Assessing the association between bisphosphonate exposure and delayed mucosal healing after tooth extraction

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Tooth extraction in patients receiving bisphosphonate (BP) therapy has been associated with a high risk of developing BP-associated osteonecrosis (BON).[1-3] BON is defined as the presence of exposed necrotic bone for at least eight weeks anywhere in the oral cavity of a person exposed to BPs and who has not received radiation therapy to the head and neck.[4,5] New cases of this oral complication also have been reported to be associated with other antiresorptive medications such as denosumab[6] and with antiangio-

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ABSTRACT

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Background. Tooth extraction in patients exposed to bisphosphonates (BPs) is considered a risk factor for osteonecrosis. The authors evaluated the time to mucosal healing and frequency of osteonecrosis after tooth extraction in participants exposed to BPs.

Methods. The authors compared wound healing after tooth extraction in participants exposed to BPs with that in control participants who had not been exposed to BPs. Variables included age, sex, type of BP therapy (oral or intravenous), BP exposure time and C-terminal telopeptide (CTX) test results. The authors followed up patients weekly or biweekly until healing was complete. They used multivariable analyses to model time to healing in the presence of covariates, and estimates provided hazard ratios (HRs) and 95 percent confidence intervals (CIs) adjusted for all variables in the model.

Results. The authors enrolled 53 participants with BP exposure and 39 control participants. Postextraction healing was significantly longer in participants exposed to BPs ($P < .001$) than it was in control participants. One patient (1.9 percent) developed osteonecrosis. A Cox proportional hazards model in which the authors controlled for age, sex and CTX values showed that BP exposure alone significantly (adjusted HR, 0.27; 95 percent confidence interval, 0.16-0.48) increased mucosal healing time.

Conclusions. The study results showed that postextraction healing was impaired in patients exposed to BPs. CTX values were not associated with delayed healing after tooth extraction.

Practical Implications. Postextraction healing was delayed in patients receiving BP therapy. However, the risk of developing osteonecrosis was low.

Key Words. Bisphosphonates; osteonecrosis of the jaw; tooth extraction; oral bisphosphonates; intravenous bisphosphonates; mucosal healing.
JADA 2013;144(4):406-414.

genics such as bevacizumab[7,8] and sunitinib.[9-11] Investigators in other studies reported that the risk of developing BON increases when patients receive antiangiogenic therapy concomitantly with BP therapy.[12,13] Thus, all patients using one of these medications are at risk of developing BON. In this study, we enrolled patients who were exposed to BPs only.

The initial reported incidence of BON in 2003 was based primarily on the results of retrospective studies, and it was less than 1 percent in patients receiving oral BP therapy and between 6 and 13 percent in patients receiving intravenous (IV) BP therapy.[14,15] Investigators in recent prospective clinical trials involving patients with cancer compared the efficacy of monthly subcutaneous administration of denosumab (an antireceptor activator of nuclear factor κB ligand monoclonal antibody) with monthly IV infusion of zoledronic acid.[6,16] The results of these studies showed an incidence of BON ranging from 1.3 to 5 percent, depending on the population studied and the duration of therapy.[6,16]

The risk of developing BON presents a dilemma for clinicians treating patients receiving BP therapy who need to undergo a tooth extraction, because the risk cannot be assessed for individual patients. Therefore, a biomarker that could help predict BON development would be beneficial. Marx and colleagues[17] proposed that testing the levels of a biomarker for bone resorption such as C-terminal telopeptide (CTX) before performing the extraction could be a predictor of osteonecrosis development. However, this is controversial and has not been confirmed by additional studies.[14]

Different pathways have been proposed to explain the mechanisms by which BON develops. These include toxicity to bone cells and suppression of bone remodeling (that is, from the inside out), toxicity to soft tissues and infection (that is, from the outside in), antiangiogenic effect, immunosuppression, genetic polymorphism or, more likely, a combination of several factors.[18-23] However, the entire mechanistic process involved still is unclear.

The development of BON appears to be more common with use of oral and IV amino-BPs (alendronate, risedronate, ibandronate, pamidronate and zoledronate) than with use of nonamino-BPs.[15] Accumulated BPs in alveolar bone are released in the presence of inflammation[24] and during bone manipulation, such as that which occurs during a tooth extraction. This release places active BPs in direct contact with the overlying epithelium.[25] This may cause epithelial destruction and exposure of the bone to the contaminated oral cavity. Inhibited osteoclastic activity, bacterial infection and biofilm formation of the exposed bone could lead to delayed healing or total inhibition of healing.[26-29] In light of the fact that BPs inhibit osteoclasts and may affect bone remodeling and healing in the oral cavity, one could expect a delayed healing time after oral surgical procedures such as tooth extractions. Experimental studies with mice[30] and dogs[31] have demonstrated that zoledronic acid can compromise and delay wound healing after tooth extraction. However, this has not been demonstrated in humans.

The purpose of this study was to evaluate mucosal healing after tooth extraction in people exposed to BPs. We hypothesized that because of the mechanism of action of BPs, mucosal healing in humans is impaired. The specific aims of the study were to measure mucosal healing after tooth extraction in patients exposed to BPs and to estimate the role of variables of interest, such as age, sex, BP exposure time, type of BPs and CTX test results.

METHODS

Study design and sample. To address the research purpose and obtain a large number of participants, we enrolled a prospective cohort of dental patients from clinics in three dental centers: College of Dental Medicine, Nova Southeastern University, Fort Lauderdale-Davie, Fla.; Department of Dental Oncology, Northeast Regional Cancer Centre, Health Sciences North, Sudbury, Ontario, Canada; and Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, University of Oslo, Norway.

The study population was composed of consecutive patients seeking routine dental care between 2007 and 2011. Investigators in each institution assigned patients to one of two groups: patients who were exposed to BPs (group 1) and patients who were not exposed to BPs (group 2). Inclusion criteria required patients to be 18 years or older, to be in need of a tooth extraction as part of their routine treatment plan, and to have no medical contraindication for the surgical procedure. We advised patients in group 1 that they could be at risk of experiencing an adverse effect that has been associated with use of BPs and invasive surgical procedures in the oral cavity, such as tooth extraction. We enrolled those who were in agreement with receiving the invasive dental procedure. We excluded patients

ABBREVIATION KEY. BON: Bisphosphonate-associated osteonecrosis. **BP:** Bisphosphonate. **CTX:** C-terminal telopeptide. **IV:** Intravenous.