

Tooth Extractions in Intravenous Bisphosphonate-Treated Patients: A Refined Protocol

Matteo Scoletta, DDS, * Valentina Arata, DDS, † Paolo G. Arduino, DDS, MSc, ‡
Ennio Lerda, DDS, § Andrea Chiecchio, PhD, || Giorgia Gallesio, DDS, ¶
Crispian Scully, CBE, # and Marco Mozzati, MD **

Purpose: The aim of this prospective hospital-based study was to refine a surgical protocol for tooth extractions in patients with a history of intravenous use of a potent bisphosphonate by modifying a previously reported protocol to produce a significantly shortened operating time.

Patients and Methods: Prospective patients with a follow-up of at least 4 months were included. Tooth extractions were performed without a vestibular split-thickness flap; healing was stimulated by filling the extraction site with autologous plasma rich in growth factors (PRGF System, BTI Biotechnology Institute, Vitoria, Spain). Local and systemic infection control was obtained with dental hygiene and antibiotic therapy.

Results: Sixty-three patients participated in the study. Two hundred two tooth extractions were performed. Differences between the present and previous protocols (the previous protocol used a vestibular flap) were analyzed and the surgical time proved significantly shorter for the present approach ($P = .00$).

Conclusions: The proposed surgical protocol appears to be a better choice for patients treated with intravenous bisphosphonates who need tooth extraction, because it seems to be faster and simpler than the previously reported successful protocol.

© 2013 American Association of Oral and Maxillofacial Surgeons
J Oral Maxillofac Surg 71:994-999, 2013

Bisphosphonates (BPs) are a commonly used class of drugs effective in the prevention and treatment of postmenopausal osteoporosis and Paget disease. They are also used intravenously in the prevention and treatment of bone metastasis associated with solid malignant tumors and multiple myeloma.

BP-related osteonecrosis of the jaws (BRONJ) is the term frequently used to describe a complication in a subset of patients receiving this medication, mainly in those receiving intravenous BPs.¹⁻⁴ BRONJ has been described as an avascular area of necrotic bone

in the maxillofacial area, with or without exposed bone, that has been evolving for longer than 8 weeks in patients without a history of irradiation in the maxillofacial region.^{4,6} Potential risk factors associated with the development of BRONJ include, above all, a history of recent dentoalveolar trauma, the intravenous use of a potent BP (eg, zoledronic acid), and long duration of BP exposure.^{7,8}

The authors' previously published successful surgical extraction protocol for patients treated with intravenous BPs⁹ includes a vestibular flap (initially full

Received from the University of Turin, Turin, Italy.

*Consultant, Oral Surgery Section, Department of Biomedical Science and Human Oncology.

†Consultant, Oral Surgery Section, Department of Biomedical Science and Human Oncology.

‡Academic Researcher, Oral Medicine Section, Department of Biomedical Science and Human Oncology.

§Trainer, Oral Surgery Section, Department of Biomedical Science and Human Oncology.

||Technician, Faculty of Mathematics, Physics, and Natural Science.

¶Consultant, Oral Surgery Section, Department of Biomedical Science and Human Oncology.

#World Health Organization Collaborating Center for Oral Health and General Health, Bristol, United Kingdom.

**Private Practitioner, Turin, Italy.

Address correspondence and reprint requests to Dr Arduino: Department of Biomedical Science and Human Oncology, University of Turin, Oral Medicine Section, Unito Lingotto Dental Institute, Via Nizza 230, 10126 Turin, Italy; e-mail: paologiacomo.arduino@unito.it

© 2013 American Association of Oral and Maxillofacial Surgeons
0278-2391/13/00050-5\$36.00/0

<http://dx.doi.org/10.1016/j.joms.2013.01.006>

thickness and then split to let the gingiva completely cover the extraction sockets), ostectomy or subsequent osteoplasty using an ultrasonic surgical apparatus, followed by filling of all postextraction sites with autologous plasma rich in growth factors (PRGF), and replacing and suturing the flap.

The aim of the present prospective study was to determine the safety and efficacy of a new and more rapid protocol for tooth extractions in patients treated with intravenous BPs simplified by avoiding the initial vestibular flap, which originally was introduced to preserve the clot as much as possible in the postoperative period.

