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Bisphophonates and dental Implants – A literature review

Rahul Sharma[1,*], Dhruv Anand[2], Ashish Choudhary[3], Jay Vikram[4], Anurag Hasti[5]

[1,2]Senior Lecturer, [3,4,5]Professor, Dept. of Prosthodontics & Crown & Bridge, School of Dental Sciences, Sharda University, Greater Noida, Uttar Pradesh

***Corresponding Author:**
Email: doczone.sharma@gmail.com

Abstract

Osteonecrosis of the jaw has been described in patients taking bisphosphonates after oral surgery procedures, including the placement of dental implants. The success of these procedures depend on the fixation of the implants which, in turn depends on the strength of the bone that holds them. Bisphosphonates are anti-resorptive drugs that act specifically on osteoclasts, thereby maintaining bone density and strength. These drugs inhibit bone resorption and are used to treat a range of pathologies, including Paget disease, osteoporosis, multiple myeloma and metastases associated with breast or prostate cancer. At present, there is no effective treatment for bisphosphonate induced osteonecrosis, so prevention is extremely important. Since quality of life deteriorates for those suffering osteonecrosis, maximum precautions should be taken with patients at risk. The aim of this study was to conduct a systematic review in order to evaluate whether patients on BP therapy are appropriate candidates for dental implants as compared to patients not taking BP drugs with respect to successful implant osseointegration and the risk of developing bisphosphonaterelated osteonecrosis of the jaw.

Keywords: Bisphosphonates, Osteonecrosis of the jaw, Osseointegration, Dental implants.

Introduction

Bisphosphonates (BPs) are pyrophosphate analogues with high affinity for the bone hydroxyapatite. Due to their pharmacological effects on the bone, they play an important role on skeletal disorders with enhanced or imbalanced bone remodelling rates. They are considered effective drugs in treatment of disease affecting bone metabolism, characterized by increased resorption like osteoporosis, Paget disease.[1,2] Intravenous BP are administered to patients with breast cancer, multiple myeloma, bone metastasis and malignant hypercalcemia, to increase survival and quality of life. The route of administration affects the skeletal uptake of the medication. Oral bisphosphonates are poorly absorbed and present less than one percent of bioavailability, whereas the intravenous are completely bioavailable.[3,4]

One of the most serious complications of BP therapy is Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ). Because of the growing number of osteonecrosis cases in the jaws associated with other Antiresorptive and antiangiogenic therapies, American Association of Oral and Maxillofacial Surgeons[5] (AAOMS) in 2014 suggested a nomenclature change from BRONJ to Medication Related Osteonecrosis of the Jaw (MRONJ). Osteonecrosis induced by bisphosphonates is characterized by exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than eight weeks in patients who have received current or previous treatment with antiresorptive or antiangiogenic agents and no history of radiation therapy to the jaws or metastatic disease to the jaws. Mandible and maxilla are bones exposed to the external environment, through the teeth.[6] First cases of BRONJ were most likely associated to previously tooth removal surgery or other condition that increases the demand for bone turnover. That is why there is controversy whether it is safe to place implants in patients taking bisphosphonates for bone diseases.

Different types of bisphosphonate in current usage

Active ingredient	Trade name	Route of Administration
Alendronate	Fosamax®,Fosavance ®	Orally
Etidronate	Osteum®, Difosfen®	Orally
Risedronate	Actonel®, Acrel®	Orally
Tiludronate	Skelid®	Orally
Zoledronate	Zometa®, Aclasta®	Intravenously
Pamidronate	Aredia®, Linoten®,Pamifos®, Xinsidona®	Intravenously
Ibandronate	Bondronat®	Orally, Intravenously
Clodronate	Bonefos®	Orally, Intravenously

Literature review

Bisphosphonates: In the decade of 1960s, the calcium pyrophosphate was discovered as physiological regulator of calcification and bone resorption; however it was inactivated by enzymes of the gastrointestinal mucosa, which prevents its oral use.[7,8,9] At the end of the 1960s, BPs were developed, which are chemical analogous of pyrophosphate, with great bone-bonding ability inhibiting the action of osteoclasts. These substances are chosen for the treatment of skeletal diseases and can be used orally. The BPs s decrease osteoclast activity, increase bone mineral density and consequently lower the risk of fractures. This group of

drugs is poorly absorbed in the gastrointestinal tract (about 1 to 2%). Once free in plasma, is excreted by the kidney. Besides the oral route of administration, the intravenous route is very employed in cancer patients. This drug can stay for a long period within the bone matrix, according to the type of treatment and duration. Once within the bone, the osteoblast failure in resorption the bone causes the die of osteoblasts and osteocytes, leaving an acellular matrix in the bone. The result is the degeneration of the capillary vascularization and increased bone fragility.

