

# Tooth Extraction in Patients Taking Intravenous Bisphosphonates: A Preventive Protocol and Case Series

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**Purpose:** To test the efficacy of a protocol in preventing the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ) after tooth extraction.

**Patients and Methods:** In this prospective case series, consecutive subjects treated with intravenous bisphosphonates who needed tooth extraction underwent a protocol aimed at reducing the risk of BRONJ, based on local and systemic infection control by means of mechanical and chemical reduction of the local bacterial load plus antibiotic prophylaxis.

**Results:** We performed 38 extractions in 23 patients treated with intravenous bisphosphonates, mainly zoledronate, for a mean of 17.5 months (range, 3-36 months). Five patients already had signs of BRONJ caused by tooth extractions performed elsewhere. The mean follow-up was 229.5 days (range, 14-965 days), and no case of BRONJ was recorded.

**Conclusions:** Despite the methodologic limitations of the study design, the proposed preventive protocol appears to reduce the risk of BRONJ after tooth extraction in a group of subjects treated with intravenous bisphosphonates.

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Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a common complication of intravenous bisphosphonates that seriously affects the quality of life of patients undergoing such treatment and produces significant morbidity.<sup>1,2</sup> Given the ineffectiveness of treatments, the prevention of BRONJ is fundamental. In patients who are about to start bisphosphonate treatment, the indications are relatively simple and include the removal of any teeth with a doubtful prognosis and the achievement of optimal oral health, whereas

the management of patients already under treatment can be more difficult. Since the first reports of BRONJ,<sup>3</sup> dental procedures have frequently been described as immediate precipitating risk factors for the condition. Although BRONJ can develop with denoalveolar surgery intervention, including periapical and periodontal surgery and implant placement, tooth extraction is considered the single intervention responsible for most BRONJ cases and is seen in up to 86% of cases of BRONJ.<sup>4</sup> According to a panel of experts, periodontal and dental abscesses expose patients to a risk of BRONJ developing that is not different from extraction, that is, both conditions increase the chance 7-fold.<sup>1</sup> In fact, many of the cases reported as "spontaneous"<sup>5</sup> may be initiated by local infections. Therefore an absolute contraindication to tooth extraction in patients taking intravenous bisphosphonates may not be the best approach, because medical, endodontic, and periodontal treatments performed to resolve local infection can be time-consuming and ineffective in subjects with serious diseases or who are undergoing immunosuppressive oncologic therapy.

This prospective study reports on the outcomes of dental extractions performed in patients who were

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taking or had taken intravenous bisphosphonates and were undergoing a preventive protocol based on local and systemic infection control.

## Patients and Methods

This was a prospective study of a group of consecutive patients taking parenteral bisphosphonates who underwent tooth extraction between May 2006 and January 2009 at the Unit of Oral Medicine, Oral Pathology and Geriatric Dentistry of the Dental School at the University of Milan, Milan, Italy.<sup>6</sup> Data were collected by a single operator (A. Salis) using a custom-designed form.

### PATIENTS

To be included in the study, the subjects had to be treated with intravenous bisphosphonates for at least 3 months. Patients with a history of radiation therapy to the jaws were excluded. Indications for extraction included nonrestorable caries, endodontic failure, root fracture, severe periodontal disease, and teeth with a poor prognosis or at high risk of infectious complications.

### EXTRACTION PROTOCOL

After the decision was made to extract 1 or more teeth, mouth rinsing with 0.2% chlorhexidine once a day was prescribed, and in the presence of clinically evident plaque and calculus, professional oral hygiene treatment was planned 2 to 3 weeks before extraction. Three days before the surgical procedure, the patients started to take 1 g of amoxicillin every 8 hours (or an alternative broad-spectrum antibiotic for subjects allergic to penicillin), and this was continued for 17 days (ie, until the second control visit).

