Clinical and Surgical Management for Placement of Osseointegrated Implants in a Patient taking Bisphosphonate Medication: Case Report

Manejo Clínico e Cirúrgico para Colocação de Implantes Osseointegrados em Paciente Em Uso de Bifosfonatos: Relato de Caso

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ABSTRACT
It is important to have knowledge about bisphosphonates, their composition, presentation, mechanism of action, dosage, benefits and adverse effects, in order to understand the
behavior of these drugs in the human body and their implication in implant dentistry. At present, the risk of medication-related osteonecrosis of the jaw (MRONJ) is being widely discussed. The aim of this study was to describe a conservative protocol, in the form of a case report, for the serial placement of osseointegrated implants in a patient with a history of continuous use of 150 mg, sodium ibandronate (Osteoban®). Case Report. To report the different clinical and surgical managements required in order to avoid or minimize the risk of patients developing MRONJ after the placement of osseointegrated implants. Materials and methods. The procedures performed began with the placement of a single osseointegrated implant, assessment of the patient's postoperative condition, and then, after a control period, concluding the treatment with a more complex surgical intervention consisting of serial placement of 6 osseointegrated implants. Results. After the period of one year, the patient’s condition was found to be normal in relation to the osseointegrated implants, and there was absence of signs of development of MRONJ. Conclusions. The preoperative conduct of instituting the drug holiday of 150 mg sodium ibandronate (Osteoban®), associated with control of the serum CTx level for an extended period allowed the installation of osseointegrated implants in a patient with long-term oral administration of bisphosphonates without the development of MRONJ occurring. The surgical steps, evolving from less complex through to the last procedures, with the installation of multiple osseointegrated implants, helped to assess the risk of the patient for developing MRONJ.

Keywords: Bisphosphonates, Dental Implants, Osteonecrosis, Oral surgery.

RESUMO
É importante ter conhecimento sobre os bisfosfonatos, sua composição, apresentação, mecanismo de ação, dosagem, benefícios e efeitos adversos, a fim de compreender o comportamento desses medicamentos no corpo humano e sua implicação na odontologia de implantes. Atualmente, o risco de osteonecrose da mandíbula relacionada a medicamentos (MRONJ) está sendo amplamente discutido. O objetivo deste estudo foi descrever um protocolo conservador, na forma de um relato de caso, para a colocação em série de implantes osseointegrados em um paciente com histórico de uso contínuo de 150 mg, ibandronato de sódio (Osteoban®). Relato de caso. Para relatar as diferentes gestões clínicas e cirúrgicas necessárias a fim de evitar ou minimizar o risco de pacientes desenvolverem MRONJ após a colocação de implantes osseointegrados. Materiais e métodos. Os procedimentos realizados começaram com a colocação de um único implante osseointegrado, avaliação da condição pós-operatória do paciente e depois, após um período de controle, concluir o tratamento com uma intervenção cirúrgica mais complexa que consiste na colocação em série de 6 implantes osseointegrados. Resultados. Após o período de um ano, a condição do paciente foi considerada normal em relação aos implantes osseointegrados, e houve ausência de sinais de desenvolvimento de MRONJ. Conclusões. A conduta pré-operatória de instituir o feriado da droga de 150 mg de ibandronato de sódio (Osteoban®), associada ao controle do nível sérico de CTx por um período prolongado permitiu a instalação de implantes osseointegrados em um paciente com administração oral prolongada de bisfosfonatos sem a ocorrência do desenvolvimento de MRONJ. As etapas cirúrgicas, evoluindo de menos complexos até os últimos procedimentos, com a instalação de múltiplos implantes osseointegrados, ajudaram a avaliar o risco do paciente para o desenvolvimento de MRONJ.

Palavras-chave: Bisfosfonatos, Implantes dentários, Osteonecrose, Cirurgia oral.
1 INTRODUCTION

With the increase in life expectancy and the consequent increase in age-related chronic diseases, it is increasingly common to find edentulous or partially edentulous patients who make continuous use of medications, and need treatment to restore their masticatory function. At present, this situation is a challenge to implant dentistry to rehabilitate patients who use anti-resorptive drugs, such as bisphosphonates. These drugs are commonly used to treat metastatic malignancies, Paget’s disease and osteoporosis. Anti-angiogenic and anti-resorptive drugs modify bone metabolism and the influence of this process on surgical implant dentistry is a topic discussed at high levels.

