

Surgical protocol in patients at risk for bisphosphonate osteonecrosis of the jaws: clinical use of serum telopeptide CTX in preventive monitoring of surgical risk

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Summary

Aim: This study investigates the association between cross linked C-terminal telopeptide test (CTX) and individual surgical risk of osteonecrosis in patients taking oral bisphosphonates.

Materials and Methods: 32 patients receiving bisphosphonate were treated surgically. Patients were divided into three groups according to type of drug administered and were subjected to a treatment of oral surgery, such as simple tooth extractions and extraction of all residual teeth of the oral cavity, upon evaluation of CTX values and antibiotic prophylaxis.

Results: Within the sample of 32 patients, 12 patients had been treated with bisphosphonates for several years and none developed osteonecrosis of the jaw upon surgery. As for CTX, patients treated with oral bisphosphonates showed a mean value of serum C-telopeptides of 0.2869 ng/ml. The mean value of CTX did not differ significantly between patients taking oral bisphosphonates and healthy patients not treated with bisphosphonates.

Conclusion: None of the patients subjected to pre-operative antibiotic prophylaxis developed osteonecrosis of the jaw after surgery. The pharmacological and surgical protocol tested appeared valid in the prevention of osteonecrosis associated to bisphosphonates.

Key words: serum C-terminal C-telopeptide (CTX), bisphosphonate, osteonecrosis of the jaw (ONJ).

Introduction

Bisphosphonates are drugs used to treat osteoporosis when taken orally (1) and in the therapy of bone metastases, multiple myeloma and Paget's disease when taken parenterally. Bisphosphonates exert their pharmacological action accumulating mainly in places with elevated bone metabolism; being inorganic pyrophosphate analogues, bisphosphonates have a high affinity for calcium and are consequently removed from the circulation and then bind to mineralized bone. After repeated doses they accumulate in the bone matrix. During resorption, the osteoclast acidifies the bone matrix, causing the dissolution of hydroxyapatite crystals and then the release of the bisphosphonate that was linked to the crystals themselves. In this way it may come in contact with osteoclasts inhibiting their resorption power. Bisphosphonates are therefore drugs able to affect bone metabolism.

Marx in 2002 (2) defined the proportions of the putative causes of osteonecrosis: dental extractions 37.8%, periodontal and endodontic surgery 12%, implants interventions 3.4%. He also indicated a generic relationship with periodontal disease in 28.6% of cases (3). Patients with osteoporosis have an estimated risk of developing osteonecrosis between 0.01% and 0.04%, which rises to 0.09-0.34% if they have performed dental extractions. Patients with multiple myeloma and bone metastases pass from 0.88% and 1.15% risk to 6.67% and 9.1% (4). The CTX is a serum test proposed by the American Society of Bone Mineral Research Task Force on osteonecrosis of the jaws. It is capable of measuring a specific marker of bone turnover and for this reason it could be used as a risk indicator in pre-operative assessment. It is considered a useful test to assess serum and urinary metabolites typical of bone resorption. The index serum CTX can detect changes in the bone remodeling in a range of time comprised between a few days up to two weeks, therefore much earlier than with the use bone mineral density (BMD). The assessment of BMD is a rough procedure, though it remains very useful in the quantitative assessment of skeletal bone mass because it measures the relative bone density. Instead, the value of CTX test is rather useful for the quantitative assessment of bone resorption through the degree of bone renewal and such information is of great importance when assessing the risk of ONJ (5).

The dosage of CTX requires the removal of 1 ml of blood collected in a test tube at room temperature. Sampling should be collected in the morning, because changes during the day could lead to elevated values in the late afternoon or evening. The serum can be analyzed af-

ter 15 minutes needed for blood clotting and provides a reliable result up to over 16 hours of storage at room temperature for three days if kept refrigerated and three months if frozen.