Patients and Methods

Patients treated intravenously with BPs from March 2010 through September 2011 were prospectively included in this dataset. Patients were treated at the Oral Surgery Unit, Lingotto Dental School, Turin, Italy.

Consent from the ethical committee was obtained and all patients included gave informed consent. Patients were informed about the possible sequelae of dental extraction under intravenous BP treatment and all provided written informed consent before enrollment, which was carried out in accordance with the Declaration of Helsinki. The study was also approved by the Lingotto Dental School (University of Turin) institutional review board.

At their first visit, patients' data were recorded in a computerized clinical file that included information on age, gender, presence of systemic disease, and drug use (Table 1).

Inclusion criteria were 1) patients at least 18 years old who used intravenous BPs for at least 2 months, 2) the ability to complete the clinical trial, and 3) no clinical signs of BRONJ during the first visit. Exclusion criteria were 1) tooth extraction in the 3 months before the study, 2) pregnant or breast-feeding women, and 3) confirmed or suspected hypersensitivity to any medication used.⁹

Patients with a follow-up of at least 4 months were included.

TECHNICAL PROCEDURES

Patients underwent dental panoramic radiography. Two weeks before tooth extraction, each patient underwent an initial treatment consisting of root scaling and oral hygiene instruction. The evening before surgery, systemic antibiotic therapy with amoxicillin/clavulanate potassium (1-g tablets every 8 hr for 6 days) was commenced or, alternatively, erythromycin (600-mg tablets every 8 hr for 6 days) was used if there was an allergy to penicillin (Fig 1, Table 2).

Extractions were performed by the same oral and maxillofacial surgeons involved in the previous

Table 1. PATIENTS' PRIMARY DISEASES AND BIPHOSPHONATES RECEIVED (N = 63 PATIENTS)

Variables	
Primary disease	
Breast cancer	30 (47.61)
Multiple myeloma	20 (31.74)
Osteoporosis	6 (9.52)
Prostate cancer	5 (7.93)
Lymphoma	1 (1.6)
Lung cancer	1 (1.6)
Bisphosphonates used*	
Zoledronic acid	54 (85.71)
Pamidronate	4 (6.35)
Ibandronate	5 (7.94)

Note: Data are presented as number of patients (percentage).

* Patients who were treated with zoledronic acid received 4 mg intravenously over 15 minutes monthly; patients treated with pamidronate received 90 mg over 1 hour intravenously monthly; patients treated with ibandronate received 6 mg by 15-minute infusion every 3 to 4 weeks.

Scoletta et al. *Tooth Extractions and Bisphosphonates*. *J Oral Maxillofac Surg* 2013.

report.⁹ Dental nerve anesthesia was achieved using 3% mepivacaine hydrochloride and epinephrine 1:100,000. Tooth luxation and avulsion were gently performed using appropriate hand instruments. An ultrasonic surgical apparatus (Mectron Piezosurgery Device, Mectron Medical Technology, Carasco, Italy)¹⁰ was used for cleaning the postextraction alveolar sockets and for minimal osteoplasty of the alveolar ridge to avoid sharp surfaces that might delay postoperative healing. Extraction sockets were then filled with scaffold-like autologous PRGF (PRGF System, BTI Biotechnology Institute, Vitoria, Spain) and sealed with autologous fibrin (both formulations obtained from the patient).^{9,11,12} A Vicryl 4-0 cross-suturing technique was used for maintaining the stability of the PRGF.

Patients were given standard postoperative instructions and instructed not to brush the teeth in the treated area but to gently clean the wound using a gauze impregnated with 3% hydrogen peroxide 3 times daily for 2 weeks. A cold semiliquid diet for the first day was suggested. Normal oral hygiene procedures were re-established after 3 days.