Medication-related osteonecrosis of the jaw (MRONJ) was first reported in 2003, but even today no treatment protocol has been defined. MRONJ is characterized by causing exposure of a necrotic bone in the oral cavity after surgical procedures, with a higher prevalence reported in the mandible compared with the maxilla, in a ratio of 2:1. Therefore, surgical procedures should be carefully indicated in patients taking bisphosphonate medications, by investigating the dose used, the route of administration and patients’ pharmacological history of up to 10 years prior to surgery. Thus, surgery for the installation of osseointegrated implants may represent a risk of developing MRONJ, resulting in the failure of osseointegration, discomfort, pain, purulent exudate, edema and fistula.

In order to reduce the risk of developing osteonecrosis, the serum CTx test is indicated as an adjunct test to assess the best time for surgical interventions in patients with a history of taking bisphosphonate medications. By means of the serum markers of C-Telopeptide, it is possible to observe indications of an increased probability of developing osteonecrosis. Therefore, serum levels above 300 pg/mg correspond to a reduced or minimal risk, while readings below 150 pg/mg represent an extremely high risk for developing osteonecrosis.

Once MRONJ has developed, the American Association of Oral and Maxillofacial Surgeons (AAOMS) suggests a treatment based on diagnostic stages ranging from stage 0 to 3, which ranges from treatment with antibiotics to more invasive procedures, such as sequestrectomies and surgical resections.

The aim of this study was to describe a conservative protocol, in the form of a case report, for serial installation of osseointegrated implants in a patient with a history of continuous use of 150 mg sodium ibandronate (Osteoban®), and to report the different
clinical and surgical managements required in order to avoid or minimize the risk of developing MRONJ after the placement of osseointegrated implants.

2 CASE REPORT

The case report was submitted to the Ethics Committee on Research with Human Beings of the University of Grande Rio (UNIGRANRIO) under the CAAE number: 51491221.2.0000.5283. All the procedures followed were in accordance with the Declaration of Helsinki.

The patient, a 63-year-old woman, with maxillary and mandibular removable partial dentures, non-smoker and hypertensive, in pain, presented to the dental office with tooth mobility Grade 2 and fracture in the dental crown of tooth 31. After anamnesis, she reported that she was a long-time user, of 150 mg Osteoban®, in addition to 10mg Enalapril Maleate, 20mg Rosuvastatin, 250 mg Lipanon, Acetyl Salicylic Acid and Calde K2.

Supported by the patient's medical history, her condition was classified as being in an “at risk” stage3,6,7, in which planning for a conservative treatment began, with immediate discontinuation of the drug Osteoban®. The following exams were requested: Cone Beam computed tomography, complete panoramic and periapical radiography, and serum CTx, a serum marker of bone resorption.

3 ROOT BURIAL

Periapical radiography showed vertical and horizontal bone loss in tooth 31 and evidence of previous endodontic treatment. To minimize the risk of developing a MRONJ due to tooth extraction, based on the history of taking Osteoban®, the decision was to perform the clinical procedure of root burial of tooth 31. This involved carefully removing the coronal region of the fractured tooth, sealing the root canal with light-cured resin, provisional cementation on the adjacent teeth, and as healing by second intention was estimated, no local suture was performed. (Fig.1)

The patient was monitored, periodically evaluated, and as the initial CTX showed a level of 150pg/ml, the patient fitted into the category of no risk for the development of osteonecrosis. Eight months after the first CTx was performed, a new serum CTX assessment was performed, with levels of 137 pg/ml, qualifying the patient as being at minimal or no potential risk. With this window of time for the evaluation, it was possible to identify a slight reduction in the serum CTx level that changed the patient's risk
classification, from “No risk” to a “minimum” risk, which reinforced the question of activity of the drug due to its accumulation, although it had been suspended for a long period.4,8

After this period of evaluation and control, the patient underwent periodontal conditioning to control the oral microflora in preparation for the surgical stage.