Upon several studies, Marx and co-workers (5) proposed guidelines for risk assessment in the laboratory of patients taking bisphosphonates: CTX values between 0.3 and 0.6 ng/ml are not associated with ONJ, values between 0.150 and 0.299 ng/ml are associated with none or minimal risk of ONJ, values between 0.101 and 0.149 ng/ml are associated with an intermediate risk of ONJ, and finally CTX values ≤ 0.100 ng/ml are associated with a high risk of ONJ.

Materials and methods

Between October 2009 and June 2010 at the Dental Clinic of the University Milano-Bicocca 32 patients were recruited of which 12 were treated with oral bisphosphonates, 11 with intravenous bisphosphonates and 9 not yet treated (Fig. 1). Our study group consisted of patients who were or are currently treated with oral bisphosphonates and about to receive invasive dental procedures. Of the 12 patients treated with oral bisphosphonates 3 patients were taking risedronate acid, 8 alendronic acid and one ibandronic acid (Fig. 2). The control group consisted of patients not receiving bisphosphonates. Patients showed up at our department and were included in the study sample depending on their bisphosphonate assumption. A complete clinical record was made for all

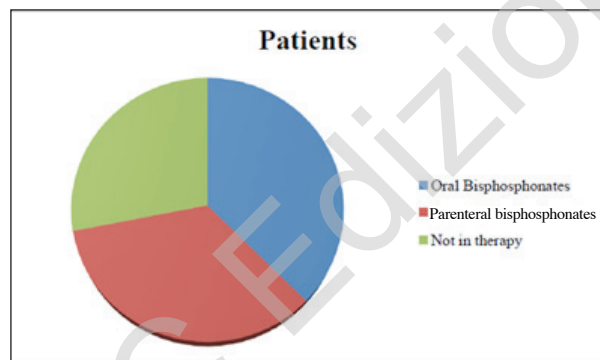


Figure 1 - Type of bisphosphonate assumption in the sample.

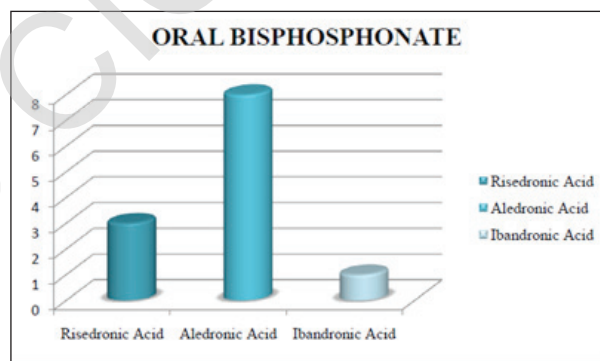


Figure 2 - Typology of oral bisphosphonate.

patients in order to obtain information concerning the remote and recent physiological, pathological and pharmacological anamnesis, and preoperative CTX test was performed in order to evaluate the residual bone turnover. The patients were scheduled for oral surgery depending on the value of CTX obtained, the clinical evaluation during the oral examination and the radiographic analysis (orthopantomography of jaws and Dentascan Tc). For patients taking oral bisphosphonates for less than three years, in the absence of obvious risk factors it is not necessary to change or delay the oral surgical treatment plan. For patients treated for less than three years but with at least one systemic risk associated, it is necessary to contact the physician to discontinue the bisphosphonate (drug holiday) at least three months before the surgical procedure and the resumption should be delayed until three months after its execution. At the first examination and three months later it is necessary to measure the CTX. Values lower than 0.150 ng/ml would advise against surgical procedures and an interruption prolonged for another three months. In case of detection of CTX values greater than 0.150 ng/ml, it may be allowed the introduction of elective surgery, informing the patients of the risk of developing ONJ, albeit very small. Bisphosphonate should not be reintroduced until three months upon healing. For patients taking oral bisphosphonate for more than three years in the absence of risk factors it is recommended to contact the physician in order to agree to an interruption of the drug for three months before to three months after the surgical session. Moreover, it is recommended to study the level of the cell turnover marker CTX at the first examination and before conducting the planned procedures. A value greater than or equal to 0.150 ng/ml is the minimum requirement to perform surgical procedures in patients who belong to this group. If there is an urgent need for oral surgery while taking oral bisphosphonates, as in the presence of odontogenic abscesses requiring extraction or abscess drainage to decrease pain and to manage infection, the patient should be subjected to the appropriate procedure rather than maintaining the condition of pain and infection. Usually, the precursors of osteoclasts regain their activity to allow good bone healing following a three-month discontinuation of the bisphosphonate. In any case, it is important to remove all odontogenic foci in the oral cavity, which are associated to an increased risk of ONJ. It is therefore necessary to inform the patient of possible risks. It has been estimated that for the first 2-3 years, the risk of developing ONJ is low for patients taking oral bisphosphonates (5-11).

