MedNEXT
Journal of Medical an Health Sciences

REVIEW ARTICLE

DOI: 10.54448/mdnt23202

Main clinical findings of oral and maxillofacial osteonecrosis, bisphosphonates and alternative treatment with photobiomodulation and magnetotherapy: a systematic review

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DOI: https://doi.org/10.54448/mdnt23202
Received: 01-08-2023; Revised: 03-10-2023; Accepted: 03-10-2023; Published: 03-10-2023; MedNEXT-id: e23202

Abstract

Introduction: Bisphosphonates are drugs of a class widely used in several medical specialties. Its main property is to inhibit calcium phosphate precipitation, decrease bone calcification and reabsorption, and reduce osteoclastic action by inducing apoptosis in these cells. Bisphosphonates have anti-angiogenic effects. Low Power Laser is widely used for surgical purposes and it acts through various effects, such as photothermal, photomechanical-acoustic, photoionizing, and photoablation. Laser with low power can be divided into 2 groups, according to the respective types of photoreceptors: Low-Intensity Laser (LIL), with endogenous action, and Photodynamic Therapy (PDT), acting in the exogenous environment, as well as magnetotherapy. **Objective:** It was to highlight the main clinical findings of oral and maxillofacial osteonecrosis through the use of bisphosphonates, as well as an alternative treatment with photobiomodulation and magnetotherapy. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was carried out from December 2022 to February 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, using articles from 1985 to 2022. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 320 articles were found, 59 articles were evaluated in full and 39 were included and developed in this systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 101 studies with a high risk of bias and 42 studies that did not meet GRADE. Patients being treated with bisphosphonates should be informed about the potential risk of bisphosphonates-related osteonecrosis of the jaws. In addition, providers responsible for breastfeeding therapy would be advised to refer patients for dental check-ups before starting treatment, allowing for patient follow-up by a multidisciplinary team. Although the morbidity of this pathology is not high, prevention must be mandatory, thus avoiding mutilating and painful processes. However, if the surgical procedure is required, the use of these new adjuvant therapies such as low-intensity laser and magnetotherapy.

Keywords: Bisphosphonates. Osteonecrosis. Treatments. Low-intensity laser. Magnetotherapy.

Introduction

In the context of oral and maxillofacial osteonecrosis, bisphosphonates (BPs) are drugs of a class widely used in several medical specialties. Its main property is to inhibit calcium phosphate precipitation, decrease bone calcification and reabsorption, and reduce osteoclastic action by inducing apoptosis in these cells [1-3]. Its prescription was initially restricted to diseases that interfered with bone metabolisms, such as Paget's disease, malignant hypercalcemia, bone metastases, osteolytic lesions, and multiple myeloma. Currently, it has also been widely prescribed for the treatment of osteoporosis and even as a prophylaxis for osteopenia [1,4].

Within the class of bisphosphonates, there are several drugs with similar action on bone tissue, varying their potency and route of administration. As an example, we can mention Sodium Risedronate, Sodium Etidronate, Zoledronic Acid, and, the one that is most prescribed, for oral use, Sodium Alendronate [1,3]. Such drugs can cause serious adverse effects in the body, it can be mentioned, among the most frequent: hypocalcemia, impaired renal function, complications in the digestive tract such as esophageal ulcer, atypical fractures of the femur, atrial/ventricular fibrillation and osteonecrosis of the jaws, the latter being the object of our study [4,5]. Patients who use this class of oral medication have the lowest prevalence of 0.01% to 0.04% of the occurrence of osteonecrosis, while those who use intravenously are affected between 8% and 12% [6].

However, it has to be reported that the complications, when they occur, are very severe and mutilating, compromising the quality of life of these patients [2]. One of the recent treatments for bone disorders is the use of anti-resorptive drugs, including hormone replacement therapy, selective estrogen receptor modulators, bisphosphonates, and denosumab, which reduce the occurrence of pain, pathological fractures, and spinal cord compression [3,7-9]. The main property of BFs is to inhibit the precipitation of calcium phosphate, decreasing calcification and bone resorption, and reducing osteoclastic action, by inducing apoptosis of these cells, which reabsorb bone tissue. These have a great affinity with bone tissue, long half-life in bones, inhibiting bone reabsorption, and can be administered orally or intravenously [4].