Pharmacology, mechanism of action of BPs: These drugs are divided into first-generation non-nitrogen-containing (clodronate, etidronate and tiludronate) and second and third generation nitrogen-containing (alendronate, risedronate, ibandronate and zoledronate) and the last ones differ from the others because they adhere more tightly to hydroxyapatite mineral in bone.[9,10] The BPs mechanism of action are similar in all the groups, and responsible for inhibiting the activity of osteoclasts, resulting in an imbalance in the bone remodelling process, and hence also affects the osteoblastic activity. From a pharmacological point of view, this drug presents a short half-life, remaining in the plasma for a few hours, but it can accumulate over the years inside the bone matrix

Osteonecrosis associated with BP's: Osteonecrosis is a clinical condition in which the maxillary or mandibular bone exposed in the oral cavity for at least 8 weeks in the absence of prior radiotherapy treatment.[11,12] It has mostly been reported in patients receiving high doses of intravenous BPs. The risk of developing Osteonecrosis of the Jaws (OJ) is mainly associated with prolonged therapy, especially in treatments for three years or more. The preference for the bones of the maxilla and mandible is because BPs accumulate exclusively in skeletal sites with high bone remodeling. The second theory is that oral mucosa is thin and can be easily traumatized during surgery, allowing contact with the infected saliva and developing osteonecrosis. Obese, immunosuppressed patients; those undergoing hemodialysis; smokers; alcoholics, diabetics are more likely to develop osteonecrosis of the jaws.[12]

Risk factors related to the drug

- Duration of therapy: the higher the duration the higher will be the therapeutic risk.
- Power BFs: zoledronate> pamidronate> oral BFs.

Local risk factors:[13,14]

- Dentoalveolar surgery (dental extractions, dental implants, peri-apical surgery) increases up to 7 times the risk of OJ.
- Local anatomy: the lesions are more common in the jaw and thinner mucosal regions on bony prominences.
- Concurrent oral disease: patients with inflammatory oral diseases are 7 times more likely to develop osteonecrosis of the jaws, when treated concomitantly with BFs.

Bisphosphonates and Implant: As BPs act directly on the bone replacement process, there is a probability that these patients have problems in osseointegration[6]. BPs end up interacting with the bone and vascular turnover, which interferes in the quality and quantity of bone tissue, so important to the Implantology, and thus cause an accumulation of micro damages and changes the properties of the tissue, affecting hemostasis of newly formed tissue around the implants.[15]

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).[16,17] 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 allows assessing the risk of the patient develops OJ:[17]

- 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.[17] In this case, the therapeutic modification or cessation of treatment should be made together with the doctor accompanying the patient. An informed consent form should be signed by the patient, in order to inform the risks.[18]

Clinical Implication of this review literature

Good quality clinical trials with well defined end point outcomes of treatment and long-term follow-up data are not yet available to support evidence-based clinical recommendations for placing implants in patients treated with BP's.[19,20] To facilitate clinical decision-making the following published guidelines are proposed.[21] Placing implants is not contraindicated in patients that are on oral BP therapy provided that the following principles are followed: (a) 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; (b) 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; (c) 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; (d) dental implants are contraindicated in patients being treated with intravenous bisphosphonates. All patients treated with BP's must (be adequately informed of the small risk of compromised bone healing) given a full explanation of the risks of BRONJ and the possibility of implant loss over the long-term for continuing to take BP's, and informed consent must be obtained before placing dental implants. Such patients should also comply with a regular recall schedule. If systemic conditions permit, modification or cessation of oral BP therapy should be done in consultation with the treating physician and the patient.[22]

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 and history of cancer).

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