All patients in the sample, two weeks before and one week after oral surgery, carried out at the dental clinic of the Milano-Bicocca University according to the criteria of minimal invasiveness and high radicality to remove any odontogenic focus, underwent a pharmacological prophylaxis (6,7). Such prophylaxis started two weeks prior to surgery and consisted of amoxicillin and clavulanic acid tablets (1 g every 12 hours), metronidazole tablets (250 mg every 8 hours) and omeprazole tablets (20 mg once daily) for the duration of antibiotic cover-

age, associated to rinsing with chlorhexidine 0.2% immediately before surgery. The 12 patients receiving oral bisphosphonates were subjected to 15 surgeries of which 2 full-mouth tooth extractions and 18 extractions of compromised dental elements (Fig. 3). In the group of patients treated with oral bisphosphonates, due to the known complications that these drugs can induce, a total of 12 surgeries were performed, of which 26 extractions of hopeless teeth and a full-mouth tooth extraction procedure (Fig. 4). The antiseptic and antibiotic prophylaxis was continued for one week after surgery to prevent infection, in order to avoid that it further delays the healing of the surgical wound. All patients in the sample underwent a close follow-up 1, 4 and 12 weeks after surgery, then every 3 months until the following year and every 6 months thereafter. At each visit the surgical sites were checked clinically and radiographically to assess epithelialization, bone sequestra and bone infections.

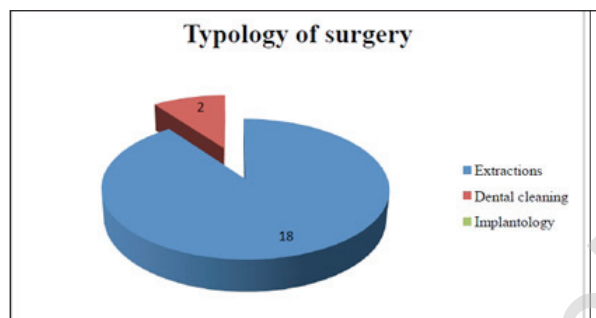


Figure 3 - Typology of oral surgery in patients treated with oral bisphosphonate in the sample.

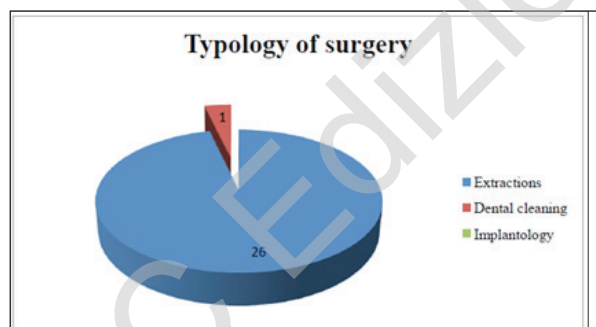


Figure 4 - Typology of oral surgery in patients not treated with bisphosphonate in the sample.