STUDY VARIABLES AND OUTCOME DATA

To confirm secondary healing of the sockets, follow-up visits were scheduled at 1, 3, 6, and 12 months. At the 6-month follow-up, a new dental panoramic radiograph and an axial computed tomographic scan were obtained and each was examined by an expert specialist oral radiologist.¹³

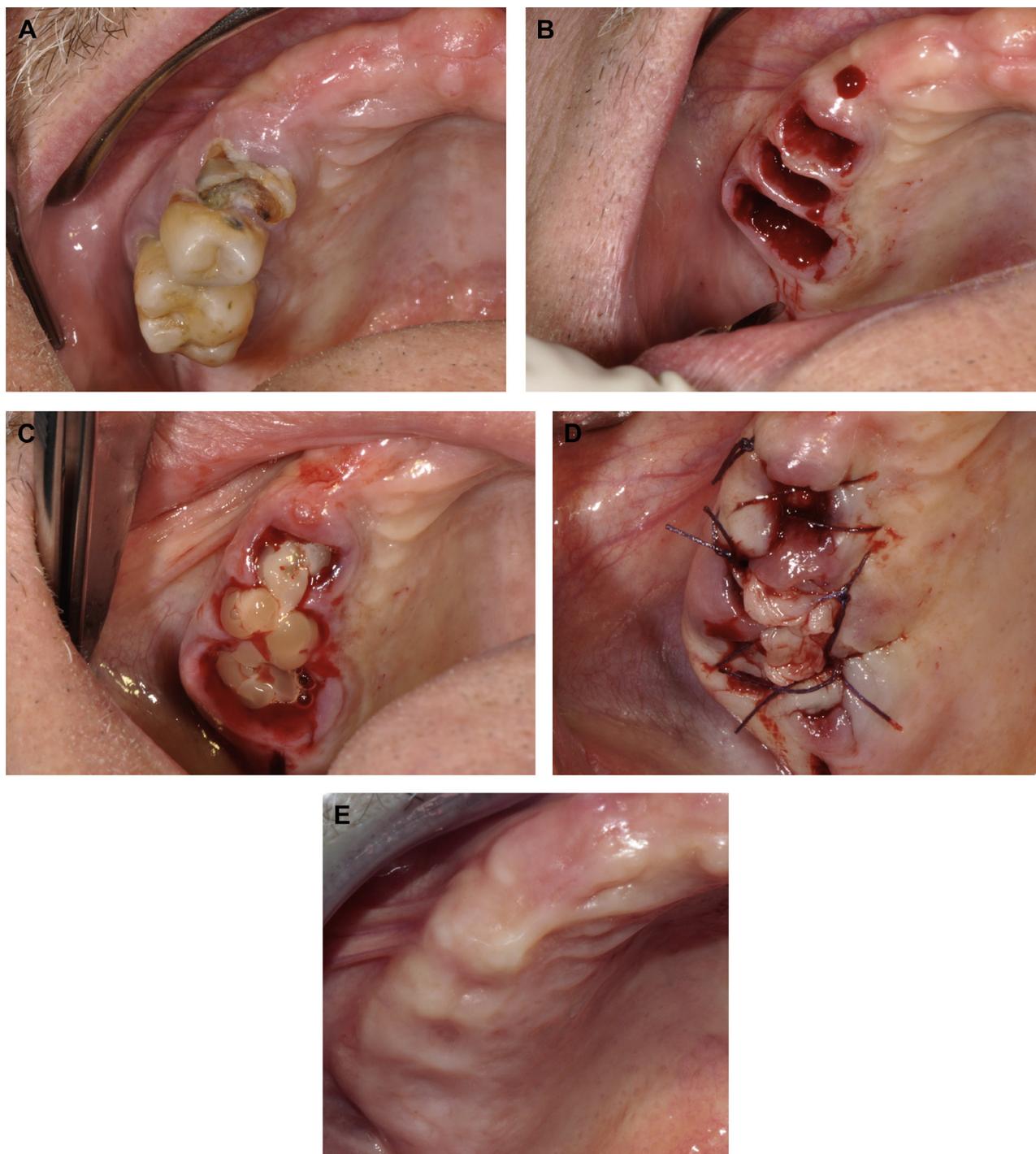


FIGURE 1. Technical protocol in patients taking intravenous bisphosphonates. *A*, Clinical evaluation. *B*, Tooth extractions. *C*, Packed plasma rich in growth factors. *D*, Sutures. *E*, Healed area after suture removal.

