

Is Dental Implant Placement Compatible in Patients Treated with Bisphosphonates? A Literature Review

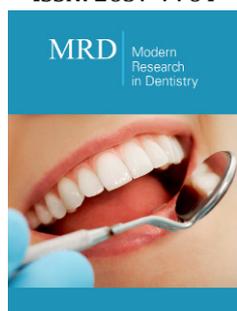
Meniz García C^{1*}, Iglesias Velázquez O², Pérez González F³, Sánchez Labrador L³ and López Quiles J¹

¹Professor at Department of Dental Clinical Specialties, Faculty of Dentistry, Complutense University of Madrid, Spain

²Graduate, Faculty of Dentistry, Complutense University of Madrid, Spain

³Department of Dental Clinical Specialties, Faculty of Dentistry, Complutense University of Madrid, Spain

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***Corresponding author:** Cristina Meniz García, Department of Dental Clinic Specialties, Faculty of Dentistry, Plaza Ramón y Cajal S/N, 28040, Complutense University of Madrid, Spain
Email: cmenizga@ucm.es

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Abstract

Background: Bisphosphonates (BP) are a group of drugs used in treatment and prevention of altered turn-over of bone diseases. Since 2003, it is known That BP are able to develop osteonecrosis of the jaw (BRONJ: Bisphosphonate-Related Osteonecrosis of the Jaw) when they are associated to any surgical trauma, even dental implant therapy.

Materials and Methods: Comprehensive research of scientific articles from ten years ago to our days in Medline (Pubmed).

Results and Discussion: 1090 dental implants placed patients treated with BP and 3472 dental implants placed in healthy patients had successfully rates of 97.6% and 97.9%, respectively. Therefore, implant placement in patients in treatment with BP does not reduce implant success rates. Besides, BRONJ appears before with intravenous vs oral administration of BP.

Conclusion: Further well-designed long-term studies are necessary to evaluate correctly the relationship between BP and dental implants.

Keywords: Dental implant; Osteonecrosis; Bisphosphonate; Bisphosphonate-related osteonecrosis of the jaw

Abbreviations: BP: Bisphosphonates; BRONJ: Bisphosphonate Related Osteonecrosis of the Jaw; CTX: C Terminal Telo peptide, TCT; AAOMS: The American Association of Oral and Maxillofacial Surgeons

Introduction

Bisphosphonates (BP) are a group of drugs used for prevention and treatment of diseases involving bone resorption (malignant tumors such as multiple myeloma, malignant hypercalcemia and other tumors with bone metastases as breast or prostate cancer) and metabolic diseases that affect bones (osteopenia and osteoporosis, present in about 200 million people worldwide). This group of drugs, being the first line therapy in diseases such as osteoporosis, where bone quality and quantity may be affected, are especially important in oral surgery and implantology [1]. These drugs are analogs of pyrophosphate molecule, and cause inhibition of bone reabsorption due to their affinity to calcium phosphate in solid phase, which allow them to bind to bone hydroxyapatite [2,3]. BPs have two forms of administration: intravenous, producing its initial effects after a few days and oral (either daily, weekly, monthly or quarterly), beginning after a few weeks because they are more difficult to be absorbed [3]. In 2003 Marx [4] warned out dental community after noticing the occurrence of osteonecrosis associated with the intake of these drugs. Many studies suggest development of osteonecrosis depends on several factors, such as the total dose, the duration and the way of the drug administration [1,5,6]. Osteonecrosis is defined as exposed

bone in the maxillofacial region for more than eight weeks, in patients treated with BPs without story of head or neck radiation, previously subjected to a dental surgery, for example an exodontia or dental implant placement. Dental implants today have become the most efficient alternative to rehabilitate missing teeth, having better results than conventional fixed and removable prosthesis. Nonetheless, the information about association between dental implants and osteonecrosis is scarce [7].

Although the mechanism of beginning and progression of osteonecrosis associated with the use of BP is unclear, there are several hypotheses suggesting that these drugs inhibit the activity of osteoclasts, suppressing bone remodeling. It seems to be related to the surgical trauma, bad hygiene or periodontal and peri implant status [5,8,9]. According to American Dental Association Council on Scientific Affairs in 2006, the incidence of osteonecrosis of the jaw associated with the use of oral BP is estimated at 0.7 cases per 100,000 persons / year of exposure [10]. The implant success depends on osseointegration, defined as the direct, structural and functional connection between the live, ordered bone and the surface of an implant under functional loading. Patients being treated with BP have an affected bone remodeling process, because of the inhibition of osteoclasts' action. This prevents the first phase, which allows osteogenesis to occur, so a successfully osseointegration is not expected to occur and implant prognosis is also questionable [5,8]. However, in the literature there are several studies showing beneficial effects of oral BP in osseointegration and bone healing around implants [5]. The aim of this review is to evaluate the behaviour of dental implants in patients treated with BP, and the protocol to follow with implants in patients employing BP as medication, or in patients who develop complications associated with its administration.