In this sense, the mechanisms of action of BFs in bone metabolism are complex and multifactorial, changing the osteoclastic cytoskeleton, stimulating apoptosis, and mainly reducing the proton pump with changes in pH and acid-base balance [1,2]. The clinical efficacy of BFs increases due to their capacity to bind strongly to the bone mineral. The initial release of BFs occurs by renal excretion or adsorption to bone minerals, extending over weeks to years. During bone resorption, the acidic pH in the resorption gap enhances drug dissociation in bone [2].

Also, BFs are synthetic analogs of organic pyrophosphates, where the unstable oxygen atom of the central structure (P-O-P) has been replaced by carbon (P-C-P), making it more resistant and cannot be broken down by enzymes [3]. BFs interfere with chemotaxis and osteoclast attachment to bone along with suppression of osteoclast function. Furthermore, they block the recruitment, activation, and differentiation of osteoclast precursors [10-14]. They inhibit the proliferation of macrophages, reducing their recruitment and differentiation into osteoclasts, in addition to reducing the number of osteoclasts, altering the cytoskeleton of these cells, depolymerizing the microtubules and retracting the rough membrane, thus hindering their adhesion to the bone [2,3,15-20].

Besides, BPs have anti-angiogenic effects. As such, impaired vascularity may come to play as one of the terrible factors in the development of osteonecrosis in the jaws [21-23]. They also act on immunity, resulting in the impairment of the function of myeloid cells, and dendritic cells and increasing the number of T cells [24-28]. These increase the antigenicity of cancer cells as targets and increase adaptive immunity. This impairment of local immunity with a greater infectious tendency may prove to be a key element in osteonecrosis of the jaws [29-32].

The first report of osteonecrosis of the jaws due to the use of bisphosphonates was made by Marx et al in 2003 [33]. Already in 2007, a position paper from the American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed for the first time its nomenclature Bisphosphonates Related Osteonecrosis of the Jaws (BRONJ). NO is the term used to describe bone cell death when the osteocyte becomes necrotic. Necrosis also destroys vascular endothelial cells within the bone tissue, impairing blood flow within it [3,23].

Moreover, patients who develop necrosis are aged between 35 and 95 years, with a higher prevalence between 65 and 68 years. Among the risk factors for the development of the disease, we can mention the dose and frequency administered, the potency of the drug, the route of administration, the duration of the treatment, and the half-life of the drug in the bone tissue diagnostic hypothesis, imaging tests should be requested, such as panoramic radiography and facial computed tomography. These exams demonstrate the presence of bone sequestration with osteolytic areas associated with surrounding osteoblastic areas and the appearance of bone tissue disorganization, destruction of bone cortices, periosteal reactions, and pathological fractures [21].

In this sense, 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 radiation emitted by the laser device denotes its characteristics, which is a monochromatic, coherent, and collimated wave. Such equipment allows this light energy to interact with specific tissue chromophores (hemoglobin and melanin), which have

an affinity for the wavelength of the respective laser light emitted, mainly through absorption [19].

In this aspect, lasers can be classified, according to Chavantes (2009), according to their power, into two large groups: High Power Laser (HPL) and Low Power Laser (LPL). The LPL uses energy greater than 5 W, emitting radiation capable of destroying tissue, employing high energy in very short times of around milliseconds to nanoseconds. LPL is widely used for surgical purposes and it acts through various effects, such as photothermal, photomechanical-acoustic, photoionizing, and photoablation. Laser with low power can be divided into 2 groups, according to the respective types of photoreceptors: Low-Intensity Laser (LIL), with endogenous action, and Photodynamic Therapy (PDT), acting in the exogenous environment [19].

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 can incur two types of tissue action, biostimulation and/or bio-inhibition (Chavantes et al 2009) [19]. The biomodulation action provoked by LPL, 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 (bioinhibition) in the tissue -irradiated target.

In this regard, LIL wavelengths (600–1000nm) have photobiomodulation properties, such as osteoblast proliferation, collagen formation, facilitating bone regeneration, pain relief, improved wound healing, and nerve repair, in addition to reepithelialization [14]. Inflammation can be characterized as a non-specific response by 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 [15].

Therefore, the present study aimed to highlight the main clinical findings of oral and maxillofacial osteonecrosis through the use of bisphosphonates, as well as the alternative treatment with photobiomodulation and magnetotherapy.

Methods

Study Design

This was followed by a systematic literature review model on the main clinical findings of mandible fractures, according to the PRISMA rules (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/).