Figure 1 – Root burial. Periapical radiograph showing the initial condition of tooth 31 (Image A), followed by removal of the fractured crown (Image B), sealing the root canal with light-cured resin (Image C) and finalization with provisional adhesive (Image D).

4 TOOTH EXTRACTION AND INSTALLATION OF OSSEOINTEGRATED IMPLANTS

According to the protocol for installing implants associated with tooth extraction in patients with a history of Osteoban® use, the patient was previously medicated 24 hours before surgery, with antibiotics, 500 mg amoxicillin every 8 hours for 7 days, 4 mg steroids, dexamethasone every 12h for 5 days, 1g of analgesic, novalgin every 6h for 5 days and rinse with chlorhexidine 4x a day for 15 days.

After the procedure of anesthesia infiltrated into the vestibular fundus and mucosa of the gum of tooth 31, tooth 31 was extracted without any trauma, with the smallest tissue flap and least trauma possible to the buccal and lingual cortical bone in this region. Immediately after tooth extraction, bone milling and the installation of an osseointegrated implant - Morse Cone 3.5mm x 11 mm (Implacil de Bortoli, Brazil) were performed, followed by inserting a transmucosal healing cap, using a Nanosynt biomaterial graft (FGM) to fill in the gap between the implant and the intramedullary surfaces, and suturing
the peri-implant region. Subsequently, the patient's provisional adhesive prosthesis was re-cemented. (Fig.2)

Four months after the operation, periapical and occlusal radiographs indicated osseointegration of the implant, without intercurrences, making it possible to install the metal abutment with a torque of 20 N, and a provisional tooth.

Figure 2 – Installation of an osseointegrated implant in the region of tooth 31. After atraumatic extraction of tooth 31 (images A and B), the osseointegrated implant (Image C) was installed and a biomaterial graft was placed at the interface of the osseointegrated implant and bone surface (Image D). After a period of 4 months, the periapical radiography (Image E) and occlusal radiography (Image F) evaluations showed implant osseointegration with normal peri-implant mucosa (Image G).

5 MULTIPLE INSTALLATION OF OSSEOINTEGRATED IMPLANTS

Five months after the first surgery for installing the osseointegrated implant, without any complications related to the history of taking bisphosphonate medication, the patient was submitted to the second surgical stage for the installation of 7 osseointegrated implants. Initially, the alveolar remnant in the edentulous area of teeth 14, 13, 12, 11, 21, 22 and 23 was evaluated. This revealed severe horizontal bone loss with alveolar bone crest thickness between 2.8 mm; 2.46mm; 1.27mm and 1.41mm in the regions with more extensive bone absorption.

The patient was instructed to begin with use of the same medication protocol previously reported 1 hour before surgery.

After bilateral infraorbital anesthesia associated with gingival mucosa anesthesia, supracrestal and oblique relaxation incisions were made, followed by raising the total alveolar mucosa flap, then the alveolar ridge was horizontally leveled by using a drill bit to perform 1mm of wear in height of the alveolar ridge. Then, intraosseous milling was performed with a 2.0 lance drill, forming the receptor bed of the osseointegrated implants.
Due to the horizontal bone loss of the bone alveolus, expansion of the receptor bed was performed by using manual bone expanders 2.5, and 3.0, in order to expand the bone receptor bone bed without needing to wear the bone bed with a drill, thus reducing surgical trauma. After the bone expansion procedure, osseointegrated, external hexagon platform 3.5 implants were installed.

In the intraoperative period, in the region of teeth 14 and 13, a slight crack was found in the buccal bone cortical, caused by bone expansion due to the reduced horizontal volume of the remaining alveolar crest. In these areas, Nanosynt particulate biomaterial (FGM) grafts were performed, covered with bovine collagen membrane (Lumina-Coat, Criteria, 2x20x30 mm), and the surgery was completed with simple sutures.

The patient was followed-up on the seventh and 15th postoperative days, when the sutures were removed.

Figure 3 – Second surgical event – Patient’s oral condition (Image A) and alveolar bone remnant (Image B), followed by bone expansion procedure in the region of teeth 14 and 13 (Image C) with installation of osseointegrated implants (Image D). Image E demonstrating the vertical crack in the buccal cortical bone, with application of a particulate graft (Image G) covered with collagen membrane (Image H). Completion of surgery with suture of the operative site (Image H).

