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Major approaches to laser therapy in regenerative processes in bucco-maxillo-facial bone defects: a concise systematic review

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Abstract

Introduction: In the context of oral and bucco maxillo regenerative processes, bone defects are caused by trauma, surgery, tumor, congenital disease, and other pathological factors. Low-level laser therapy (LLLT) can regulate cellular functions by affecting cell growth and cytokine secretion, thereby exerting a variety of biological effects. **Objective:** It was to carry out a concise systematic review of the main stimulatory and regenerative effects of laser therapy on bone formation processes in maxillary oral surgery for bone defects. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was carried out from February to March 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, using articles from 1993 to 2022. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed accordingly, according to the Cochrane instrument. **Results and Conclusion:** A total of 114 articles were found, 48 articles were evaluated and 29 were included and developed in this systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 16 studies with a high risk of bias and 40 studies that did not meet GRADE. It was concluded that there is scientific evidence of the positive effect of low-intensity laser energy on bone regeneration within a certain relationship between dose and output power. The low-intensity laser stimulates cellular metabolism, increasing protein synthesis and subsequent bone regeneration. A high dose combined with low potency or a low dose combined with high potency appears to produce a positive effect.

Keywords: Laser. Laser therapy. Bone regeneration. Bone defects.

Introduction

In the context of oral and bucco maxillo regenerative processes, bone defects caused by trauma, surgery, tumor, congenital disease, and other pathological factors impair both structure and function, seriously affecting the quality of life and the physical and mental health of patients [1,2]. The treatment of bone defects mainly includes autologous and allogeneic bone transplants or filling with biomaterials [3]. For successful tissue engineering bone repair and regeneration, it is essential to restore nutritional supply and promote osteogenic differentiation of stem cells as early as possible [4-6].

In this regard, the vascularization speed of engineered bone tissue grafts is slow due to insufficient blood supply in the initial stage, resulting in graft ischemia and necrosis [7-9]. In bone modeling associated with endochondral ossification, hypertrophic chondrocytes express high levels of vascular endothelial growth factor (VEGF), which promotes vascular invasion of cartilage and recruits chondroclasts to resorb hypertrophic cartilage and osteoblasts to build bone matrix [7,10-12].

In this sense, hypoxia-inducible factor 1α (HIF-1α) is a transcription factor directly regulated by hypoxia [13-15]. Studies have shown that endothelial HIF-1α is an important promoter of H-type vessel formation in the metaphysis. Specific deletion of HIF-1α in endothelial cells resulted in a significant reduction of osteoprogenitors, associated with a decrease in

trabecular bone formation [12]. HIF-1α signaling plays a vital role in regulating the abundance of H-type vessels and couples angiogenesis with osteogenesis.

In this context, low-intensity laser therapy (LLLT), also known as photobiomodulation (PBM), is a treatment that uses low-intensity lasers or light-emitting diodes (LEDs) to modulate cellular functions. LLLT can regulate cellular functions by affecting cell growth and cytokine secretion, thereby exerting a variety of biological effects [16-18]. Many studies have shown that LLLT has positive photobiostimulatory effects on cell proliferation, angiogenesis, osteogenic differentiation, bone regeneration, and fracture healing [19-21]. ROS can promote the oxidation of ferrous ions (Fe^{2+}) and inhibit the activation of proline hydroxylases, thus inhibiting HIF-1α degradation [22,23]. Thus, the ROS/HIF-1α signaling pathway plays a critical role in osteogenic progression induced by LLLT treatment. Furthermore, the transforming growth factor β (TGF-β) superfamily is encoded by 23 different genes, which have been shown to form complex interactions and dependence in the regulation of pluripotency and stem cell differentiation in several experimental models. Previous studies reported that LLLT could activate latent TGF-β inducing ROS in a dose-dependent manner, and TGF-β can induce differentiation of human dental stem cells into odontoblastic cells *in vitro* [24,25].

Therefore, the present study aimed to carry out a concise systematic review of the main stimulatory and regenerative effects of laser therapy on bone formation processes in oral maxillofacial surgery for bone defects.

Methods

Study Design and Data Sources

This was followed by a systematic literature review model, according to the PRISMA rules. The literary search process was carried out from February to March 2023 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 1993 to 2022, using the descriptors (MeSH Terms): *Laser. Laser therapy. Bone regeneration. Bone defects,* and using the Booleans "and" between the descriptors (MeSH Terms) and "or" between the historical findings.

