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Professional paper

DENTAL IMPLANT PLACEMENT IN PATIENTS ON BISPHOSPHONATE THERAPY

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Abstract

Bisphosphonates are antiresportive medications used to prevent and treat a wide range of diseases such as osteoporosis, Paget disease of bone, malignancies metastatic to bone, multiple myeloma and hypercalcemia of malignancy. One of the most important complications at the patients who are taking therapy with bisphosphonates is osteonecrosis of the jaw related to bisphosphonates (BRONJ).
This review aimed to consider dental implant placement in patients who have been treated with or are currently on bisphosphonate medication, based on research using electronic databases PubMed, Google Scholar and Elsevier, under the following keywords: dental implants, bisphosphonates, ostheonecrosis, BRONJ .
We performed a literature review to explore the relation between dental implants and bisphosphonates depending on several factors such as the way of administering (oral or venous), the length of the therapy, the dose of the medicine, other chronic therapies that the patient has taken and which affects the bisphosphonates. The way of administering bisphosphonates is crucial because patient treated with intravenous bisphosphonates seemed to have a higher chance of developing implant-related osteonecrosis of the jaw. The intraorally treated patient group appeared to have more successful results.
Benefits that bisphosphonates offer to patients clearly outbalance the risk of potential side effects; however, any patient for whom prolonged bisphosphonate therapy is indicated, should be provided with preventive dental care in order to minimize the risk of developing this severe condition and to have high success rate of dental implants.

Keywords: Dental implant, bisphosphonates, osteonecrosis, BRONJ

Introduction

Osteonecrosis of the jaws, which is associated with bisphosphonates, is a well-known side effect in patients receiving bisphosphonates as a medical treatment for osteoporosis, multiple myeloma, or malignancies with bone metastases.

According to Walter C.1 and colleagues, the incidence of this phenomenon ranges between 0.1% (in patients with primary osteoporosis) and 1% (in patients with secondary osteoporosis). If patients receive bisphosphonates for the treatment of malignant conditions, then the percentage can rise to 20% if additional predisposing factors defined as general and local risk factors are added to it.

From the systemic ones, we will distinguish metabolic diseases, diseases that are treated with antiresorptive therapy, additional radiation therapy in certain regions and others.

Among the local factors, the most commonly identified are periodontopathy, tooth extractions, decubitus wounds from inadequate prosthetic compensations and installation of dental implants in the jaws.

The most common occurrence of osteonecrosis of the jaws is registered in patients aged 69 ± 10 years, for two reasons. In these patients, we often encounter compromised general health and the need for systemic therapy, as well as compromised oral health with the loss of a large number of teeth, which further represents the need for implantological and bone augmentative rehabilitation of the patients. In order to avoid these side effects, the world guidelines for placing dental implants in this group of patients should be followed.

The method of administration of bisphosphonate therapy largely determines the safety of implant therapy, which is a very important anamnestic data, whether the administration is oral or intravenous. The largest number of osteonecrosis occurs with intravenous bisphosphonates, which does not mean that there are no successful implant procedures in this group of patients.

Aim of the research

This review aimed to consider dental implant placement in patients who have been treated with or are currently on bisphosphonate medication, based on research using electronic databases PubMed, Google Scholar and Elsevier, under the following keywords: dental implants, bisphosphonates, osteonecrosis, BRONJ.

Material and methods

To achieve the objectives in this paper, scientific papers found by searching PubMed, Google Scholar and Elsevier databases were reviewed and analyzed using the keywords: dental implants, bisphosphonates, osteonecrosis, BRONJ.
The analyzes were aimed at determining the incidence of osteonecrosis of the jaw, the possibilities of prevention and treatment modalities in patients who are planning dental treatment with dental implants and who have already been treated with implants.

Bone metabolism

Bones are the solid, mineralized supporting tissue of an organism with several basic functions:

- Structural support of internal organs
- Protection of brain structures
- Mineral reservoir of calcium and phosphorus
- Acidity regulator

There are two types of bone structure, trabecular (spongy) and cortical (dense, hard) bone. In human jawbones, the maxilla has a more trabecular structure, while the mandible is cortical bone on the outside and trabecular on the inside.[2]
The bone matrix is composed of an organic and an inorganic part. The organic one is represented by collagen type 1, and collagen type 3, 5, 10 and 12 is also present in smaller amounts. Collagen is a protein with about 1000 amino acids in its composition and a thread length of about 300 nm. In reaction with osteoblasts, they produce the triple helix of procollagen, which gives bones their elasticity.
From the non-collagen group of proteins, there are fibronectin, osteopontin, osteocalcin and bone sialoprotein in the organic matrix.
The inorganic part is represented by 65-70% of the mass of the bone. It serves as an ion reservoir for calcium, phosphorus and magnesium

