Tooth extraction in patients on zoledronic acid therapy

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Summary

Objectives: Surgical management of patients following zoledronic acid therapy is particularly difficult, since the dental extraction is the main cause of BRONJ.

Methods: A case-control study was conducted on 176 patients treated with intravenous (IV) bisphosphonates for oncologic pathologies who also underwent dental extractions. The study was divided randomly into two groups: 91 were treated with Plasma Rich in Growth Factor Plasma (PRGF) (study group) and the other 85 were not treated with the growth factor preparation (control group).

Results: Panoramic X-ray and computed tomography were performed both before and 60 months after surgery. By clinical and radiological diagnosis, BRONJ was diagnosed in only 5 patients in the control group at an average of 91.6 days after tooth extraction.

Conclusions: We hypothesize that Plasma Rich in Growth Factor (PRGF) is important for the successful treatment of patients on bisphosphonates to restore the osteoblast/osteoclast homeostatic cycles via autologous cytokines. Moreover, this protocol reduces the risk of BRONJ when it is necessary to perform dental extractions in patients undergoing IV bisphosphonate treatment.

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Introduction

Osteonecrosis of the Jaw (ONJ) has been associated with the use of bisphosphonates. BRONJ (Bisphosphonate-Related Osteonecrosis of the Jaw) is defined as a necrotic bone area with or without an area of exposed avascular necrotic bone in the maxillofacial region. BRONJ is usually associated with bone that has been exposed for at least 8 weeks, in a patient who received and/or is receiving bisphosphonates, with no previous history of irradiation to the maxillofacial region.1

Over the past few years, the number of ONJ cases associated with intravenously administered bisphosphonate treatment has risen, in particular among oncology patients with bone metastasis.3

Although Marx3 first reported in 2003 that bone necrosis might be a side effect of the use of zoledronate or pamidronate, the underlying pathophysiology of bisphosphonate-associated osteonecrosis of the jaw is still an issue of debate in international literature, which reports several theories and an exhaustive list of proposed mechanisms. Ruggiero et al.4 have reported that the etiology of bone osteonecrosis is related to an excess of osteoclast activity, resulting in an alteration of normal bone turnover.5 Conversely, an associated inhibition of osteoclastic activity has also been reported.6,7

However, these hypotheses do not justify the onset of BRONJ exclusively in the jaw. It is also hypothesized that bisphosphonates trigger osteonecrosis by inhibiting angiogenesis, which is essential for the healing process of a fresh extraction socket.8–10 This hypothesis was further supported by Fournier et al. in 2002 via an in vitro and in vivo study that documented how bisphosphonates reduced endothelial cell proliferation by inducing apoptosis, which consequently resulted in lower vessel densities due to a reduction in the formation of new capillaries.11 The literature also reports a possible connection between osteonecrosis of the jaw and the toxic effects of bisphosphonates on the oral mucosa.12

The toxic effects of bisphosphonates on gastric mucous have also been established.13,14 Indeed, a study carried out in 2008 documented how pamidronate suppressed cell proliferation, leading to the inhibition of oral wound healing.15 Most of the BRONJ cases reported in literature show a strong correlation with dental extractions and/or oral surgical procedures (69% cases).16–18

This is why management protocols of these patients now tend to be preventive approaches. Such prevention and treatment strategies include the elimination of any potential infection sites in patients who are treated with IV bisphosphonates, in an effort to guarantee sufficient oral health status and to reduce the risk of BRONJ related to dental pathologies and/or prospective oral surgical procedures.7,19
Despite growing evidence of the risks of surgery in patients treated with IV bisphosphonates, the necessity to remove strongly compromised dental elements does arise. Therefore, the need to identify treatment protocols that can reduce the incidence of this “newly recognized” oral syndrome is ever more pressing.

Consequently, surgical protocols that favor both bone and mucosal healing processes while concurrently limiting surgical damage to minimum levels must be researched and adopted for patients who are treated with IV bisphosphonates.

In the present study, preparations rich in growth factors were used as a means of biotechnological support to accelerate post-extraction alveolar bone regeneration. Among these preparations rich in growth factors, in literature we can find Platelet Rich Plasma (PRP) and Plasma Rich in Growth Factors (PRGF). In this study we considered PRGF, in fact, the hypothesized efficacy of using it to support surgical dental procedures in patients on IV bisphosphonates is based on the contribution PRGF makes in accelerating the healing process where these drugs have been a source of inhibition. The growth factors in PRGF, which are usually inhibited by bisphosphonates, are a supplementary source of stimulation to the physiological deficit, and they promote angiogenesis as well as bone and mucosal wound healing.

