Oral Oncology 48 (2012) 817–821

Contents lists available at SciVerse ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Tooth extraction in patients on zoledronic acid therapy

Marco Mozzati, Valentina Arata, Giorgia Gallesio *

Department of Clinical Physiopathology, Oral Surgery Unit, Dentistry Section, University of Turin, Turin 10126, Italy
Department of Biomedical Sciences and Human Oncology, Dentistry Section, University of Turin, Turin 10126, Italy

ARTICLE INFO

Article history:
Received 31 January 2012
Received in revised form 12 March 2012
Accepted 13 March 2012
Available online 5 April 2012

Keywords:
Acid zoledronic
Bisphosphonates
BRONJ
Tooth extraction
PRGF
Bone healing
Socket healing
Wound healing

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.

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.[2]

Although Marx,[3] 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]

* Corresponding author. Address: Department of Biomedical Sciences and Human Oncology, Dentistry Section, UNITO LINGOTTO DENTAL INSTITUTE c/o Lingotto, Via Nizza 230, Turin 10126, Italy. Fax: +39 0116331503.
E-mail addresses: marco.mozzati@libero.it (M. Mozzati), arata.valentina@libero.it (V. Arata), giorgiagallesio@libero.it (G. Gallesio).

1368-8375/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.oraloncology.2012.03.009

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.[20] Among these preparations rich in growth factors, in literature we can find Platelet Rich Plasma (PRP)[21] 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.[22] 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.[23]

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.

Table 1
Dental extractions performed in a group of patients receiving zoledronic acid.

Tooth pathology	Study group (dental elements extracted)	Control group (dental elements extracted)
Residual roots	75	92
Semi-impacted third molars with pericoronitis	8	11
Root fracture	11	17
A 2° to 3° grade mobility	67	75
Destructive tooth decay involving the roots	47	51
Apical granuloma (untreatable by any means other than extraction)	67	21

Table 2
Principal patient characteristics included in the study.

		Study group (number)	Control group (number)
Gender	Males	36	39
	Females	55	46
Teeth extracted	Mandible	142	145
	Maxilla	133	122
Age	44–60	22	27
	60–70	43	36
	70–83	26	22
Smoking habit	No	76	64
	<15/die	11	15
	>15/die	4	6
Systemic pathology	Prostatic carcinoma	33	27
	Breast Carcinoma	17	34
	Multiple myeloma	36	21
	Lung Carcinoma	3	2
	Ovarian Carcinoma	2	1
Other medications (at the time of the study)	Steroids	47	58
	Chemotherapy	21	15

A professional oral hygiene session was given to each patient one week before surgery. All patients were administered the antibiotics amoxicillin/clavulanate 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 ($CaCl_2$ 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