biostimulation) for VHL; (intravascular laser irradiation of blood) AND (low level light therapy) AND (laser therapy) AND (blood irradiation) for Web of Science; (intravascular laser irradiation of blood) OR (ilib) AND (low-level light therapy) for Scopus. Inclusion criteria: articles published in the period from 2000 to 2022, full text, English, Portuguese, Russian or Spanish language, primary studies with grade A and B recommendation according to "Oxford Center for Evidence-based Medicine - levels of Evidence (March 2009) ". Exclusion criteria were: duplicated articles between databases and animal studies. For critical analysis of the results, the levels of evidence of Oxford Center for Evidence-based Medicine- levels of Evidence, with its last update in March 2009, that enable the organizational structuring of hierarchical form of the studies according to their methodological rigor (Souza *et al.,* 2010). Finally, the discussion of the results was carried out from the identification and critical analysis of the contributions and limitations of the studies for the understanding of the effects of the ILIB therapy, for the suggestion of future researches and use in clinical practice.

RESULTS

The search in the databases made it possible to capture 52 articles, in which a selection was carried out and, from that, 38 were excluded according to the determined criteria. Then, 14 articles were read in full, choosing those that strictly fit the inclusion criteria. Thus, 7 were selected for the composition of the integrative review. Next, Figure 01 presents a flowchart with the synthesis of the step-by-step process carried out in the data collection, showing the course of the research.
Research results. Adapted from PRISMA (2020). Table 01 presents the compilation of these articles, describing the author and year, the objectives of the study, the ILIB protocol used and the results found.

DISCUSSION

From the analysis of the selected articles, four thematic categories were identified: Blood rheological factors under the influence of ILIB therapy; The anti-inflammatory and immunological effects of ILIB therapy; The therapeutic action on the metabolism of metabolites and The antioxidant effect by ILIB irradiation.

Blood rheological factors under the influence of ILIB therapy

Blood rheological parameters are related to blood flow behavior, such as erythrocyte sedimentation rate (ESR) and blood viscosity. From this, adequate tissue perfusion remains within the limits of these parameters, so any significant change can contribute to the development of a condition or disease, increasing viscosity and altering blood flow (Hiatt; Brass, 2013; Musawi *et al.*, 2016). Several factors can impact blood viscosity, the main parameter of blood rheology, such as erythrocyte concentration, red blood cell deformability and aggregation, and plasma viscosity (MI *et al.,* 2004). The erythrocyte aggregation, in turn, corresponds to a determinant function in terms of blood viscosity and the decrease in flow velocity, since this presents itself according to the increase in aggregation (Carrera *et al.*, 2006). Laser irradiation by ILIB can modulate ESR by reducing erythrocyte aggregation, which suggests the study of Mi *et al.* (2004), when the experimental group, which had blood hyperviscosity, decreased its rates by 7.5% in all samples after the application of the therapy. According to research by Musawi*et al.* (2016), blood plasma samples irradiated by ILIB also showed changes in ESR, from the interference in the serum concentration of fibrinogen and globulins, since fibrinogen is a large erythrocyte aggregator.