The aim of the study is to confirm PRGF effectiveness in the treatment of patients following a zoledronic acid therapy who need dental extractions.

Materials and methods

The study was carried out in the Oral Surgery Department of the Dental School of the University of Torino, Italy, from January 2005 to December 2009.

The study design was reviewed by a senior specialists about the treatment of patients who take IV bisphosphonate therapy.

176 patients (75 males and 101 females), with ages ranging from 44 to 83 years, were included in this study.

At the time of the first visit, patients were included in a computerized clinical file, which also recorded information on age, gender, smoking habits, systemic pathology and use of any drugs were also detailed. In particular, we asked if they were taking steroids or they were undergoing chemotherapy.

Inclusion criteria were (1) current IV bisphosphonate therapy and (2) the necessity for removal of strongly compromised dental elements (Table 1). Exclusion criteria included (1) any previous history of irradiation to the maxillofacial area and (2) dental extractions before the study period. The local ethics committee approved the clinical protocol used for the study, and all enrolled study patients provided written informed consent. The patients had been prescribed IV bisphosphonates for oncological pathologies, which included breast carcinomas, prostatic carcinomas, ovarian carcinomas, lung carcinoma and multiple myeloma (Table 2).

All patients were taking zoledronic acid. Patients on zoledronic acid preparations had a 4-mg infusion every 21 days.

The surgical protocol involved a delicate surgery and closure by first intention. The study cohort was divided into two similar groups: 91 patients were treated with PRGF (study group) and 85 patients were not treated with the growth factor preparation (control group). The randomized group distribution was set up specifically to obtain groups that were homogenous for gender, age, smoking habits, systemic pathology based on the computerized clinical file we used in the first visit. A total of 542 extractions were necessary: 287 in the mandible and 255 in the maxilla (Table 1).

The surgical protocol included investigative radiology: orthopantomography and CT (Fig. 1). Scans were done to evaluate the extraction sites preoperatively and six months postoperatively.

A professional oral hygiene session was given to each patient one week before surgery. All patients were administered the antibiotic amoxicillin/clavulanic potassium, at a dosage of 1-g tablet every 8 h for a total of 6 days, starting from the evening before the surgical appointment or erythromycin, at a dosage of 600-mg tablets every 8 h for 6 days, when an allergy to penicillin was declared. A 15 ml blood sample was drawn from the peripheral veins of the 91 patients in the study group before surgery. The sample was centrifuged into 5 ml blood-collecting tubes with anticoagulants at 580 g for 8 min at 1800 rpm in an appropriate system (PRGF System, Biotechnology Institute [BTI], Vitoria, Spain). Two main fractions were obtained: (1) red blood cells at the bottom of the test tube and (2) the uppermost plasma fractions from above the red blood cells. The plasma fraction was divided into 2 parts with disposable sterile pipettes, PRGF and autologous fibrin membrane, which were activated with 50 μl of calcium chloride (CaCl₂ for each millimeter of PRGF) and introduced into the post-extraction alveolus.

An alveolar troncular nerve block was administered to both groups via local or regional anesthesia (3% mepivacaine with 1:100,000 epinephrine), depending on the dental site. To prevent interference with the healing process, no intraligamentous or intrapapillary infiltrations were made. Surgical extractions were