Scoletta et al. Tooth Extractions and Bisphosphonates. J Oral Maxillofac Surg 2013.

STATISTICAL METHODS

Data are reported as mean and standard deviation, unless stated otherwise.

The duration of BP exposure was defined as the number of infusions from the date of the first administration to the last recorded administration. The authors also recorded if patients had stopped the medication

and for how many months. The interval to develop BRONJ was determined as the time in months from the date of surgery to the date of the BRONJ diagnosis.

Differences between the present and previously reported protocols were recorded and analyzed. Descriptive analyses were performed using the *t* test for continuous variables and the Fischer exact test for

Table 2. TECHNICAL PROTOCOL IN PATIENTS TAKING INTRAVENOUS BISPHOSPHONATES

Day 0	Clinical evaluation
Day 10	Dental panoramic radiograph scaling + oral hygiene instruction
Day 20	Antibiotic regimen for 6 days
Day 21	Tooth extractions + piezo surgery + PRGF
Day 28	Clinical control
Day 35	Clinical control and suture removal

Note: The protocol is illustrated in Figure 1.

Abbreviation: PRGF, plasma rich in growth factors.

Scoletta et al. *Tooth Extractions and Bisphosphonates. J Oral Maxillofac Surg* 2013.

categorical variables. The statistical significance level was set at .05. Data analyses were conducted by STATA 9.2 (StataCorp LP, College Station, TX).

Results

Sixty-three consecutive patients took part in this study, 18 of whom were men (28.57%). The mean age at presentation was 65.82 years (standard deviation, 8.82 yr). Patients were treated with BPs for a mean of 16.84 infusions (standard deviation, 13.95 infusions) by the time of surgery. Thirty-nine patients were no longer on BP therapy at the time of surgery; the mean time after BP discontinuation was 19.03 months. Eighteen patients (28.57%) received concomitant systemic corticosteroid therapy. Two hundred two tooth extractions were performed. One hundred eleven extractions (54.95%) were from the mandible and 91 (45.05%) were from the maxilla.

Forty percent of extractions were performed because of caries that had destroyed enough of the tooth structure to prevent restoration, 47% because of periodontal disease, and 13% because of periapical infections. The mean surgical time was 6.51 minutes (range, 3 to 14 min).

During the follow-up period, healing of the oral mucosa in most patients (62 of 63) did not differ from that expected in normal healthy patients, and computed tomographic scans depicted normal alveolar bone healing. At the most recent follow-up visit, all patients had intact mucosa and no additional signs of inflammation. However, a 60-year-old woman who had had 12 administrations of zoledronic acid for breast cancer developed BRONJ in 2 postextraction sites (0.99%) in the maxilla.

A comparison of the present protocol and previously published protocol is presented in Table 3. The surgical operating time was significantly shorter for the new approach ($P = .00$), but no other differences were detected.

Discussion

Although BRONJ may develop spontaneously, up to 80% of cases are related to dental extraction or other surgical interventions involving intraoral bone exposure.¹⁴⁻¹⁶ To date, few protocols have been suggested to decrease the development of BRONJ in patients treated with intravenous BPs.^{17,18} Most current publications have proposed that dental treatment in BP-treated patients should be conservative; above all, extraction and all types of surgical interventions involving bone exposure should be avoided; however, no technique that could fulfill these

Table 3. COMPARISON OF PROTOCOLS

	Present	Previous	P Value
Study group			
Patients	63	64	—
Female-to-male ratio	44:20	45:18	.45
Age (yr)	65.82	64.81	.57
Mean of BP intravenous infusions at time of surgery	16.84	19.59	.31
Mean time after BP discontinuation (mo)	19.03	16.20	.32
Tooth extractions performed (in mandible)	202 (111)	220 (113)	.26
Protocol and outcomes			
Surgical time (min)	6.51	12.51	.00
Oral hygiene before session	yes	yes	—
Antibiotic regimen	yes	yes	—
Use of piezo surgical system	yes	yes	—
Use of PRGF	yes	yes	—
Adverse events/tooth extractions (n)	2/202	5/220	.07

Abbreviations: BP, bisphosphonate; PRGF, plasma rich in growth factors.