On the day of the intervention, a full-thickness mucoperiosteal flap was reflected, with the patient under local anesthesia, at the surgical site, and the involved tooth was extracted with minimal trauma to the cortical plates. Then, the extraction socket was debrided meticulously and curetted to remove all granulation and infected tissues. Mesial and distal vertical releasing incisions allowed the flap to be advanced coronally. Finally, the flap was sutured to realize soft tissue primary closure. The patients were instructed to apply 1% chlorhexidine gel on the surgical wound 3 times a day until the second control visit. The extractions were performed by various oral surgery residents and students in the last year of dental school. One week after surgery, the suture was released. All patients were seen for follow-up at 1, 2, and 4 weeks; 2, 3, and 6 months; and 1 year.

Any complications noted by the patient or observed by the operator were recorded on the previously mentioned form. In these patients BRONJ was

defined as exposed, necrotic bone in the maxillofacial region that had persisted for more than 8 weeks.

When more than 1 extraction was needed, extractions were planned, whenever possible, as single-tooth interventions to avoid large osteonecrotic lesions.

## Results

Twenty-three patients underwent 1 or more tooth extractions in the period considered. They consisted of 15 women and 8 men, with a mean age of 68.2 years (range, 44-83 years). All had taken intravenous bisphosphonates: 20 were treated with zoledronate, 2 with pamidronate, and 1 with clodronate. The mean duration of the therapy was 17.5 months (range, 3-36 months). The reasons for taking intravenous bisphosphonates included multiple myeloma (11 patients), bone metastasis of breast cancer (8 patients) or other solid tumors (kidney in 1 patient and larynx in 1 patient), and severe osteoporosis (2 patients).

Five patients already had manifestations of osteonecrosis of the jaw caused by tooth extractions performed elsewhere.

We performed 31 interventions—23 involved a single tooth, 4 involved a single root, 3 involved 2 teeth, and 1 involved 3 teeth and 2 roots—for a total of 38 extractions. Of the interventions, 5 involved the upper jaw only, 23 involved the lower jaw only, and 2 involved both jaws. A majority of teeth were molars ( $n = 25$ ), 8 were premolars, and 4 were canines.

All stages of the extraction protocol were completed in 19 interventions; for 10 interventions, professional oral hygiene was not performed because it was not deemed necessary, whereas in 2 other interventions, antibiotic therapy was started only after the extraction.

No intraoperative complications were recorded. All patients came to the first follow-up after 7 days for stitch removal, and only 3 patients reported mild postoperative pain in the days after the intervention, which resolved after medical treatment with nonsteroidal anti-inflammatory drugs.

The mean follow-up for the 31 interventions was 229.5 days (range, 14-965 days). No case of BRONJ was recorded. In 1 case a small area of bone was exposed after 1 month, but it had resolved completely by the following visit (2-month follow-up) and was not classified as BRONJ. Even in the 6 interventions performed in the 5 patients who had BRONJ resulting from previous extractions, no complications occurred and the extraction sockets healed normally.

Bisphosphonate treatment was never suspended for a reason related to tooth extraction or other oral health procedures.

## Discussion

BRONJ is a major problem of uncertain prognosis and without an effective treatment, mostly affecting severely debilitated patients. Despite the large number of articles published on the subject (on searching PubMed for "osteonecrosis AND bisphosphonates" in February 2009, 840 records were found), recommendations for the management of patients with this condition are based mainly on expert opinions.<sup>1</sup>

In the absence of effective treatment, great emphasis has been placed on prevention as the only feasible approach to BRONJ. Prevention is relatively simple in subjects about to begin bisphosphonate treatment, because it requires an aggressive approach directed toward the extraction of any unsalvageable tooth, completion of all invasive dental procedures, and maintenance of good oral health to avoid future infection, inflammation, and dentoalveolar surgery.<sup>1</sup> The design of an effective preventive protocol in already-treated patients might be difficult because of the uncertainty regarding most aspects of the condition, including its etiopathogenesis and local or systemic risk factors.

