Use of platelet-rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw


Abstract. Platelet-rich plasma is a concentrate of growth factors and osteoconductive proteins, which can play a major role in bone biology by accelerating and enhancing bone repair and regeneration. This paper describes the results of using platelet-rich plasma in the management of bisphosphonate-associated necrosis of the jaw. Eight patients with a diagnosis of bisphosphonate-associated necrosis of the jaw were surgically treated for debridement and removal of necrotic bone, followed by application of autologous platelet concentrate enriched with growth factors and primary suture of the wound. Patients underwent periodic clinical and radiological follow-up examinations. All patients showed clinical improvement and oral lesions resolved 2–4 weeks after treatment. After an average 14-month follow up period, patients remained asymptomatic. Although not conclusive, the combination of necrotic-bone curettage and platelet-rich-plasma to treat refractory osteonecrosis of the jaw yielded promising results.

Key words: bisphosphonates; treatment; platelet-rich plasma; osteonecrosis; jaw; zoledronate; pamidronate; alendronate.

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In a letter to the Editor of the Journal of Oral and Maxillofacial Surgery, submitted in 2003, Marx et al.1 reported 36 cases of infected necrotic bone closely resembling osteoradionecrosis (ORN) in patients who had undergone maxillary surgery, particularly, tooth exodontia. Marx proposed the bone dehiscence detected could be due to avascular necrosis secondary to intravenous administration of bisphosphonates (BPs). Also in 2003, Carter and Gross2 reported on five new cases of maxillary osteonecrosis. In 2004, Ruggiero et al.3 described 63 new cases of avascular necrosis of the jaw whose clinical characteristics were similar to those reported by Marx et al.1 Hellstein and Marek4 also published an article reporting on 28 cases of osteochemonecrosis and coined the term bis-phossy jaw. Although some of the cases reported were asymptomatic, most of them presented common signs and symptoms: frequent histories of unhealed exodontia, painful or non-painful exposed bone, soft-tissue inflammation, purulent exudates, inflammation, and oral-cutaneous fistula. Even though the aetiopathogenesis of this entity remains unknown, the American Association of Oral and Maxillofacial Surgeons (AAOMS)5 named it bisphosphonate-related osteonecrosis of the jaw (BRONJ), the American Academy of Oral Medicine6 named it bisphosphonate-associated osteonecrosis of the jaw (BAONJ), and more recently, some
### Materials and methods

This prospective, descriptive study was carried out at the Department of Oral Surgery and Oral Medicine, University Hospital Coventry and Warwickshire, Coventry, UK, to test the hypothesis that the use of platelet-rich plasma (PRP) in the management of bisphosphonate-related osteonecrosis of the jaw (BRONJ) will improve healing outcomes. The authors proposed an approach based on surgical classification of the platelet concentrates in four categories: PRP; pure platelet-rich fibrin (L-PRF; e.g. Chohrumpf’s PRF); platelet-rich fibrin (L-PRF; e.g. Vivostat); platelet-rich plasma (L-PRP; e.g. ZymoGenetics PRF). The authors chose the SmartPReP system because the supplying company allowed them to keep the material on deposit and to pay only for that which was used. In addition, L-PRP was considered as the best option in our case. The authors also proposed an approach based on surgical classification of the platelet concentrates in four categories: PRP; pure platelet-rich fibrin (L-PRF; e.g. Chohrumpf’s PRF); platelet-rich fibrin (L-PRF; e.g. Vivostat); platelet-rich plasma (L-PRP; e.g. ZymoGenetics PRF). The authors also proposed an approach based on surgical classification of the platelet concentrates in four categories: PRP; pure platelet-rich fibrin (L-PRF; e.g. Chohrumpf’s PRF); platelet-rich fibrin (L-PRF; e.g. Vivostat); platelet-rich plasma (L-PRP; e.g. ZymoGenetics PRF).