Scoletta et al. *Tooth Extractions and Bisphosphonates. J Oral Maxillofac Surg* 2013.

requirements has been suggested in the English-language literature. However, the authors' recently published surgical technique offered a possible choice for patients treated with intravenous BPs who needed tooth extractions.⁹

In the present study, the authors refined the protocol to be simpler and faster because it excluded the raising of a flap; initially, the authors used a flap technique to preserve the clot as much as possible, but they discovered this could be achieved with PRGF alone. The PRGF technology uses a scaffold-like PRGF full of growth factors and a biocompatible and biodegradable fibrin membrane to fill and seal the alveolar sockets.^{12,19} Very recently, a series of patients with BRONJ was treated by resection of the necrotic bone with primary closure of the mucosa over the bony defect using PRGF, also yielding positive results for this approach.²⁰

To date, no consensus has been reached concerning the role of infection in the etiopathogenesis of BRONJ. However, in periodontal tissues pre-exposed to BP, bacterial infection at tooth extraction sites has been shown to decrease keratinocyte growth factor in gingival fibroblasts, leading to a delay in the epithelial wound-healing process that was mitigated by antibiotics.^{21,22} Therefore, the authors propose the use of antibiotic prophylaxis and this approach has been supported by recent findings that reported that the adoption of preventive measures (antibiotic prophylaxis) in invasive dental procedures resulted in a significant decrease in BRONJ.²³ Moreover, another published protocol has found that antimicrobial prophylaxis can lower the risk of occurrence of BRONJ in patients taking zoledronate.²⁴ However, a randomized controlled trial would be useful to state the real utility of antibiotic regimes in such patients undergoing tooth extraction.

Very recently, the authors' group published more preliminary data on tooth extraction in patients on zoledronic acid therapy, reporting that PRGF is important for the successful treatment of patients on BPs to restore the osteoblast and osteoclast homeostatic cycles using autologous cytokines.²⁵ It was also reported that BRONJ developed only in patients not treated with PRGF, but the protocol still used a flap.

Platelet concentrates for surgical use are designed for the local release of platelet growth factor to stimulate tissue healing or regeneration. Four main categories of products can be easily defined, depending on their leukocyte content and fibrin architecture: pure platelet-rich plasma (such as PRGF), leukocyte- and platelet-rich plasma, pure platelet-rich fibrin, and leukocyte- and platelet-rich fibrin.²⁶ The main difference among these is the fibrin architecture; this parameter considerably influences the healing potential and the therapeutic protocol associated with each

platelet concentrate technology.²⁷ In the present series, PRGF was chosen for its clinical characteristics, which allow good adaptation in the postalveolar socket, and its biological features, which improve tissue healing.

In conclusion, this modified protocol appears to minimize BRONJ, is faster and simpler, and could be used by general dentists. Tooth extractions are performed without a vestibular flap; healing was stimulated by filling the extraction site with autologous PRGF, and improved dental hygiene and antibiotic therapy were included.