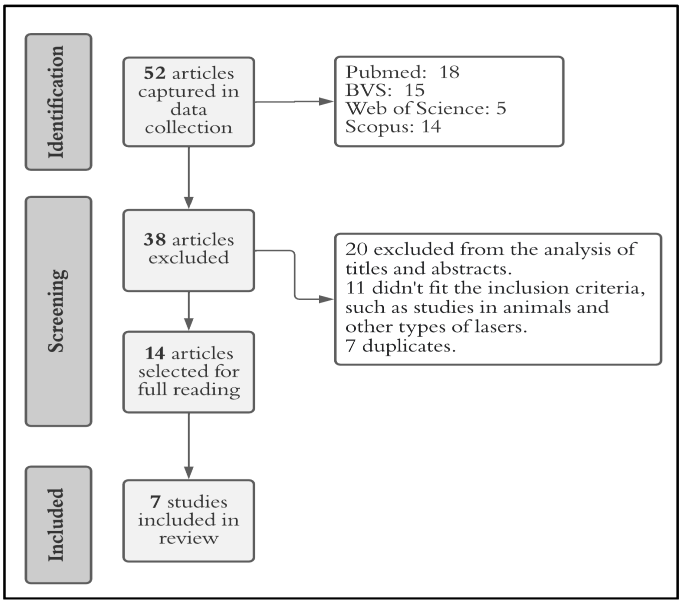
One of the consequences of this aggregation is the formation of thrombus, which are composed of degenerating fibrin, platelets, erythrocytes and leukocytes. A thrombus can cause ischemia or even infarction, and, consequently, symptoms and conditions arising from the affected tissue or organ (SEBBEN, 2012). Yang's case report *et al.* (2017) showed that stroke patients can eliminate the appearance of Crossed Cerebellar Diaschisis (CHD) in the subacute post-stroke stage, with the use of ILIB therapy. ILIB becomes an alternative to traditionally used thrombolytic agents, since, in general, the authors report that patients may not diagnose CHD in time to receive thrombolytic drugs, and may develop complications and be referred to the intensive care unit. From that point on, Isabella *et al.* (2019) analyze that Russian university clinics use ILIB irradiation to avoid thromboembolic complications and optimize postoperative recovery, as suggested by Yang *et al.* (2017). Therefore, stimulation of fibrinolytic capacity and reduction of platelet aggregation are points that contribute to reducing blood viscosity, thus preventing thrombus formation. ILIB interferes with the arachidonic acid cascade, an important pro-inflammatory pathway in the body, generating an anti-inflammatory action, and inducing a greater production of prostacyclins, a vasodilator resource and platelet aggregation inhibitor. In this way, an aspect of greater blood fluidity is provided, which facilitates the passage of red blood cells through narrow capillaries and hypoxic tissues, making it difficult to develop cardiovascular problems and minimizing inflammation. From these studies, ILIB therapy was shown to be effective in improving blood microcirculation and rheological properties (MI *et al.*, 2004; MUSAWI *et al.*, 2016).

The anti-inflammatory and immunological effects of ILIB therapy: Interference in the arachidonic acid cascade occurs through stimulation of protein synthesis of superoxide dismutase (SOD CuZn) by ILIB, which blocks the production of prostaglandins in the cascade, generating an anti-inflammatory effect, and induces the production of prostacyclins, improving blood flow. (DA SILVA LEAL *et al.*, 2020). Furthermore, it's possible that the therapy influences the increase in the production of anti-inflammatory interleukins (IL-4, IL-10) and the reduction of pro-inflammatory ones (TNF-α, IL-1β, IL-8, IF-γ, IL-18), modifying local inflammatory