Material and Methods

A literature search was conducted in different digital databases like Medline (Pubmed) and Cochrane using keywords ("implant dental" AND "osteonecrosis" AND "dental implant failure") AND ("bisphosphonate" AND "bisphosphonate-related osteonecrosis of the jaw ") until May 2019. The search was carried out by a single subject (OI). According to the keywords and search strategy, 5971 results were obtained. The search was limited to journal articles in the last 15 years and the field of Medicine, Dentistry and Pharmacology, limiting the search to 2618 publications. The selection of studies was limited further by focusing on the field of Oral and Maxillofacial Surgery, publications with highest level of scientific evidence and written mainly in English. Articles about one case, case series and follow-up less of six-months were excluded. Thus 39 publications were included.

Result and Discussion

The high incidence in the Spanish society of diseases such as osteoporosis, one of the oldest in the world (affecting about 35% of women over seventy years) is a public health problem. This disease, where bone quality and quantity are affected, seems to be a contraindication for dental implants. If these patients are taking oral

or intravenous BPs, the problem seems to be even greater¹⁰. Dental implants placement in patients treated with BP is a controversial option. For some authors, these drugs represent a contraindication to perform any oral surgery [4]. In fact, there is a consensus to contraindicate the use of implants in cancer patients treated with intravenous BP due to high risk of BRONJ, in order to prevent the development of complications such as those mentioned by Marx [4] (pain, infection and necrosis) [5]. However, several studies do not share this theory, by inducing osteoporosis in a group of rabbits (giving them zoledronate) they concluded BPs could reverse the effects of osteoporosis and facilitate osseointegration, and even could also be an effective strategy to promote osseointegration of implants in patients with metabolic bone diseases [11,12].

Ata Ali et al. [13] published a systematic review that analyses the impact of BP for implant success. Their analysis included fourteen studies: Ten retrospective, two prospective and two case series; even though it was focused mainly on eight studies. They evaluated a total of 386 cases of patients with BP and 902 healthy subjects where 1090 and 3472 implants were placed, respectively. They obtained a success rate of 97.61% in the group with BP and 97.81% in the healthy group, so there is enough evidence to ensure that BP have no negative effect on implant survival [13]. Jeffcoat [14] in a study of 25 patients with oral BP achieved similar success rates to the healthy group [14] and Bell & Bellet [15] evaluating 100 implants in the group with oral BP reached similar results to healthy group [15]. In this way, these studies match a study in postmenopausal women treated with oral BP, which recorded a success rate of 100% implants with one year of follow-up [16].

The systematic review of Madrid & Sanz [6] analyzed four studies: one prospective controlled nonrandomized, which compared patients with and without BP up to 36 months after implant placement and without patients developing osteonecrosis, with a satisfactory implant's response. The other three studies were retrospective, and had similar results, because all patients taking oral BP did not develop osteonecrosis and reported success rates of dental implants close to 100%. Anyway, these results should be interpreted carefully because the sample was limited and in all four studies the duration of BP exposure regarding implants was quite short (less than four years). The systematic review concluded that risk of osteonecrosis is minimal when the administration of BP is less than five years [5], but the use of BP presents similar results to healthy patients. However, there are also different cases in the literature that showed implant failures [17,18]. Even they say BP oral intake increases the probability of develop osteonecrosis 2.69 times [19]. According to several studies, the appearance of osteonecrosis is related to the type of BP, dose, potency or way of administration. It has also been found that may be associated with poor hygiene, smoke or systemic condition [1,3,4,6]. Regarding the way of administration, osteonecrosis develops earlier in patients taking intravenous versus oral administration. Marx [11] reported a success rate of 97,5% in dental Implants placed in patients treated with oral BP [20], Ruggiero 89% [20], Mavrokokki 77% [21] or Abu-Id 93% [22]. The systematic review of Madrid & Sanz showed a

success rate of 100% in patients treated with oral BP [5]. However, although osteonecrosis tends to appear faster in patients receiving intravenous therapy, it does not exist a significant difference in the form of administration, the dose and the development of osteonecrosis [4]. Recently, a systematic review of Gelazius et al. [9] reported success rates of 100% in most studies evaluated, finding the lowest success rates in patients treated with intravenous BP [8,23].

One of the absolute contraindications in oral and maxillofacial surgery is implants placement in patients with intravenous BP for cancer treatment. Despite this, a study in Japan on six patients with implants reported a single case of osteonecrosis. Although the sample size is not significant, they considered that implants did not represent a risk factor in these patients [24]. Another study in cancer patients who developed osteonecrosis in relation to implants concluded that, despite being Osseo integrated, the disease could be developed in the long term and not only in relation with the surgical act [25]. This statement is consistent in Giovannacci et al. study, which reported some cases of osteonecrosis both in patients who undergo implant placement surgery and in those who were already Osseo integrated. In addition, the study concluded that the incidence of this pathology is greater in the posterior regions of the jaws and in patients who have been using BP for more than three years, increasing the risk even more if these drugs are administered intravenously or the patient are simultaneous being treated with corticosteroids [26].