Pathogenesis

According to the studies of Drake M. and colleagues, osteonecrosis of the jaws caused by bisphosphonates, i.e. BRONJ (Bisphosphonate related osteonecrosis of the jaws) is defined as an exposed part of the jawbone in the oral cavity that persists for more than eight weeks despite the given therapy , and the patient gives negative anamnestic data when asked whether he has received or is currently receiving radiotherapy, as well as about the existence of bone metastases.[3]

Symptoms

Typical signs and symptoms include pain, swelling and soft tissue infection, tooth loss, and persistent suppuration. Signs and symptoms that may precede the development of clinically apparent osteonecrosis include a sudden change in periodontal health or soft tissue condition, inability of the oral mucosa to heal, undiagnosed mouth pain, tooth loss, or soft tissue infection.[4]
Hayashida et al. describe that some patients may also have atypical signs such as tingling or a feeling of a heavy jaw, as well as varying degrees of dysesthesias.

The American Association of Oral and Maxillofacial Surgeons in 2014 lists the clinical stages of the disease:

1. Patients at risk
2. Clinical stage 0 - non-specific clinical findings and symptoms without the appearance of exposed necrotic bone in the oral cavity
3. Clinical stage 1 - there is exposed or necrotic bone without signs of infection
4. Clinical stage 2 - there is exposed or necrotic bone with signs of infection, pain and erythema.
5. Clinical stage 3 - exposed and necrotic bone extends below the alveolar part of the bone, which may result in pathologic fracture, extraoral fistula, oroantral or oronasal communication.[5]

Bisphosphonates

Bisphosphonates are a class of drugs that prevent bone loss, and are used in the treatment of osteoporosis and related diseases.
They are the most commonly prescribed drugs used in the treatment of osteoporosis. They are called bisphosphonates because they contain two phosphonate (PO(OH)2) groups in their structure
In bisphosphonates, the central oxygen atom is replaced by a carbon atom. All bisphosphonates share a phosphorus-carbon-phosphorus structure with two side chains (R1 and R2). The R2 side chain determines the chemical properties of the drug, and distinguishes the individual bisphosphonates. This chemical structure enables a high affinity for calcium hydroxyapatite, enabling rapid and specific targeting to the skeleton. [6]
The main function of bisphosphonates is to inhibit osteoclast bone resorption through an intracellular mechanism. The deposition of bisphosphonates is on the surface of bones, which results in their direct contact with osteoclasts. They also promote osteoclast apoptosis by reducing osteoclast progenitor development and mobilization.
Placing implants is not contraindicated in patients that are on oral BP therapy provided that the following principles are followed:[8] If the patient has been treated with oral BP's for less than 3 years and has no clinical risks, dental implants can be placed without altering the conventional surgical treatment.
If the patient has been treated with oral BP's for less than 3 years and is treated jointly with corticosteroids the prescribing provider should be contacted to consider discontinuation of the oral BP for at 3 months before implant placement, if systemic conditions permit. BP must not restarted until the bone has completely healed
If the patient has taken oral BP for more than 3 years with or without corticosteroid medication, the prescribing provider should be contacted to consider discontinuation of the oral BP for 3 months before implant placement, if systemic conditions permit. The BP should not be restarted until bone has completely healed.
Dental implants are contraindicated in patients being treated with intravenous bisphosphonates.

Holziger [9] investigated the time to development of osteonecrosis of the jaw associated with the use of bisphosphonates in patients who had dental implants placed. He divided the subjects into 3 groups: a group with implants placed before treatment with bisphosphonates, a group with implants placed during bisphosphonate therapy and a third group of subjects with implants placed after bisphosphonate therapy.
Accelerated development of osteonecrosis has been observed in implants placed during or after bisphosphonate therapy.