Table 01. Distribution of studies selected for the integrative review

Author	Purposes	Study design/ Grade of recommendation/ Level of evidence / Database	ILIB Protocol	Results
HUANG *et al* ., 2012.	Investigate the clinical effects of therapy ILIB no oxidative stress and mitochondrial dysfunction in individuals with Chronic Spinal Cord Injury (ICME).	Randomized Clinical Controlled Trials A 1B MEDLINE	Wavelength: 632.8 nm Radiant power: 4mW Application time: 1h per session Number of sessions: 15 sessions in 3 weeks	Reduction of oxidative stress and mitochondrial dysfunction. Increase: HDL, copies of mitochondrial DNA Reduction: LDL.
DERKACZ *et al* ., 2013.	To determine the effect of low-level intravascular laser irradiation on use during the inflammatory activity of the Percutaneous Coronary Intervention (PCI) process.	Randomized Clinical Controlled Trials A 1B ELSEVIER	Wavelength: 808 nm Radiant power: 100 mW/cm² Application time: duration of PCI. Number of sessions: 1	Decreased risk for restenosis in percutaneous coronary intervention.Increased anti-inflammatory interleukin: IL-10 Reduction of pro-inflammatory interleukins: IL-1β and IL-6
KAZEMI KHOO *et al.* 2013	To evaluate the effects of ILIB on blood metabolites in type 2 diabetic patients.	Clinical Trial B 2C MEDLINE	Wavelength: 405nm Radiant power: 1.5 mW Application time: 30min Number of sessions: 1	Effects on the production of metabolites. Reduction: Glucose, Glucose-6-phosphate, L-histidine, L-Alanine, acid dehydroascorbic, (R)-3-hydroxybutyric acid. Boost: L-arginine
4- KAZEMI KHOO; ANSARI, 2014.	To compare the effects of blue and red lights on blood sugar levels in patients with type 2 diabetes.	Clinical Trial B 2C MEDLINE	Wavelength: 632.8 nm (red light) and 405 nm (blue light) Radiant power: 1.5 mW Application time: 30 min Number of sessions: 7 red light and 7 blue light	Serum blood sugar level reduction in all samples from 24 patients.
5- BURDULI; GABUEVA, 2016.	Elucidate the influence of low-level laser radiation on test results. nitroblue tetrazolium (NBT) in patients with community-acquired pneumonia.	Randomized Clinical Controlled Trials A 1B MEDLINE	Wavelength: 405 nm Radiant power: 1mW Application time: 5-7 min Number of sessions: 7	Positive effect on the functional activity of leukocytes. Increase: Neutrophil phagocytosis. Significant reduction in test values of the nitroblue.
6- YANG *et al.* , 2017.	Investigate the clinical effects of therapy *Intravascular Laser irradiation* (ILIB) on diaschisis Cerebellar Crusade and to evaluate the therapeutic effect in the subacute stage after stroke.	Case report B 3B ELSEVIER	Wavelength: 632.8 nm Radiant power: 3.5 to 4.0 w/cm² Application time: 60 min Number of sessions: 10	Improves blood perfusion of the affected cerebellar hemisphere by AVE.Increased energy and muscle strength. It promoted the formation of neuronal cells.
7- DA SILVA LEAL *et al.,* 2020	To evaluate the effects of ILIB in reducing pain and improving quality in patients with Diabetic Neuropathy.	Randomized Clinical Controlled Trials A 1B MEDLINE	Wavelength: 660 nm Radiant power: 100mW Application time: 30 min Number of sessions: 30	Decreased pain and increased quality of life (SF-36, pain Detect and EVA)

Figure 01- Flowchart of bibliographic research results.



Source: Research results. Adapted from PRISMA (2020).

activity (Derkacz *et al.*, 2013; Chiran *et al*., 2013; Konoplya *et al.*, 2016). Among the cardinal signs of inflammation with ILIB irradiation, pain was reduced in patients with diabetic neuropathy studied by Da Silva Leal *et al.* (2020). Moreover, this study evidences the improvement in the quality of life of these people, through specific questionnaires for quality of life and pain applied before and after therapy, highlighting its analgesic effect. In the article by Konoplya*et al*. (2016) chose women diagnosed with chronic endometritis (CE), a disease characterized by perennial inflammation, which can be caused by microorganisms such as *Streptococcus spp.* and *Chlamydia.* Among the main clinical implications are pelvic pain, dyspareunia and bleeding, and, in addition, CE can strongly influence the levels of immune cells in the endometrium. In this research, it was confirmed that the use of ILIB as a treatment implies, mainly: in the stimulation of the intracellular metabolism of immunocompetent cells; in rebalancing the synthesis of cytokines, both pro-inflammatory and anti-inflammatory, and members of the complement system (C4). Blood irradiation by ILIB promotes oxygenation and decreases CO_2 pressure, thus, stimulates metabolism and tissue regeneration and activates non-specific mechanisms of immunity. On these immune mechanisms, ILIB promotes increased activity of the complement system, as also evidenced by Konoplya*et al*. (2016), it reduces the amount of C-reactive protein, which indicates infection, stimulates the production of T and B cells, and promotes an increase in the level of immunoglobulins (Timofeyev *et al.*, 2000; Khoo; Ansari 2014).

Another immunological factor analyzed was the phagocytic activity of neutrophils, by Burduli and Gabueva (2016), the authors bring from the literature that it varies according to antigens and toxins and, within the context of acute inflammation caused by community-acquired pneumonia (CAP) happens a hyperactivation of the release of neutrophils, enzymes and bactericidal factors in the extracellular environment. The functional activity of neutrophils was evaluated by the nitroblue tetrazolium test, capable of measuring the phagocytic level of neutrophils. After treatment with intravenous laser, patients in the main group showed a significant reduction to the normal rates of this test, this event is considered by the authors as a positive effect of laser radiation on the immune reaction (phagocytosis) to inflammation.