Results

All patients taking bisphosphonates orally or parenterally who addressed our department to undergo surgery were treated according to the aforementioned surgical protocol. In addition, patients were asked to go to a laboratory for CTX testing to determine the bone turnover. The values of CTX obtained from the patients in the sample were as follows:

- the mean value of CTX in patients with oral bisphosphonates was 0.2869 ng/ml;

- the mean value of CTX in patients not yet treated with bisphosphonates was 0.225 ng/ml, which falls within the range of values reported in literature indicating values between 0.150 and 0.299 ng/ml. In our control sample, including patients not treated with bisphosphonates, one subject showed a CTX value of 0.88 ng/ml. This value does not conform to the rest of the sample. A possible explanation may be sought in medical history of this patient that revealed she was suffering by bone metastases from breast cancer. Marx in his 2005 study claimed that the CTX is reliable only in non-cancer patients and in cancer patients without bone metastases, because the latter could alter the real value of bone turnover(4).

After having categorized patients belonging to the group treated with oral bisphosphonates in ascending order according to the duration of drug exposure we proceeded to observe the change in the CTX value (Fig. 5). Based on the values of CTX belonging to patients in our study treated with oral bisphosphonates, it was performed a statistical test of hypothesis to compare the CTX values in patients taking oral bisphosphonates with those in patients of the control group. Null hypothesis was that CTX values in the two groups are equivalent. The value of the test statistic ($z = 0.4166$) was lower than the value of t-Student ($t(n-1) = 2.262$). In addition, the confidence interval at 95% indicated, including 0, that it was not possible to exclude the null hypothesis.

Thus, in the sample considered for the study, the difference in CTX values between patients taking oral bisphosphonates and patients of the control group, was not statistically significant. In the group of patients taking oral bisphosphonates, on a total of 15 surgeries no signs of osteonecrosis in the longitudinal follow-up were found. Nine patients showed an uneventful healing, that is with a full epithelial filling of the surgical site within 30-45 days after surgery, while 6 surgical wound showed a delayed healing within 45-90 days (Figs. 6-7). In the group of patients that at the time of surgery did not take bisphosphonates, 10 surgical sites showed a normal healing within 30-45 days and two a delayed healing within 45-90 days (Figs. 8-9).

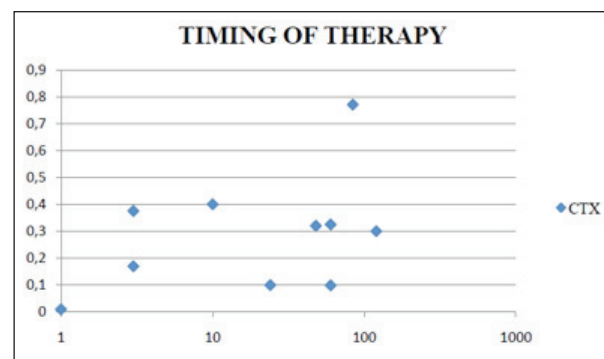


Figure 5 - CTX values in patients treated with oral bisphosphonate versus timing of the therapy.

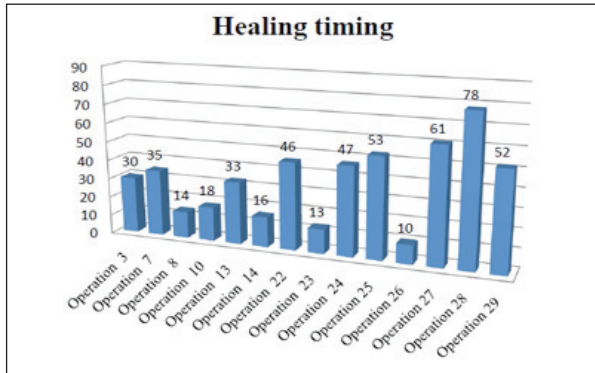


Figure 6 - Timing of wound healing in patients treated with oral bisphosphonate.