### Table 1. Clinical case description.

<table>
<thead>
<tr>
<th>N</th>
<th>Gender</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Bisphosphonate</th>
<th>Adm. route</th>
<th>Dose (mg)</th>
<th>Total administered dose (mg)</th>
<th>Risk factors</th>
<th>Trigger factor</th>
<th>Location</th>
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<td>76</td>
<td>Osteoporosis</td>
<td>Alendronate</td>
<td>Oral</td>
<td>10</td>
<td>41,050</td>
<td>NIDDM</td>
<td>Multiple exodontia</td>
<td>Mandible</td>
</tr>
<tr>
<td>2</td>
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<td>Multiple myeloma</td>
<td>Pamidronate</td>
<td>IV</td>
<td>90</td>
<td>1,080</td>
<td>NIDDM corticosteroid</td>
<td>Exodontia</td>
<td>Mandible</td>
</tr>
<tr>
<td>3</td>
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<td>Zoledronate</td>
<td>IV</td>
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<td>160</td>
<td>Corticosteroid</td>
<td>Unknown</td>
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</tr>
<tr>
<td>4</td>
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<td>Breast neoplasia</td>
<td>Zoledronate</td>
<td>IV</td>
<td>4</td>
<td>96</td>
<td>NIDDM corticosteroid</td>
<td>Prosthesis</td>
<td>Mandible</td>
</tr>
<tr>
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<td>Multiple myeloma</td>
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<td>IV</td>
<td>4</td>
<td>164</td>
<td>NIDDM corticosteroid</td>
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<td>Mandible</td>
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<tr>
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<td>Pamidronate</td>
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<td>NIDDM corticosteroid</td>
<td>Exodontia</td>
<td>Mandible</td>
</tr>
<tr>
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<td>Pamidronate</td>
<td>IV</td>
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<td>228</td>
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<tr>
<td>8</td>
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<td>21,560</td>
<td>NIDDM</td>
<td>Exodontia</td>
<td>Maxilla</td>
</tr>
</tbody>
</table>

Table names: Zoledronate (Zometa®); Pamidronate (Aredia®); Clodronate (Bonefos®); Alendronate (Fosamax®) (Fosavance®).  
Abbreviations: non-insulin-dependent diabetes mellitus (NIDDM).
incipient BRONJ stage. Patients with neoplastic involvement of the jaw were excluded.

The AAOMS\textsuperscript{5} proposes using the following staging categories: Stage 1, exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection; Stage 2, exposed/necrotic bone in patients with pain and clinical evidence of infection; Stage 3, exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border.

Eight patients were selected in stage 2 (six female and two male), aged 66 years on average. Their underlying diseases were: multiple myeloma (50%), breast cancer (25%) and osteoporosis (25%). Patients were selected according to their clinical stage and the size of their radiographic bone lesions (which had to be smaller than 3 cm).

After providing informed consent, the patients underwent surgical debridement of necrotic bone (removal of necrotic bone and curettage of the underlying bone) and received autologous platelet concentrate enriched with growth factors, produced by the system SmartPreP \textsuperscript{2} – Harvest\textsuperscript{16}.

SmartPreP is a multifunction system with a specific collection and separation kit requiring little manipulation when used. This two-chamber device is designed to transfer automatically the upper layers (PPP and buffy coat) into the second chamber based on variations in weight and centrifugation speed. The centrifuge can also be used to concentrate stem cells from bone marrow aspirates.\textsuperscript{12}

This system produces viable platelet levels four-fold or more over baseline and can be used to accelerate wound healing, enhance management of graft material, improve graft fixation on surgical areas and optimize healing of bone and soft tissue.\textsuperscript{17} Additionally, it offers quick results, high yields, and reliable outcomes with reduced variability, compared to other systems.\textsuperscript{18}

L-PRP is prepared with the patients’ autologous blood through activation of a platelet concentrate. The authors used the APC-20 Procedure Pack, which produces 3 ml of autologous platelet concentrate (APC\textsuperscript{1}); 20 ml of blood are centrifuged to separate the three blood components: erythrocyte layer, platelet-rich plasma and platelet-poor plasma. Activation consists of mixing autologous thrombin with plasma in a 1:3 proportion (1 ml thrombin:3 ml plasma). The result is 3 ml of platelet-rich fibrin, easy-to-handle gel.

Once the L-PRP was placed, primary wound suture was carried out. Patients were prescribed amoxicillin-clavulanic acid (875 mg every 8 h for 7–10 days), exhaustive oral hygiene, mouthwash with chlorhexidine 0.12%, and a follow-up visit 2 weeks later, to have the suture removed. Follow-up visits were scheduled 4, 6, 10 and 14 weeks after surgery.