References

- Coleman RE: Bisphosphonates: Clinical experience. *Oncologist* 9:14, 2004
- Marx RE, Sawatary Y, Fortin M, et al: Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention and treatment. *J Oral Maxillofac Surg* 63:1567, 2005
- Migliorati CA, Schubert MM, Peterson DE, et al: Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: An emerging oral complication of supportive cancer therapy. *Cancer* 104:83, 2005
- Sarin J, DeRossi SS, Akintoye SO: Updates on bisphosphonates and potential pathobiology of bisphosphonate-induced jaw osteonecrosis. *Oral Dis* 14:277, 2008
- Ruggiero SL, Mehrotra B: Bisphosphonate-related osteonecrosis of the jaw: Diagnosis, prevention, and management. *Annu Rev Med* 60:85, 2009
- Fedele S, Porter SR, D'Aiuto E, et al: Nonexposed variant of bisphosphonate-associated osteonecrosis of the jaw: A case series. *Am J Med* 123:1060, 2010
- Durie B, Katz M, Crowley J: Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 353:99, 2005
- American Association of Oral and Maxillofacial Surgeons: Position paper on bisphosphonates-related osteonecrosis of the jaw. *J Oral Maxillofac Surg* 3:369, 2007
- Scoletta M, Arduino PG, Pol R, et al: Initial experience on the outcomes of teeth extractions in intravenous bisphosphonate-treated patients: A cautionary report. *J Oral Maxillofac Surg* 69:456, 2011
- Kotrikova B, Wirtz R, Krempien J, et al: Piezo surgery—A new safe technique in cranial osteoplasty? *Int J Oral Maxillofac Surg* 35:461, 2006
- Anitua E, Orive G, Aguirre JJ, et al: Clinical outcome of immediately loaded dental implants bioactivated with plasma rich in growth factors: A 5-year retrospective study. *J Periodontol* 79:1168, 2008
- Anitua E, Orive G: [Treatment of post-extraction defects using PRGF technology: Case-series study]. *Ital Oral Surg* 9:115, 2010
- Bianchi SD, Scoletta M, Bozzalla Cassione F, et al: Computerized tomographic findings in bisphosphonate-associated osteonecrosis of the jaws in patients with cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 104:249, 2007
- Migliorati CA, Siegel MA, Elting LS: Bisphosphonate-associated osteonecrosis: A long term complication of bisphosphonate treatment. *Lancet Oncol* 7:508, 2006
- Van den Wyngaert T, Huizing MT, Vermorken JB: Bisphosphonates and osteonecrosis of the jaw: Cause and effect or a post hoc fallacy? *Ann Oncol* 17:1197, 2006
- Assael LA: A time for perspective on bisphosphonates. *J Oral Maxillofac Surg* 64:877, 2006
- Lodi G, Sardella A, Salis A, et al: Tooth extraction in patients taking bisphosphonates: A preventive protocol and case series. *J Oral Maxillofac Surg* 68:107, 2010
- Regev E, Lustmann J, Nashef R: Atraumatic teeth extraction in bisphosphonate-treated patients. *J Oral Maxillofac Surg* 66:1157, 2008

19. Anitua E, Troya M, Orive G: Plasma rich in growth factors promotes gingival tissue regeneration by stimulating fibroblast proliferation and migration and by blocking TGF- β 1-induced myodifferentiation. *J Periodontol* 83:1028, 2012
20. Mozzati M, Galesio G, Arata V, et al: Platelet-rich therapies in the treatment of intravenous bisphosphonate-related osteonecrosis of the jaw: A report of 32 cases. *Oral Oncol* 48:469, 2012
21. Abtahi J, Agholme F, Sandberg O, et al: Bisphosphonate-induced osteonecrosis of the jaw in a rat model arises first after the bone has become exposed. No primary necrosis in unexposed bone. *J Oral Pathol Med* 41:494, 2012
22. Mawardi H, Giro G, Kajiya M, et al: A role of oral bacteria in bisphosphonate-induced osteonecrosis of the jaw. *J Dent Res* 90:1339, 2011
23. López-Jornet P, Camacho-Alonso F, Martínez-Canovas A, et al: Perioperative antibiotic regimen in rats treated with pamidronate plus dexamethasone and subjected to dental extraction: A study of the changes in the jaws. *J Oral Maxillofac Surg* 69:2488, 2011
24. Ferlito S, Puzzo S, Liardo C: Preventive protocol for tooth extractions in patients treated with zoledronate: A case series. *J Oral Maxillofac Surg* 69:e1, 2011
25. Mozzati M, Arata V, Galesio G: Tooth extraction in patients on zoledronic acid therapy. *Oral Oncol* 48:817, 2012
26. Dohan Ehrenfest DM, Bielecki T, Mishra A, et al: In search of a consensus terminology in the field of platelet concentrates for surgical use: Platelet-rich plasma (PRP), platelet-rich fibrin (PRF), fibrin gel polymerization and leukocytes. *Curr Pharm Biotechnol* 13:1131, 2012
27. Dohan Ehrenfest DM, Bielecki T, Jimbo R, et al: Do the fibrin architecture and leukocyte content influence the growth factor release of platelet concentrates? An evidence-based answer comparing a pure platelet-rich plasma (P-PRP) gel and a leukocyte- and platelet-rich fibrin (L-PRF). *Curr Pharm Biotechnol* 13:1145, 2012