Data sources and research strategy

The literary search process was carried out from December 2022 to February 2023 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 1985 to 2022, using the descriptors (MeSH Terms): "*Bisphosphonates. Osteonecrosis. Treatments. Low-intensity laser. Magnetotherapy*", 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 of Literary Findings

A total of 320 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 160 articles. A total of 59 articles were evaluated in full and 39 were included and developed in this systematic review study (**Figure 1**). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 101 studies with a high risk of bias and 42 studies that did not meet GRADE.

Figure 1. Selection of studies.

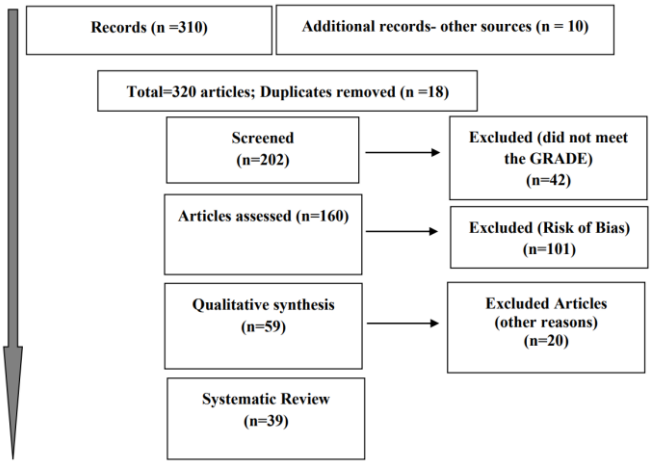
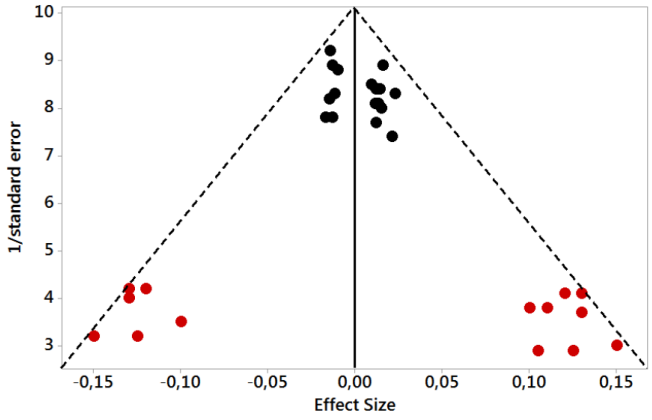


Figure 2 presents the results of the risk of bias in the studies using the Funnel Plot, through the calculation of the Effect Size (Cohen's Test). The sample size was determined indirectly by the inverse of the standard error. The graph showed symmetric behavior,

not suggesting a significant risk of bias in studies with small sample sizes (red studies), 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 = 39 studies).



Source: Own authorship

Major Findings

According to the Ministry of Health, osteoporosis is an osteometabolic disease characterized by a decrease in bone mass and destruction of the microarchitecture of bone tissue with increased bone fragility. Its clinical complications include fractures, chronic pain, depression, deformities, loss of independence, and increased mortality. It is estimated that approximately 50% of women and 20% of men aged 50 years or older will suffer an osteoporotic fracture in their lifetime. Among the drugs that reduce osteoporotic fractures, oral bisphosphonates are the first choice drugs in the treatment of osteoporosis [34].

Such drugs can reveal several adverse effects, among them osteonecrosis of the jaws, which affects 0.01% to 0.04% of patients who use the drug orally, however, although rare, complications when they occur are severe and mutilating, impairing the quality of life of these individuals [2,6]. According to the AAOMS Guideline, the clinical treatment of Osteonecrosis consists of improving the signs and symptoms, with anti-inflammatories, antibiotic therapy, analgesics, and irrigation with chlorhexidine, which can last for months, aggravating the local conditions. Surgical treatment, for removal of necrotic bone and curettage of bone sequestration, has higher success rates than conservative treatment, but with a high rate of recurrence, causing infections, lack of tissue for primary closure, and the need for new resections with the mutilation of the face [1,21,23].

In this context, for the treatment of osteoporosis and evaluated the action of Photobiomodulation and Magnetotherapy as auxiliaries to the repair process, supporting the surgical treatment of BRONJ [3]. In dentistry, treatment with low-intensity laser is already consolidated, being carried out since the 80s, with good results when we talk about inflammation modulation, tissue repair, and analgesia. In the search for less invasive treatments for osteonecrosis, Vescovi 2013 et al.2013 [6] developed a new preventive methodology using low-intensity laser after dental extractions in 217 patients treated with BFs and only 5 patients observed bone exposure.