### Results

The authors used PRP in the surgical treatment of the eight BRONJ patients selected. Two of them were treated bilaterally, although in different sessions. Table 1 shows the main data corresponding to these patients. None of them were smokers, although four women were former smokers; six patients (75%) had good dental hygiene habits; the most frequent concomitant disease was non-insulin-dependent diabetes mellitus (NIDDM), which affected six patients (75%). Additionally, six patients (75%) were undergoing chemotherapy treatment and five patients (62.5%) were undergoing corticosteroid treatment (Table 1).

Regarding the onset of BRONJ, the initial symptom was inflammation in four patients (50%), pain in three patients (37.5%) and exposed bone in one patient (12.5%). The most frequent signs and symptoms were: exposed bone in seven patients (87.5%), suppurative in seven patients (87.5%), pain in six patients (75%), bone loss in five patients (62.5%) and tooth loss in two patients (25%).

The patients’ panoramic radiographs in the first visit showed radiolucent areas associated with BRONJ lesions in all of them, and radiopaque areas associated with bone sequestration in 60% of cases. The average lesion size was 2 cm (1.2–3 cm); cases of extensive lesions or extra-or oral fistulas were excluded because the potential side effects of the treatment were not known.

As part of the therapeutic approach, which was based on local oral surgery, the authors used autologous platelet concentrate enriched with growth factors produced with the SmartPreP \textsuperscript{2} – Harvest\textsuperscript{16} system. All patients were treated by the same surgical team. All of the patients showed improvement and oral lesions resolved 2–4 weeks after surgery.

When examining the patients, the panoramic radiograph showed radiolucent areas associated with bone loss. The margins were clear and there was no evidence of bone sequestration (Fig. 1). Patients continued to be monitored and remained asymptomatic showing no exposed bone after an average 14-month follow up period (range 12–26 months).

### Discussion

The action mechanism of BP remains unclear. These drugs are selective inhibitors of the osteoclastic action in the bone remodelling cycle. Their anti-resorptive action reduces bone remodelling and, by accelerating secondary mineralization, a rapidly evident increase in bone density is produced. Apparently, they also act on osteoblasts, by reducing apoptosis and stimulating the release of osteoclast recruitment inhibitors. Additionally, an anti-angiogenic effect has been described, through inhibition of endothelial cells, by reducing proliferation and inducing apoptosis.\textsuperscript{19}

Since these drugs inhibit bone resorption and are used to prevent and treat skeletal complications, their apparent association with BRONJ is difficult to understand. The fact that maxillary bones are under high bone-remodelling rates and in close contact with the buccal septic environment\textsuperscript{20} may contribute to these findings.

To date, no universally accepted therapeutic protocol is available to eradicate BRONJ lesions because their aetiopathogenic mechanism remains unclear. The incidence of this entity is higher in patients with poor quality of life due to previously existing malignancies. The treatment goal should be to eliminate pain and control the progression of bone infection and necrosis.

The effectiveness of hyperbaric oxygen therapy was not demonstrated. The response to radical surgery is less predictable than in other situations involving bone necrosis, such as radiotherapy or osteomyelitis.\textsuperscript{5} Aggressive surgical debridement is controversial due to the risk of worsening bone exposure. Occasionally, bone is left exposed, due to the difficulty of treating the lesion.\textsuperscript{21} In such cases, the use of general antibiotic therapy and mouthwash with chlorhexidine 0.12% are useful to prevent progression to BRONJ.\textsuperscript{22} Thus, conservative or minimally aggressive treatments seem to be the most suitable approach.\textsuperscript{5} A small number of observational studies showed positive results when treating BRONJ\textsuperscript{9–11} with PRP. PRP halves the time required for healing and regeneration and noticeably improves postoperative outcome. L-PRP is free of antigenic effects since it is prepared with the subject’s autologous blood, thus preventing events such as rejection, allergy or reaction to a foreign body. Thus,
the use of L-PRP constitutes an ideal adjunctive treatment in graft therapy, contributing to packing and retaining graft material (both autologous and other biomaterial) by providing stability and adhesion. Additionally, L-PRP is a good osteoconductive and osteoinductive agent, which favours maturation of bone grafts by promoting osteoblast differentiation.23 Marx et al.17 reported better outcomes of bone graft therapy with adjunctive PRP administration than without it. Scoletta et al.24 proposed using a surgical protocol combined with PRP in patients under IV BP treatment who needed exodontia, in order to reduce the incidence of BRONJ. Yokota et al.25 observed accelerated angiogenesis of necrotic bone in rabbits by combining vascular tissue and a single PRP injection.