Periimplantitis is one of the most frequent complications in Implant treatments [27,28]. In a study of 316 patients where the 39% of implants (n=117) showed any signs of periimplantitis (inflammation and bone loss). Of 117 implants, 111 were placed before initiating therapy with BP, so the use of these drugs is a risk factor for developing periimplantitis [29]. Prevention in these patients must be vital, consisting in regular visits to the dentist making evaluations of the periodontal status and informing patients about the negative effects of this type of drugs in the oral cavity, spontaneously or in relation to dental activity. One of the practices that is carried out is the "drug-holiday" or BP break. Some authors accept this theory based on the blood determination of CTX levels (C-terminal telopeptide, TCT). It is a specific marker that is released in the serum by the action of osteoclasts and indicates the risk of developing osteonecrosis. When the values are above 150pg/ml, the risk of developing osteonecrosis is minimal. On the other hand, when these values are lower, it is recommended to suspend the BP three months before placing the implants and waiting another three months to restore the use, in order to achieve a correct healing. However, the AAOMS (The American Association of Oral and Maxillofacial Surgeons) warn that stopping medication does not reduce the risk of osteonecrosis [3,6,15]. In contrast, the study by Koka et al. comparing a group with implants and BP and another group without medication, does not find a statistically significant difference, so it would not be necessary to perform the "drug-holiday" [29], coinciding with other studies where the difference was not significant either [30]. Marx [4] argues that any form of prevention of osteonecrosis associated with BP is very complicated

and the works of Hewitt et al. or Farah et al., recommend performing any surgical treatment before starting pharmacological therapy [31]. In other hand, alternative therapies involving different materials or biomolecules has been also investigated like the possibility of using substitutes for BP locally, with growth hormone or calcium and phosphate supplements, noticing an acceleration in bone formation and improvement in osseointegration [32-36].

On the other hand, the possibility of modifying the surface of the implants with calcium and phosphate molecules or with BP has been studied. The meta-analysis of Alghamdi et al. [37] showed an improvement in osseointegration when the implants surface is treated with these compounds. However, more studies are needed to confirm these hypotheses [36-38]. When osteonecrosis is developed, there are different approaches: an aggressive posture, combining the treatment of kidnappings with explantation [4,25]; or a more conservative approach consisting in stopping administering BP and prescribing an antibiotic therapy for several months. If after a long period there are no signs of improvement, explantation is carried out. Thus, a study in 27 patients who developed osteonecrosis associated with the implants, received a dose of amoxicillin (n=7) and doxycycline (n=20).

Patients who had taken oral BP showed a more satisfactory response to those who received intravenous BP. Besides, those treated with doxycycline had a better recovery (due to the higher bone affinity of this antibiotic to the bone) compared to the amoxicillin group [1]. Special care should be taken with new generation drugs such as Denosumab (Prolia®, Xgeva® [Amgen Technology Ireland (ADL) Dublin, Ireland]). These are monoclonal antibodies used, among other things, for arthritis and osteoporosis. It has been seen that they produce a reduction in bone resorption close to 80% in the first months [3]. Even so, both the FDA (Food and Drug Administration), and the AEMPS (Spanish Agency for Medicines and Health Products) and different authors, warn about the risk of developing osteonecrosis associated with these drugs [39]. The potential risk of developing osteonecrosis in patients under treatment with BP should be explained, before or after the placement of the implants. The AAOMS recommend a protocol for dental implants placement:

- a. If the patient has taken oral BP for less than 3 years and does not have any other risk factor: treatment plan should not be changed, but it is recommended to make an adequate informed consent, and make an interconsultation with the doctor in order to inform and allow to change the medication if it is necessary.
- b. If the patient has taken oral BP for less than 3 years but also has any risk factor (e.g. taking corticosteroids): it is recommend to contact the doctor, to stop the treatment if it is possible, from 3 months before implant placement up to 3 months later, to get an adequate bone remodeling.
- c. If the patient has taken BP for more than 3 years, with or without any concomitant therapy: an interconsultation should be performed to assess the possibility of stopping the treatment from 3 months before to 3 months later of implants placement.

d. If the patient takes intravenous BP, dental implants placement is considered an absolute contraindication in cancer patients being treated with zoledronate and pamidronate.

Conclusion

The success rate of implants in patients with oral BP is very high, so it does not seem to be a risk factor. However, long-term studies with a representative sample are necessary to evaluate the relationship of BP and implants. In addition, to assess the real behaviour between BP and dental implants, studies criteria must be unified taking into account the form of administration, the duration of the treatment, the cessation or not of the drug, relative aspects to dental implant placement or individual characteristics of patients. The professional must advise the patient of the adverse effects of the BP in relation to the surgical intervention and perform an adequate informed consent.

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