Intra- and extraoral examinations

Intra and extraoral examinations, imaging and laboratory examinations as complete blood count and coagulation tests, fasting blood glucose, urea, creatinine should be requested to assess the health condition of the patient, together with a specific examination to evaluate bone reabsorption, called C-terminal telopeptide (CTX).
The CTX allows assessing the risk of osteonecrosis in patients who are being treated with BF for more than three years. Serum levels of this test allow assessing the risk of the patient develops OJ:

- values less than 100 pg / ml - high risk;
- values between 100 and 150 pg / ml – moderate risk;
- values between 150 and 299 pg / ml - low risk;
- greater than 300 pg / ml - no risk

Low CTX values demonstrate the need of the drug discontinuation for at least 6 months to normalize the serum levels. If stopping the medicine is not possible, the patient should instructed about the risk of OJ. These patients who make use of BFs for more than three years, or associate with corticosteroids, it is recommended stopping treatment six months before and after the installation of implants, returning its use after complete healing of the tissues involved. [10]

Types of therapy

According to Blues et al., BRONJ is a significant clinical problem characterized by pain, mucosal ulceration, infection, and bacterial colonization that prevents wound healing in the area of exposed bone. It dramatically affects the quality of life of patients because these patients require alternative treatments for BRONJ.
BRONJ treatment alternatives are mainly focused on conservative or surgical procedures, depending on the clinical stage. Interruption of bisphosphonate therapy can be considered after consultation with the specialist who prescribed it and depending on the patient's health.

Specific treatment for each stage:

Patients at risk: Patient education is required

Stage 0: Symptomatic treatment, which includes analgesics and antibiotics.

Stage 1: Antibacterial oral solutions (0.12% p-op of chlorhexidine), Clinical follow-up at three months

Stage 2: Oral antimicrobial solutions (0.12% p-op chlorhexidine), symptomatic treatment with oral antibiotics, debridement to stop soft tissue irritation and control infection

Stage 3: Antibacterial mouthwashes, antibiotic therapy and pain control, surgical debridement/resection for long-term management of infection and pain. [11]

Conclusion

Clinical judgment is always essential, in patients who may require extensive invasive oral surgery, as well as those with multiple risk factors for ONJ (i.e. drug related factors: BP potency, route of administration and duration of therapy and local and systemic factors: (poor oral hygiene, smoking, periodontal disease, glucocorticoid treatment, diabetes, immune deficiencies, obesity).

References

[1]. Walter C., Al-Nawas B., Wolff T., Schiegnitz E., & Grötz K. A. (2016). Dental implants in patients treated with antiresorptive medication - a systematic literature review. International journal of implant dentistry. 2(1):9.

[2]. Yoshinobu Ide , Hiroko Agematsu. Structure of jaw bone (2007). Clin Calcium; 17(2):164-71

[3]. Drake M. T., Clarke B. L. & Khosla S. (2008). Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clinic proceedings. 83(9): 1032–1045.

[4]. Hayashida S., Soutome S., Yanamoto S., Fujita S., Hasegawa T., Komori T., Kojima Y., Miyamoto H., Shibuya Y., Ueda N., Kirita T., Nakahara H., Shinohara M., & Umeda M. (2017). Evaluation of the Treatment Strategies for Medication-Related Osteonecrosis of the Jaws (MRONJ) and the Factors Affecting Treatment Outcome: A Multicenter Retrospective Study with Propensity Score Matching Analysis. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research. 32(10): 2022–2029.

[5]. Salvtore L.R., Dodson T.B., Aghaloo T., Carlson E. R., Ward B. B., Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws—2022 Update. Journal of Oral and Maxillofacial Surgery. Volume 80(2):920-943

[6]. Rogers M.J., Marcia J.K., Munoz M.A. (2020) Molecular mechanisms of action of bisphosphonates and new insights into their effects outside the skeleton. Bone; 139:115493

[7]. Hughes D. E., Wright K. R., Uy, H. L., Sasaki A., Yoneda T., Roodman G. D., Mundy G. R., & Boyce B. F. (1995). Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research. 10(10): 1478–1487.

[8]. Sharma, Rahul & Anand, Dhruv & Choudhary, Ashish & Vikram, Jay & Hasti, Anurag & Lecturer, Senior. (2017). Bisphophonates and dental Implants – A literature review. Annals of Prosthodontics and Restorative dentistry. 3: 60-62.

[9]. Holzinger D., Seemann R., Matoni N., Ewers R., Millesi W., & Wutzl A. (2014). Effect of dental implants on bisphosphonate-related osteonecrosis of the jaws. Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons, 72(10); E1:1937-1938.

[10]. Cheng A., Daly C., Logan R., Stein B. and Goss A. (2009). Alveolar bone and the bisphosphonates. Australian Dental Journal. 54: S51-S61.

[11]. Blus C., Szmukler-Moncler S., Giannelli G., Denotti G., & Orrù G. (2013). Use of Ultrasonic Bone Surgery (Piezosurgery) to Surgically Treat Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ). A Case Series Report with at Least 1 Year of Follow-Up. The open dentistry journal. 94-101.