The therapeutic action on the metabolism of metabolites: Khoo's study *et al.* (2013) demonstrates that intravenous laser therapy lowers glucose, cholesterol, and stabilizes the body's immune and hormonal status. In this research, it is suggested that irradiation with blue light can increase the production of arginine, causing the release of several hormones such as insulin and glucagon, and nitric oxide, promoting vasodilation, microcirculation and decreasing the infarct area. Therefore, as there is an increase in the production of prostaglandins, reducing inflammation, together with accelerated microcirculation, edema is reduced and the accumulation of catabolites is eliminated, meaning a reduction in the consumption of oxygen and glucose by the cells. Thus, the reduction of glucose in the face of the use of ILIB therapy may reduce the risk of developing diabetes. Erythrocyte aggregation can also influence changes in diabetic patients, such as skin lesions. In this way, blood rheological parameters can precede the appearance of lesions such as diabetic foot, requiring premeditated treatment so that the condition does not evolve. Importantly, the pancreas can regenerate tissue, restoring its function, Ramdown (1999) provided this pancreatic ability after reducing the serum glucose level without using hypoglycemic agents, suggesting that laser therapy can stimulate tissue regeneration, including beta cells of the Islets of Langerhans (Ramdawon, 1999; Khoo; Ansari, 2014). Therefore, ILIB can be an alternative for both internal and external symptoms of diabetes (Carrera *et al.*, 2006; Khoo *et al*., 2013).

Furthermore, in the study by Huang *et al.* (2012) there is a significant reduction in the levels of Low-density lipoprotein (LDL), the bad cholesterol, and an increase in the levels of High-density lipoprotein (HDL), the good cholesterol. Therefore, ILIB can influence lipid metabolism and assist in the management of dyslipidemia-related diseases.

The antioxidant effect by ILIB irradiation: Oxidative stress is a state of imbalance caused by the excessive release of free radicals, highly reactive molecules, which are produced in different pathways and situations, such as mitochondrial metabolism. This imbalance can harm the organism, becoming insufficient to eliminate such molecules and, with that, they can degrade other adjacent biological structures, influencing the risk of developing inflammatory reactions and, consequently, diseases (Santana, 2021). Mitochondria are notable producers of reactive oxygen species (ROS), which can harm lipids, proteins and mitochondrial DNA (mtDNA), influencing their malfunction. The absorption of low-intensity radiation increases the metabolism and synthesis of Superoxide Dismutase, the main protein that regulates the body's oxidative system. ILIB works by stimulating the enzyme CuZn Superoxide Dismutase (SOD), which protects against the superoxide radical, the initial radical from oxygen that, despite damaging the cell, the absence of its neutralization can be even more harmful, as it leads to the formation of the hydroxyl radical, highly harmful to the cell and, consequently, to the tissues. Thus, by stimulating this enzyme, ILIB therapy can protect cells against neoplasms and aging, presenting an antioxidant effect (Huang *et al*., 2012; Yang *et al*., 2017; DA Silva Leal *et al*., 2020). In Huang's study *et al.* (2012) individuals with chronic spinal cord injury were analyzed, which, when compared to the control group, obtained a reduction in oxidative stress and mitochondrial dysfunction caused by their condition. From this, the ILIB biostimulation encourages ATP synthesis and improves cell signaling, it is able to contribute to the regulation of cell antioxidant defense (Zhang *et al.*, 2008).

CONCLUSION

The systemic action of the ILIB therapy is proven in the bibliographic results of this study, in which it is observed that the cellular biomodulation generated by the intravascular laser is able to provoke a series of biological responses in the body. Therefore, the forms of application of this therapy involve acute and chronic clinical conditions, since the treatment can be alternative or complementary to traditional medications. In addition, ILIB irradiation can contribute to shortening the treatment period of the disease, increasing the duration of remission and providing a greater sense of well-being and quality of life for the patient. However, randomized clinical trials are still needed in order to promote the dissemination of knowledge to health professionals and to elucidate the mechanism of action in the body.

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