After 2 months of the postoperative period with follow-up, the patient returned with edema in the gingival area, erythema (redness) with pain when the region of implants 11, 21 and 22 were touched. When the clinical condition was correlated with the periapical radiography, the loss of implant cap 21 and loosening of implant cap 11 were
visualized, causing gingival inflammation due to tissue trauma. The gingival tissue was manipulated, with exposure of the implant platform and resection of this inflamed tissue. The patient was instructed to return to the use of Peroxidin gel 2 to 3 times a day for 15 days. After this period, the region was found to be normal, without other complications (Fig.4).

Figure 4 – 2-month postoperative period. Gum inflammation due to trauma (Image A) caused by loosening of the implant cap (Image B and C, yellow arrow) and loss of the implant cap from position 21 (Image B and C, yellow arrow) and loss of the implant cap from position 21 (Image Normality of the osseointegrated implants was visualized on radiographs.

After 12 months, the definitive prosthesis of the osseointegrated implants and radiographic evaluation of the osseointegrated implants were completed (Fig. 5) showing implant osseointegration and absence of development of MOAM.

Figure 5 – Radiographic control 12 months after the surgical procedures, indicating maintenance of osseointegration in the maxillary implants (Image A, B, C and D) and mandibular (Image E) no indications of development of MOAM.
6 RESULTS

The preoperative implementation of the 150 mg sodium ibandronate (Osteoban®) drug holiday associated with control of the serum CTx level for an extended period, allowed the installation of osseointegrated implants in a patient with a history of continuous oral administration of bisphosphonates.

Root burial of tooth 31 improved the patient’s pain condition and provided temporary attainment of esthetics and function, thereby ensuring the time needed to assess the patient’s serum CTx levels. Thus the CTx examination made it possible to classify, the patient’s risk for the development of MRONJ.

The surgical steps that evolved from less complex to the last procedures, with the installation of multiple osseointegrated implants, helped to assess the patient’s risk for developing MRONJ. This was possible because when each procedure was performed, a time interval of evaluation was determined, with the purpose of waiting for the occurrence of possible adverse effects such as the development of MRONJ.

The radiographic control 12 months after the surgeries performed indicated osseointegration of the implants installed, without the development of MRONJ.

7 DISCUSSION

There is no consensus in the literature about a definitive protocol with the aim of establishing preventive and therapeutic measures for MRONJ. The scenario is especially difficult for patients using antiresorptive medications, and who need dental treatment with osseointegrated implants.9 There are several risk factors associated with implant failure. In patients who use antiresorptive medications, bone metabolism is altered, and postsurgical response is less predictable and potentially more subject to failure. However, well positioned and functional implants do not seem to be involved with the occurrence of MRONJ.10

As occurred in the report presented in this study, Torres et al,(2008)11 reported the successful installation of 6 osseointegrated implants in a patient with Polyostotic Paget Disease, who was also a user of Risedronate sodium for 12 years. Pre-surgical planning with tracking of serum CTX levels together with the drug holiday suggested minimization of the risk of developing MRONJ. Yet Leite et al. (2015)12 reported the installation of multiple osseointegrated implants without knowing that the patient had been using Alendronate sodium for several months. Six months after the operation, the patient
presented purulent secretion in the osseointegrated implants of teeth 35, 36 and 37, and an en bloc resection of this necrotic area was performed.\(^{12}\)

Published works have suggested that there was no correlation between the occurrence of MRONJ in patients who were submitted to the placement of osseointegrated implants and who used oral bisphosphonate medications for the treatment of osteoporosis.\(^ {13}\) For patients undergoing treatment with bisphosphonate medications for osteoporosis and who need tooth extractions, or any other procedure that involves access to bone tissue, such as installation of dental implants, treatment of periodontal disease and treatment of periapical lesions, there is a consensus that medication should be suspended 3 months before the intervention, and it should remain suspended for further 3 months after the intervention. However, there is no evidence that this short-term pharmacological interruption will change the risk for the incidence of osteonecrosis in these patients.\(^ {14}\) The clinical and surgical management reported in the present report concerned a patient with the same characteristics, using bisphosphonate medication as therapy for osteoporosis. However, the team opted for a more conservative procedure, with a longer period of drug withdrawal, after which the patient would then be submitted to surgeries with a higher risk for developing MRONJ.