Study Quality and Risk of Bias

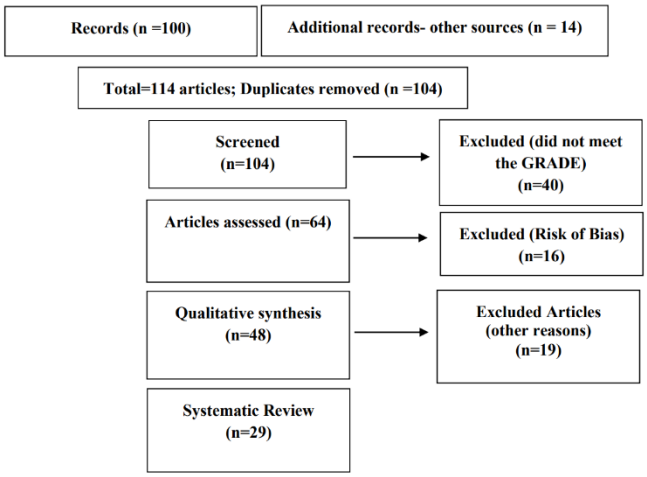
The quality of the studies was based on the GRADE instrument, with randomized controlled clinical studies, prospective controlled clinical studies, and studies of systematic review and meta-analysis listed as the studies with the greatest scientific evidence. The risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

Summary

A total of 114 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the theme of this article, resulting in 64 articles. A total of 48 articles were evaluated and 29 were included and developed in this systematic review study (**Figure 1**). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 16 studies with a high risk of bias and 40 studies that did not meet GRADE.

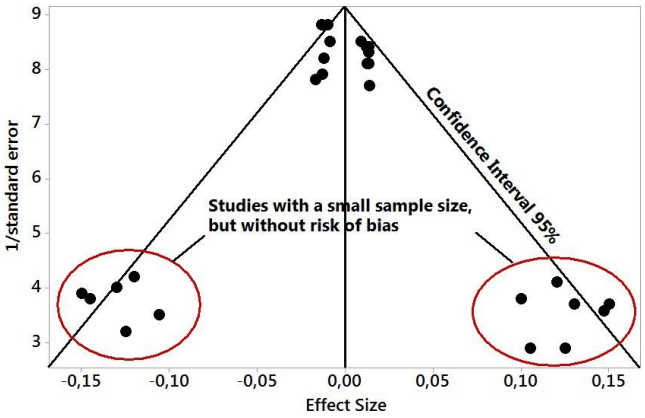
Figure 1. Selection of studies.



Source: Own authorship

Figure 2 presents the results of the risk of bias in the studies using the Funnel Plot (Effect Size - Cohen's Test). The sample size was determined indirectly by the inverse of the standard error. The graph showed symmetric behavior, not suggesting a significant risk of bias in studies with small sample sizes, which are shown at the bottom of the graph.

Figure 2. The symmetric funnel plot does not suggest a risk of bias between the small sample size studies that are shown at the bottom of the graph (N = 29 studies).



Source: Own authorship

Major Findings

Several energy-based devices have been used with substantial clinical improvement in the treatment, as listed in the medical literature, however with a limited number when applied in clinical studies. In the health area, these devices are widely used in various types of treatment, such as LASER, LED, TEMs, infrared devices, Ultrasound, and radiofrequency, among others. The Low-level laser therapy (LLLT), with endogenous action and Photodynamic Therapy (PDT), acts in the exogenous environment [1,2].

This device promotes a photobiomodulation action at the molecular level in cells, tissues,

and organs. LLLT is when optical radiation interacts with an endogenous photo acceptor and produces cellular/tissue biomodulation. While this interaction occurs, in the presence of molecular O2, exogenous substances carry out the process of photodynamic therapy (PDT), performing a cytotoxic action on the treated tissue [5,6].

In the treatment of photobiomodulation with a low-power laser, there should not be an increase in the temperature of the irradiated tissue. The thermal rise must not exceed 1°C and the power must always be less than 1 Watts. Photobiomodulation may involve two types of tissue action, biostimulation and/or bioinhibition. The biomodulation action provoked by LLLT, depending on the parameters of use (intensity, duration, wavelength, focus size, and optical properties of the target tissue), can cause both positive stimulation (biostimulation) and inhibition (bio-inhibition) in the tissue -irradiated target [5-7].

Due to the irradiation having a very low intensity, the biological action comes from the direct action of the radiation at the level of cellular photo acceptors, mainly in the components of the respiratory chain in the mitochondria, as well as, in cell membranes, at the level of Ca^{++} channels and pumps of Na^{+} and K^{+}, having a cumulative action and not incurring in local temperature elevation [8].