Also, magnetotherapy was approved by the FDA and studies have shown the benefits of the electromagnetic field for the treatment of edema, osteoarthritis, wounds, hemodynamic modulation, pain relief, inflammation, tissue regeneration, and bone formation. Being an important physiotherapy tool around the world, as it is a noninvasive, safe, and easy-to-use method [24,26].

Thus, photobiomodulation aims to remove the cause of the injury, contain its extent, and prepare the site for cellular repair. The first event is hemostasis, through vasoconstriction, increasing local blood viscosity, allowing clot formation, through the release of epinephrine by platelets and recruiting calcium to convert prothrombin to thrombin, to transform fibrinogen into fibrin fibers, forming a tangle of platelets to form a clot [16].

Also, an improvement in blood viscosity in the Laser and Magneto groups can be observed, with an average reduction in the number of platelets compared to the initial moment, thus improving the visceral blood supply and facilitating the local antiinflammatory response. Weber et al. 2016 [35] found studies demonstrating favorable results with surgical therapy, combined with laser treatment. According to Li et al. 2020 [36], in a systematic review, observed that there was a significant change in the pain score after LIL and in the assessment of analgesia by VAS, we observed that in the first 7 PO days, the Laser group presented a significant reduction in pain compared to the placebo and Magneto groups, a fact that stabilized after 14 days.

Besides, Lorenzo-Pouso et al. 2019 [37] in a systematic review suggests that currently there are no markers available to assess the risk of BRONJ. However, the work indicates that a paradigm shift in bone remodeling, angiogenesis, and endocrine biomarkers could be useful in further research. According to Vieira (2007) [38], during bone formation, the production of the collagen matrix precedes mineralization. The phase of collagen matrix production coincides with the highest production of alkaline phosphatase, in addition to being more effective for bone formation at the beginning than in the later stages, because in the first stage of bone

healing, cellular components are more important and, therefore, more susceptible to the action of the laser. Further, LIL in bone tissue causes an increase in the amount of mRNA used to synthesize type I collagen, which stimulates bone tissue formation and repair [35,39].

Furthermore, the infrared laser (808nm) can be used as an anti-inflammatory and repairing therapeutic window, acting on sodium and potassium pumps and calcium channels, thus increasing protein and ATP synthesis, leading the tissue to cellular, tissue, and organic homeostasis, thus signaling a new possibility of preventive treatment for BRONJ. Its main actions are the deviation of electrically charged particles in motion, and the production of currents induced by the piezoelectric effect in bone tissue and collagen, at the cellular level it normalizes the membrane potential, increases the solubility of substances, stimulates cellular metabolism, promoting an acceleration of all restorative phenomena with regenerative, anti-inflammatory and anti-edematous action, without demonstrating side effects. Thus, in living tissues, one finds mainly alternating fields, as well as a combination of electric and magnetic fields, with cell movements, ionic fluxes, fluids in circulatory systems, mitochondrial electron transport chain, and action potentials in membranes [35-37].

Added to this, lactate dehydrogenase (LDH) is an intracellular enzyme that is present in virtually all body tissues and participates in the process of transforming glucose into energy in the animal, plant, and even bacterial cells. LDH is released into the bloodstream when cells are damaged or destroyed, increasing LDH levels in the circulation, and can be detected in a blood test. The higher concentration of this enzyme in the extracellular environment is related to the rupture of the plasma membrane and consequent cell death.

Finally, creatine phosphokinase (CPK) is an enzyme found in the heart, brain, skeletal muscle, and many other tissues. CPK catalyzes the conversion of creatine and consumes adenosine triphosphate (ATP) to create creatine phosphocreatine (PCr) and adenosine diphosphate (ADP). This CK enzyme reaction is reversible and therefore ATP can be generated from PCr and ADP. In skeletal and cardiac muscle cells, most of the energy is used for muscle contraction. A CPK increase usually indicates muscle damage. It was observed in studies that the use of photobiomodulation and magnetotherapy can maintain normal CPK levels.

Conclusion

Patients being treated with bisphosphonates should be informed about the potential risk of bisphosphonates related osteonecrosis of the jaws. In addition, providers responsible for breastfeeding therapy would be advised to refer patients for dental check-ups before starting treatment, allowing for patient follow-up by a multidisciplinary team. Although the morbidity of this pathology is not high, prevention must be mandatory, thus avoiding mutilating and painful processes. However, if the surgical procedure is required, the use of these new adjuvant therapies such as lowintensity laser and magnetotherapy.

Acknowledgement

Not applicable.

Funding

Not applicable.

Ethics 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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