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Dental extractions performed in a group of patients receiving zoledronic acid.</th>
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<tbody>
<tr>
<td>Tooth pathology</td>
<td>Study group (dental elements extracted)</td>
</tr>
<tr>
<td>Residual roots</td>
<td>75</td>
</tr>
<tr>
<td>Semi-impacted third molars with pericoronitis</td>
<td>8</td>
</tr>
<tr>
<td>Root fracture</td>
<td>11</td>
</tr>
<tr>
<td>A 2° to 3° grade mobility</td>
<td>67</td>
</tr>
<tr>
<td>Destructive tooth decay involving the roots</td>
<td>47</td>
</tr>
<tr>
<td>Apical granuloma (untreatable by any means other than extraction)</td>
<td>67</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Table 2</th>
<th>Principal patient characteristics included in the study.</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>Study group (number)</td>
</tr>
<tr>
<td>Males</td>
<td>36</td>
</tr>
<tr>
<td>Females</td>
<td>55</td>
</tr>
<tr>
<td>Teeth extracted</td>
<td>Study group</td>
</tr>
<tr>
<td>Mandible</td>
<td>142</td>
</tr>
<tr>
<td>Maxilla</td>
<td>133</td>
</tr>
<tr>
<td>Age</td>
<td>Study group</td>
</tr>
<tr>
<td>44–60</td>
<td>22</td>
</tr>
<tr>
<td>60–70</td>
<td>43</td>
</tr>
<tr>
<td>70–83</td>
<td>26</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>Study group</td>
</tr>
<tr>
<td>No</td>
<td>76</td>
</tr>
<tr>
<td>&lt;15/die</td>
<td>11</td>
</tr>
<tr>
<td>&gt;15/die</td>
<td>4</td>
</tr>
<tr>
<td>Systemic pathology</td>
<td>Study group</td>
</tr>
<tr>
<td>Prostatic carcinoma</td>
<td>33</td>
</tr>
<tr>
<td>Breast</td>
<td>17</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>36</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3</td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Ovarian Carcinoma</td>
<td>21</td>
</tr>
<tr>
<td>Other medications (at the time of the study)</td>
<td>Study group</td>
</tr>
<tr>
<td>Steroids</td>
<td>47</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>21</td>
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carried out via intrasulcular incisions and detachment of full thickness flaps to allow wound healing via primary intention to leave the post-extraction alveolus in contact with the oral cavity bacteria. To ensure nontraumatic avulsion, the dental extraction was followed by delicate curettage and osteoplastic procedures on the more fragile bone septum and cortical bone areas (Fig. 2).

Lastly, the patients in the study group were treated with a PRGF fraction inserted into the alveolus. A membrane comprised of a plasma fraction poor in growth factors was then placed between the bone tissue and the mucosal flap to promote healing (Fig. 3). Conversely, no material was placed into the post-extraction alveolus in the control group, where coagulation and stabilization took place. Suturing was done in all cases with resorbable material (Vycril® 4/0, Ethicon, Inc., Somerville, New Jersey, US) using a simple detached technique ensuring a hermetic closure at the wound margins to enable healing via primary intention (Fig. 4). Written oral hygiene and postoperative instructions were then given to all of the patients.

Clinically programmed monitoring of mucosal healing was carried out at 3, 7, and 14 days postoperatively, when suturing was removed. Monitoring was continued at 21, 30, 60, 90 and 120 days. The patients were always examined by evaluating the clinical signs of BRONJ that were mentioned above: pain, swelling, non-healing, exposed necrotic bone, and/or fistulas with connection to the bone. The absence of these clinical signs was determined to indicate successful treatment.

Radiographic control was carried out 6 months after surgery by orthopantomography and CT scans (Fig. 5).24

Subsequently, the follow-up protocol included 6 monthly orthopantomography and concomitant professional hygiene sessions, followed by annual CT scans. The study group had a total follow-up period of 24–60 months.

Results

No intraoperative complications were observed in either of the two groups. There was no evidence of postoperative bisphosphonate-associated osteonecrosis of the jaw in any of the extractions in the study group at the time of follow up (542 extractions). Five (out of 267 extractions) early symptomatic osteonecrotic lesions with diameters <0.5 cm of exposed mandibular bone were diagnosed in the control group. The average period of BRONJ occurrence was 91.6 days postoperative, and it was diagnosed at the clinical evaluation and radiographic control examinations using standards proposed in the literature.2,24 All patients who showed
these osteonecrotic lesions had multiple myeloma, and they were all taking zoledronic acid (more than 12 months). Moreover, at the time of BRONJ diagnosis, the five patients had not yet completed their chemotherapy cycles with Vincristine. All five BRONJs were surgically treated: during bone excision surgery PRGF was used with excellent success.