It was suggested that PRP, being a blood clot, might promote infections, because blood agar is used in microbiology to culture bacteria. PRP is not a substrate different from blood clots naturally occurring on wounds; thus bacterial growth is expected to be similar to that occurring on any blood clot. Furthermore, PRP pH values range between 6.5 and 6.7, which comparatively are more acidic than those of mature blood (7.0–7.2), and therefore expected to be less favourable to bacterial growth.13 There is no report of this type of

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**Fig. 1.** Evolution of Case 5. (a) Suppuration related to prior exodontia of 36 and 46. Panoramic radiograph shows radiolucent areas containing radiopaque areas within. (b) Surgical intervention on the left side and PRP application. (c) Examination after 21 months of follow-up. (d) Panoramic radiograph during the week 4 examination, revealed bone loss surrounding 36 and 46 with sharp margins and no bone sequestration.
complication in the literature and the authors observed no postoperative infections in their case series.

A further issue to be considered is the over-expression of growth factors and their receptors, associated with tumour and dysplastic tissue, which suggests the possibility of inducing carcinogenesis or metastasis.26,27 Therapeutic growth factor-rich concentrates could act as promoters (rather than initiators) of carcinogenesis by promoting division and growth of mutant cells.26 Since growth factors are metabolized in 7–10 days, any possible carcinogenic effect is likely to require more prolonged administrations than those involved in the therapy of this study. Nevertheless, it seems reasonable to avoid the use of PRP in patients with pre-cancerous oral lesions or with a history of oral squamous cell carcinoma.27

Regarding the possibility of promoting metastasis, it must be borne in mind that platelets coat tumour cells thus improving their survival and adhesion to vessel walls, which favours permeation to extra-vascular surrounding tissues, a process that is primarily mediated by the vascular endothelial growth factor (VEGF). Tumour cells promote aggregation of platelets, which releases the VEGF necessary for them to invade extra-vascular tissue. These observations need to be considered in case where PRP is applied to areas close to a possibly metastasizing tumour.28 In a review of the literature, no evidence of a relationship between the therapeutic use of PRP and cancerous transformation of normal and/or dysplastic tissue was found. The use of PRP should be avoided in patients with platelet-associated disorders and exercised with caution in patients taking aspirin or anti-platelet agent therapy.

As far as the authors know, only five studies involving a total of 19 cases have been published on the use of PRP to treat BRONJ. Adornato et al. published a 12 case series, with successful results in 10 of them after a 6-month follow-up period; in one of the unsuccessful cases, early wound healing was followed by subsequent re-infection and bone dehiscence, and in the other one, the wound never healed. Cetiner et al. described a case of zolendronate-associated ONJ after tooth exodontia in a 68-year-old man with multiple myeloma, which was treated with surgical debridement plus PRP with a good outcome after a 6-month follow-up period. Curi et al. reported using this treatment in three cases of jaw lesions followed up for 6 months in two cases and 8 months in one case, although Badr and Oliver indicated some inaccuracies in that study, which led to doubts about the conclusions. Lee et al. reported two successfully treated cases, which were secondary to complications of dental implants: one involving left oral sinus communication (9-month follow-up) and one involving a lesion on the left jaw ramus (6-month follow-up).

The present eight patients were treated by the same surgical team. Patients were selected with lesions of 2 cm average size and excluded if they had extensive lesions or extra-oral fistulas; this was based on some authors and followed the recommendations of conservative treatment, in order to avoid major surgery.

All the patients improved in a mean period of 3 weeks (2–4 weeks) after treatment, with fast mucosal healing, reduced need for analgesics and resolution of mouth lesions. These patients continued with follow-up visits, without evidence of exposed bone after 14 months.

Although the findings in this study may not be conclusive, the results with a combination of necrotic bone curettage and PRP application seem to be promising for the treatment of refractory BRONJ. Since an efficient standard treatment has not been established, the authors’ approach can be considered a treatment option. Nevertheless, establishing a causal relationship requires further research, based on prospective randomized double-blind controlled trials. So long as such trials are not undertaken, the use of PRP should be avoided in patients with oral precancerous lesions or with a history of oral squamous cell carcinoma.

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Competing interests

None declared.

Ethical approval

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References


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