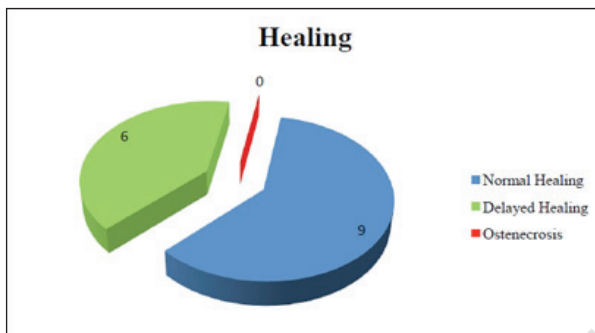


Figure 7 - Wound healing in patients treated with oral bisphosphonate.

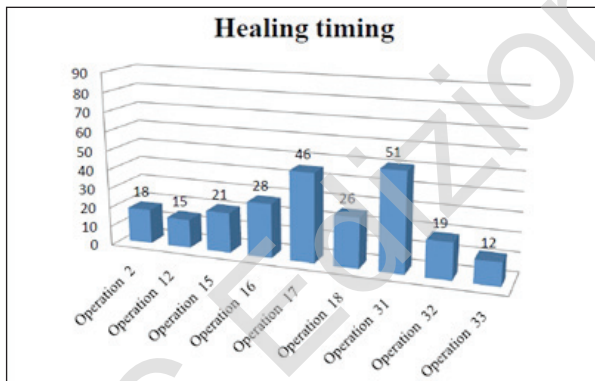


Figure 8 - Timing of wound healing in patients not treated with bisphosphonate.

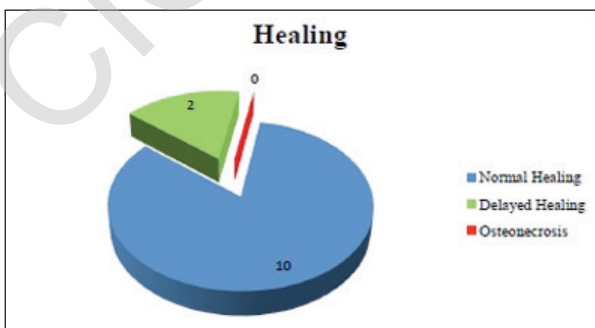


Figure 9 - Wound healing in patients not treated with bisphosphonate.

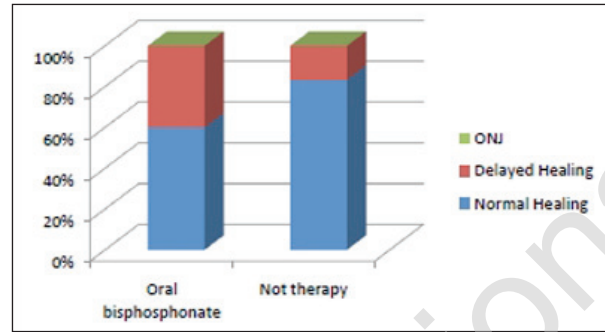


Figure 10 - Healing comparison between patients treated with oral bisphosphonate and patients not treated with bisphosphonate.

Therefore, comparing the two groups, study and control, it can be observed that patients not taking bisphosphonates had a better post-operative healing than patients treated with BF, in which we should consider the possible delayed healing and therefore it becomes necessary a rigid follow-up (Fig. 10).

Case report

A woman (about 55 years old) addressed our department for the simultaneous extraction of 3.6 and 4.7 residual roots. Antibiotic prophylaxis was administered in accordance to the protocol, since different operating sessions would require antibiotic administration at close times. From the compilation of medical records the patient resulted treated with oral bisphosphonates for about ten years. After preoperative evaluation by means of orthopantomography (Fig. 11), we performed the intraoral examination (Fig. 12) and CTX test, which was found to be 0.3 ng/ml, so with associated low risk of osteonecrosis of the jaw. We then proceeded with the administration of antibiotic prophylaxis, as previously described. The extraction of residual roots was performed following the surgical protocol previously explained (Fig. 13). After the surgery a suture 3/0 was performed, which was removed after 8 days (Fig. 14). The patient continued the antibiotic prophylaxis and the antimicrobial therapy with chlorhexidine 0.2% for one week after the surgery. Follow-up checks were scheduled at 2, 4, 6 and 12 months (Fig. 15).