Discussion

Bisphosphonate compounds have the capacity to reduce secondary skeletal-related events (SREs) due to bone metastasis from solid tumors and myelomas. As such, they are increasingly incorporated in the treatment of oncologic pathologies, with the aim of improving patient quality of life. Investigators first reported an apparent association between bisphosphonate use and the oral syndrome of osteonecrosis of the jaw in oncologic patients in 2003. The American Association of Oral and Maxillofacial Surgeons (AAOMS) report a 0.8–12% incidence of BRONJ in patients on IV bisphosphonate therapy, which is frequently associated with dental extractions and/or oral surgery procedures. Such publications gave rise to the development of prevention-oriented management protocols. These protocols include establishing as good a health status as possible under the circumstances for all patients before administration of these drugs, as is common practice for those scheduled to receive irradiation of the head and neck areas. The literature on the implementation of these dental preventive measures reports a decrease in the occurrence of osteonecrosis of the jaw in solid tumor patients with bone metastasis treated with bisphosphonates. However, despite these efforts, there are clinical situations in which surgical intervention in these patients cannot be avoid.

The protocols proposed in the literature for such cases recommend a conservative approach associated with antibiotic prophylaxis and a debridement cleaning with chlorhexidine. Some authors recommend a 20-day period of antibiotics and chlorhexidine cleansing, twice daily for a two-month postoperative period. However, to the best of our knowledge, there has been no protocol proposed to date for tooth extractions in patients on IV bisphosphonate treatment. Therefore, this study was developed to meet the demand for such a protocol in an attempt to enhance healing and reduce the risk of BRONJ. The use of preparations rich in growth factors was investigated to address this issue.

Bisphosphonates accumulate in the mineralized matrices of bone and are taken up by osteoclasts, leading to an inhibition of osteoclast activity that compromises the physiological activity of bone remodeling and deposition. Moreover, as demonstrated by Landesberg et al., bisphosphonates also inhibit the proliferation of oral mucosal cells and, consequently, hinder the healing processes. These results have recently been confirmed by Kobayashi et al. using an animal model. The authors demonstrated that zoledronic acid reduced the migration of epithelial cells, which had a negative effect on the healing process of the post-extraction alveolus. Delaying the re-epithelization process seems to prolong alveolus exposure to the oral cavity bacteria, increasing the risk of BRONJ.

In 2009, Hikita et al. analyzed the effect of bisphosphonates on the post-extraction alveolus healing process in rats. The histological and morphometric data demonstrated that inhibiting osteoclast activity delayed the post-extraction alveolus healing processes when treated with bisphosphonates when compared to untreated rats. The first 7 postoperative days seem to be the most critical for the onset of inflammatory processes that may inhibit healing processes and induce osteonecrosis. Not only does the use of compounds rich in growth factors seem to reduce these untoward events, it also appears to enhance hemostatic action and accelerate epithelial closure. Indeed, Anitua et al. demonstrated in that epithelization was accelerated in post-extraction sites treated with PRGF and that the trabecular bone thus obtained was more organized than that of untreated post-extraction sites. These results demonstrated that filling the post-extraction alveolus with PRGF offers clear advantages in the early healing phases, improving hemostasis and protecting the alveolus during the early stages to promote epithelization.
triggered by the potent mitogens vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) (versus endothelial and osteoblastic cells) protects the alveolus in the early healing stages, reducing the risk of infection and the onset of BRONJ. All of these benefits indicate that the use of platelet-rich compounds may provide support in both single and multiple extractions, especially in cases associated with the need to stimulate the healing process.

The study reported here in confirms the aforementioned data with a 100% success rate for the surgical treatment of patients on IV bisphosphonate treatment (study group). Conversely, five patients in the untreated control group had BRONJ in the mandible. All these patients had multiple myeloma. They were taking zoledronic acid more than 12 months and have been undergoing active chemotherapy with Vincristine at the time of the study (Table 2).

According to another study of ours, the 5 BRONJ were surgically treated: during bone excision surgery PRGF was used with excellent success. Results seem to show how patients with multiple myeloma have difficult management and healing and is better to use PRGF with them.

Finally these results confirm a previous case-control study of 100 patients survey, that we recently published.

Conclusions

In conclusion, our data on the use of compounds rich in growth factors further enhance the results published in the international literature. Therefore, we believe that the clinical protocol herein reported is a valid proposal when dental extraction surgery is inevitable in patients on IV bisphosphonate treatment because the protocol may reduce healing times and it is a user-friendly technique with a good cost-benefit ratio.

Conflict of interest statement

None declared.

References


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