We started this study because we realized that in addition to tooth extractions, untreated inflammatory lesions could lead to osteonecrotic lesions; that few cases of extractions in patients who did not defer their bisphosphonate treatment, but received prophylactic antibiotic treatment, had normal postextraction healing; and that in most of the patients affected by osteonecrosis, antibiotic treatment could ameliorate the symptoms. Therefore we established a protocol designed to avoid infection of the alveolar socket by minimizing the oral bacterial load (professional oral hygiene and chlorhexidine mouthwash) and avoiding local infection (antibiotic treatment, soft tissue primary closure, and chlorhexidine gel). Our aim was to conduct this study as a phase II trial, to evaluate the potential benefit of the intervention, establishing the sample size and power required for a randomized controlled trial (RCT). When we realized that osteonecrosis of the jaw was not developing in any of the patients, we decided to continue with the uncontrolled design mainly for ethical reasons, because based on such positive results, a placebo study would be unacceptable to any ethical committee.

The results of this case series are very promising because BRONJ did not develop in any of the patients. No data on the real risk of BRONJ after a single tooth extraction are available. We know that a large proportion of the affected subjects have a history of dentoalveolar surgery and that BRONJ can develop in up to 10% of special groups of patients undergoing bisphosphonate therapy.<sup>7</sup> However, we do not know the exact proportion of tooth extractions performed on at-risk subjects that result in osteonecrotic lesions.

Therefore the possibility exists that the number of interventions we performed was small, as well as that BRONJ would not have developed in our patients anyway. However, we believe that this is unlikely for several reasons. First, the duration of the bisphosphonate treatment, the main risk factor for BRONJ development, and the underlying condition placed most of our patients in a high-risk group.<sup>8</sup> Second, 5 subjects were affected by previous osteonecrotic lesions and thus, by definition, were at high risk. Third, a recent retrospective study suggested that nearly 1 in 3 invasive dental procedures not associated with antibiotic prophylaxis (27%) can result in BRONJ.<sup>9</sup> We agree that a larger group can make our study sounder, and we are continuing to collect data. However, we also know that, on the basis of previous retrospective data, our sample is large enough to indicate some efficacy of the protocol. For this reason, we decided to submit our results for publication at this point, because we think that if our study can prevent the development of osteonecrosis of the jaw in some (even few) patients, it will be a successful study.

Other procedures for reducing the risk of BRONJ have been proposed, including an alternative technique for atraumatic tooth extraction performed by use of orthodontic elastics placed around the roots, causing slow, gradual exfoliation of the tooth.<sup>10</sup> Although no complications followed a series of 21 extractions performed in this manner, this technique requires a mean of 6 weeks for each exfoliation. In addition, the likelihood exists that both professionals and patients would be uncomfortable with this unusual approach. Our protocol is based on common procedures and drugs, adopted in the routine practice of any dentist or oral surgeon.

We are aware of the many methodologic limitations of our study. Indeed, the best study design to test the efficacy of a preventive intervention is an RCT. This is not even a controlled study and, consequently, ranks very low in the ideal hierarchy of evidence. We decided not to start an RCT for this intervention because we did not have the data to plan it properly. In particular, we were unable to establish an effect of the protocol and, as a consequence, could not calculate the sample size for such a study. In addition, we also faced ethical problems, because not providing local and systemic measures to prevent infection to a group of oncologic and immunosuppressed subjects would have been unfair. However, some aspects attest to the validity of this case series. First, we had the striking result that none of the cases resulted in BRONJ; a dramatic effect is one situation in which randomized trials are unnecessary.<sup>11</sup> In fact, even if the results of observational studies are known to provide larger treatment effects, it is unlikely that they can give rise to an extremely large artifactual differ-

ence compared with previous data.<sup>12</sup> In addition, our study seems to confirm the results of a retrospective study showing a significant protective effect of antibiotic prophylaxis in reducing the incidence of BRONJ in subjects with multiple myeloma.<sup>9</sup> Another positive aspect of our study is that patients were enrolled consecutively: every patient seen in the period considered for whom extraction was judged the best option available was enrolled in the study, without exception, giving our results good external validity and making them generalizable.

Finally, we believe that our study gives some insight into the pathogenesis of BRONJ. In fact, the preventive protocol adopted was designed to prevent local and systemic infectious complications by means of mechanical, antibacterial, and antibiotic measures. Whether the preventive effect of this or similar protocols is confirmed, our findings indicate that bacteria and other micro-organisms play a key role in the pathogenesis of this condition.

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