Figure 11 - Pre-operative orthopantomography.



Figure 12 - Pre-operative clinical situation.

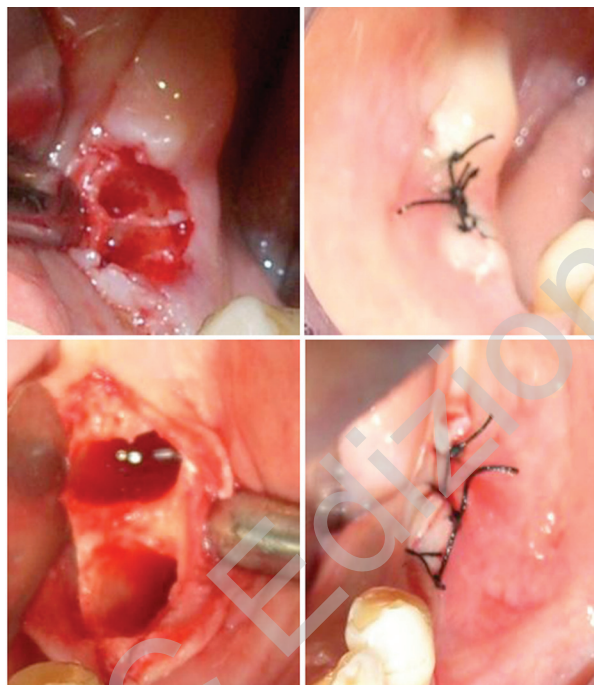


Figure 13 - Extraction of 3.6 and 4.7 and suture.



Figure 14 - Clinical situation after 8 days.



Figure 15 - Orthopantomography two months later.

Discussion

According to current knowledge, bisphosphonates are a very useful and effective therapeutic aid in the treatment of cancer-induced and metabolic bone diseases, beneficial effect an increasing number of patients makes prolonged use of these drugs; especially in post-menopausal women (8,9), the use of bisphosphonates has become so ordinary that sometimes it is not even specified in anamnesis before performing a dental surgical therapy. However, patients should be informed of possible complications related to the bisphosphonates intake after invasive surgical treatments (10).

According to what stated above and based on the results collected by the pharmacological and surgical protocol adopted in the dental clinic of the University of Milano-Bicocca, inside the Hospital of San Gerardo of Monza, it is essential to consider patients treated with bisphosphonates at risk of ONJ. For this reason, it is necessary to monitor these patients during dental treatment after the surgery, in order to act quickly in case of complications. The observed operative protocol is based on an adequate and well-defined system of pre-operative prophylaxis, a surgery conducted in a sterile environment and aimed to be minimally invasive, the complete debridement of all infected and inflammatory tissue, a suture warranting a rapid healing, and finally on a close follow-up program. Given the excellent results obtained by applying the above pharmacological and surgical protocol in terms of reductions in the number of osteonecrosis developed after oral surgery, it should be emphasized the importance of applying this protocol to all patients treated with oral, intramuscular or intravenous bisphosphonates two weeks before and one week after surgery. Finally, as regards the use of serum telopeptide CTX in terms of preventive monitoring of the risk of developing ONJ in patients with oral bisphosphonates in the sample of the study, compared with the values of CTX in healthy patients, at present there is no sufficient evidence to affirm that the difference between the CTX values obtained in the two patient groups is statistically significant, perhaps because of the limited sample size. Nevertheless, it is important to highlight that the relevance of CTX as an indicative value to consider patients treated with bisphosphonates at potential risk of osteonecrosis.

For this reason, this serum test is an important clinical support in the therapeutic planning of the patient treated with bisphosphonates.

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