In this regard, the laser used at low power could produce biological effects. LLLT enables anti-inflammatory effects and tissue repair, inducing light stimulation in cells and gradual reactions in tissues (photobiostimulation). The electro-microscopic responses of irradiation, observed with laser in open wounds, were through the synthesis of collagen, induction of neovascularization, and increase in the synthesis of enzymes. The modulating effects of the laser can help repair processes, elevating the inorganic matrix of bone and osteoblasts, stimulating the growth of lymphatic and blood capillaries, and facilitating cell proliferation and tissue healing. The wavelengths (600- 1000nm) of LLLT have photobiomodulation properties, such as osteoblast proliferation, collagen formation, facilitating bone regeneration, pain relief, improving wound healing, nerve repair, and re-epithelialization [1-4].

Also, inflammation can be characterized as a nonspecific response of the body, the defense against aggressive agents. The inflammatory response begins by trying to isolate the agent and minimize its damage, with a set of vascular, morphological, and biochemical changes in the connective tissue. Inflammation can be classified into acute and chronic depending on its duration. Injured cells activate the mononuclear phagocytic system (circulating monocytes and tissue macrophages), initiating the cascade of events through the secretion of cytokines from the interleukin 1 family (IL-1β) and tumor necrosis factor (TNF-α). Locally, these molecules have pleiotropic action on matrix cells or tissue stroma, acting mainly on fibroblasts and endothelial cells, causing the release of a second set of cytokines. These include IL-1β and TNF-α, as well as IL-6, IL-8, inflammatory (MIP-1), and chemotactic (MCP) proteins from macrophages. This last protein, together with IL-1β, IL-8, and transforming growth factor beta (TGF-beta) attracts monocytes and neutrophils to the inflammatory focus. Which, in turn, secrete a third set of cytokines, including TNF-α and other chemotactic factors, which feed back the inflammatory process [26,27].

The vascular endothelium plays a central role in communicating the inflammatory site and circulating leukocytes. Both by the expression of adhesion molecules, which facilitate the tissue migration of defense cells (monocytes and neutrophils), as well as the modification of vascular tonus, mediated by metabolites of arachidonic acid (prostaglandins, thromboxanes, and leukotrienes). This occurs by the breakdown of phospholipase A2, nitric oxide (NO), and kinins, causing vasodilation (erythema), increasing vascular permeability by histamine (edema), and incurring arterial hypotension. Prostaglandins are produced by the enzyme cyclooxygenase (COX). COX-1 regulates normal physiological functions, and COX-2 is essentially inflammatory and important in resolving this process. The therapeutic advantages of photobiomodulation involve the increase of local microcirculation, promotion of angiogenesis, vasodilation, inhibition of COX inflammatory mediators, such as prostaglandin E2 (PGE2), activation of defense cells, antioxidant effects, and acceleration of healing [7,8].

In this scenario, several studies demonstrate the benefits of LLLT in bone neoformation, increasing proliferation and differentiation in bone cells and calcification. In osteoblast cultures, electron microscopy demonstrated an improvement in cellular functions, increased alkaline phosphatase activity, and collagen

type I mRNA synthesis. The formation of vascularized bone is fundamental for bone tissue engineering. The growth of specialized blood vessels called type H is associated with bone formation [28].

The laser has been proposed as an effective tool to aid in bacterial decontamination and modulation of peri-implant tissue inflammation. Thus, a pilot clinical study evaluated the adjuvant benefits of Er: YAG laser irradiation for regenerative surgical therapy of bone defects associated with peri-implantitis. A total of 24 patients diagnosed with peri-implantitis with radiographic intraosseous defect were randomized into two groups. Both test and control groups received the following treatment: mechanical open-flap debridement, suprarenal implantoplasty, bone grafting using a mixture of human allograft with human allograft mass of demineralized bone matrix, and then covered with acellular dermal matrix membrane. The only difference in the test group was the adjunctive use of the Er: YAG laser to modulate and remove inflammatory tissue, as well as to decontaminate the implant surface. Clinical assessments including pocket depth (PD), clinical attachment level (CAL), and gingival index (GI) were performed by calibrated masked examiners for up to 6 months after surgery. Standardized radiographs were also taken to assess linear bone gain and bone filling of the defect. Student t-tests were used to analyze these clinical parameters. Both groups showed significant reductions in PD, GI, and CAL gain over time. The test group demonstrated significantly greater PD reductions at the site level compared to the control group. No statistical differences were found in CAL gain, GI reduction, radiographic linear bone gain, or proportional reduction in defect size [29].

Conclusion

It was concluded that there is scientific evidence of the positive effect of low-intensity laser energy on bone regeneration within a certain relationship between dose and output power. The low-intensity laser stimulates cellular metabolism, increasing protein synthesis and subsequent bone regeneration. A high dose combined with low potency or a low dose combined with high potency appears to produce a positive effect.

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Ethical Approval

Not applicable.

Informed consent

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

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