The existence of osseointegrated implants that were installed in patients with previous peri-implant diseases, represented an increased risk for the development of MRONJ when treatment with antiresorptive medications is initiated.\(^ {10}\) Whereas, in the same way, patients with a history of antiresorptive drug administration, who were submitted to the undergoing installation of osseointegrated implants, showed an increased risk for MRONJ around the implant area.\(^ {10}\)

However, the prognosis does not seem so favorable when it concerns the treatment for oncological diseases with the use of antiresorptive drugs in high doses.\(^ {13}\) As regards patients being treated for neoplasms with intravenous bisphosphonates or Desonumab\(®\), only elective treatments must be performed, while more invasive procedures must be avoided whenever possible, since there is increased risk for occurrence of osteonecrosis in these patients.\(^ {14}\)

Therefore, this suggests that osteoclast activity monitored by means of biological markers of bone remodeling, such as CTX, would be helpful for indicating the best time to perform surgical procedures in patients with a history of antiresorptive medication use.\(^ {14}\) Mattis \textit{et al.}\(^ {15}\) followed-up the CTX levels of a patient using bisphosphonate, for a month, in order to perform removal of an implant with bone loss. The patient’s rates
ranged from 0.067ng/mL to 0.160ng/mL. In the report presented here, an 8-month follow-up of serum CTX levels was proposed. This revealed a reduction in levels from 150pg/ml to 137 pg/ml, demonstrating that even after it had been suspended, its action in the body did not decrease, but suggested the existence of peaks of drug release. This corroborated the action of the drug due to its accumulation, even when it had been suspended for a long period.\textsuperscript{4,8} However, up to now, the use of these markers has not been validated. Therefore, the use of dosage of these markers is not recommended. Nevertheless, research in this area continues in the search for a risk predictor.\textsuperscript{14}

Furthermore, patients using bisphosphonates should be followed-up periodically to assess peri-implant complications. Mattis \textit{et al.}\textsuperscript{15} reported osteonecrosis that occurred [in a patient’s implant] only 2 years after the osseointegrated implant had been installed.

It is worth emphasizing that the ideal would be perform a detailed evaluation of the patients’ entire oral environment, before initiating treatment with antiresorptive and antiangiogenic medications. If the systemic condition allows this, therapy with antiresorptive medications should not be initiated, but must be postponed until the adequacy of the oral environment has been established.\textsuperscript{14} When conditions such as the presence of tooth mobility, periodontal disease, residual roots, carious lesions, periapical pathologies, lack of prosthesis stability and possible traumatic areas are identified, they must be observed with extreme attention to maintaining the health of the patients oral tissues for the purpose of preventing osteonecrosis of the jaws. Moreover, it is important to motivate patients to maintain proper oral hygiene, topical application of fluoride, mouthwash with chlorhexidine, since one of the etiological hypotheses is related to the patient's level of hygiene.\textsuperscript{14}

Recently, several studies have demonstrated the efficacy of therapy with teriparatide, a drug that stimulates bone formation. The action of teriparatide in the body occurs through stimulation of the parathyroid hormone receptor 1 in osteoblasts and their precursors, by stimulating anabolic activity that leads to the formation of greater bone mass.\textsuperscript{16}

\section{8 CONCLUSION}

The preoperative conduct of instituting the \textit{drug holiday} of 150 mg sodium ibandronate (Osteoban\textsuperscript{®}), associated with control of the serum CTx level for an extended period allowed the installation of osseointegrated implants in a patient with long-term oral administration of bisphosphonates without the development of MRONJ occurring.
The surgical steps, evolving from less complex through to the last procedures, with the installation of multiple osseointegrated implants, helped to assess the risk of the patient for developing MRONJ. This was achieved because when each procedure was performed, a time interval of evaluation was determined, for the purpose of waiting for possible adverse effects to manifest, such as the development of MRONJ, thus ensuring greater safety in the surgical procedures of larger extension.
REFERENCES


