

Phosphate buffer-stabilized 0.1% chlorine dioxide oral rinse for managing medication-related osteonecrosis of the jaw

SRINIVAS RAO MYNENI VENKATASATYA, DDS, PHD, HOWARD H. WANG, DDS, MBA, MPH, MS, SWETHA ALLURI, BS & SEBASTIAN G. CIANCIO, DDS

ABSTRACT: Purpose: This is a review of the literature on nonsurgical treatment of non-healing medication related osteonecrosis of the jaw (MRONJ) utilizing a phosphate buffer-stabilized 0.1% chlorine dioxide mouthrinse. **Methods:** A literature search in PubMed revealed only six case reports. MRONJ lesion site description, patient's medication history, the healing time, and the MRONJ treatment protocol followed by those authors were recorded. Additional literature review of the scientific mechanism, risks and benefits, safety and efficacy of the phosphate buffer-stabilized 0.1% chlorine dioxide mouthrinse was also performed and discussed. **Results:** Many of the authors of the published case reports utilized 0.12% chlorhexidine as the initial mouthrinse, but the lesions did not decrease in size. After switching to a phosphate buffer-stabilized 0.1% chlorine dioxide mouthrinse for a duration ranging from 1-12 months, there was complete healing of the MRONJ lesions in all of the cases. The phosphate buffer-stabilized 0.1% chlorine dioxide mouthrinse can be helpful in the management of active MRONJ lesions as well as the prevention of recurrent MRONJ lesions in the susceptible patient population. (*Am J Dent* 2017;30:350-352).

CLINICAL SIGNIFICANCE: This literature review supports the use of phosphate buffer-stabilized 0.1% chlorine dioxide mouthrinse in the management of MRONJ lesions either as a first line of therapy or after 0.12% chlorhexidine had not been effective.

✉: Dr. Srinivas Rao Myneni Venkatasatya, Dept. of Periodontology, Stony Brook University, 108 Rockland Hall, Stony Brook, New York, USA. E-✉: Srinivas.mynenivenkatasatya@stonybrookmedicine.edu

Introduction

There are few conditions in dentistry that can present as maliciously as medication-related osteonecrosis of the jaw (MRONJ), formerly known as bisphosphonate-related osteonecrosis of the jaw (BRONJ). Osteonecrosis of the jaw is a severe disease that, if poorly managed, can result in resection of all affected regions across the maxillary and mandibular arches, as well as of other bones of the head and neck region; it is associated with high morbidity and sometimes even death. The etiology of MRONJ is the use of antiresorptive agents such as bisphosphonates and denosumab that can cause inhibition of normal osteoclastic bone resorption and remodeling for treatment of osteoporosis and/or cancer-related conditions such as multiple myeloma.¹ Other aspects that influence the pathophysiology of MRONJ include inhibition of angiogenesis, inflammatory and/or infectious components, soft-tissue toxicity of the anti-resorptive medications and possibly dysfunction of the immune system.²⁻⁵

MRONJ lesions vary in size from a small focal point with a fistula or involvement of a large segment of the maxilla or mandible. The lesions can occur spontaneously or after a dental procedure.⁶ As many as 52%-65% of MRONJ patients report tooth extraction to be the triggering event, as was shown in a longitudinal cohort study of 162 cancer patients on IV bisphosphonates.⁷ In 2002, 21.3 million prescriptions for bisphosphonates were dispensed, and this increased by 46% to 31 million in 2007 and 2008.⁸ The goal of treatment for MRONJ is primarily prevention, providing a treatment plan that incorporates risk aversion. For example, treatment of a hopeless tooth can be accomplished by performing endodontic procedures and utilizing orthodontic extrusion for removal rather than a surgical extraction. However, as some

MRONJ cases can develop spontaneously, this is not always possible, and secondary prevention should be carried out to reduce the impact of MRONJ for the patient so that there is no increase in severity. It is most likely that the diagnosis of MRONJ will occur at an early stage, and the recommended treatment is to place the patient on an antibacterial mouthrinse with careful monitoring. Despite the importance of use of the mouthrinse in the treatment of MRONJ lesions, few articles evaluated the effects of different mouthrinses on MRONJ lesions.⁹ Some clinicians prescribe 0.12% chlorhexidine gluconate rinse for treatment of MRONJ based on anecdotal evidence, but the literature offers other alternatives that have scientific credibility. This review paper evaluated the body of evidence for the use of phosphate buffer-stabilized 0.1% chlorine dioxide-containing mouthwash for the treatment of MRONJ.

Materials and Methods

A literature search revealed that several clinicians have described cases that were successfully treated with the use of a phosphate buffer-stabilized 0.1% chlorine dioxide-containing mouthwash. Due to the sporadic incidence of MRONJ, a clinical trial is difficult to perform. A total of six case reports were found (Table).

Results

All six reports involved patients on bisphosphonates; three cases involving oral alendronate and three cases with IV zoledronic acid infusions. It is important to note that the clinicians in these reports were able to successfully manage the MRONJ lesions at their early stage (stage 0 or stage 1), and prevent them from progressing in severity. The treatment protocols for four cases included more frequent follow-up

Table. Summary of the case reports.

Author/Year	MRONJ site descriptions	Patient medication history	MRONJ treatment protocol	Healing time (Months)
Marder et al, 2008 ¹⁰	2 mm diameter ulceration on posterior lobe of a torus palatinus that affected the entire lobe within 6 months	80 yr-old F alendronate - 5 yrs	Rinse with a phosphate buffer-stabilized 0.1% chlorine dioxide containing mouthrinse for 30 seconds, 3-4 times/day	12
Marder et al, 2008 ¹⁰	3.5 mm diameter of asymptomatic exposed bone at lingual of tooth #30 region	83 yr-old F alendronate - 3 yrs	Rinse with a phosphate buffer-stabilized 0.1% chlorine dioxide containing mouthrinse for 30 seconds, 3-4 times/day	3
Marder et al, 2008 ¹⁰	3 mm diameter bone exposure with surrounding inflammation that had mild discomfort	79 yr-old F alendronate - 6 yrs, Stopped and resumed for 18 months	Rinse with a phosphate buffer-stabilized 0.1% chlorine dioxide containing mouthrinse for 30 seconds, 3-4 times/day	2
Marder et al, 2008 ¹⁰	3 mm diameter inflamed tissue in the mid lateral area of the largest lobe of the torus palatinus	63 yr-old F zoledronate- 1 yr, bevacizumab for metastatic breast cancer	Rinse with a phosphate buffer-stabilized 0.1% chlorine dioxide containing mouthrinse for 30 seconds, 3-4 times/day	1
Soolari et al, 2010 ¹¹	2×4×2 mm size lesion on extraction site #24 that was initially asymptomatic but became aggressive and increased in size and symptomatic	64 yr-old M zoledronate & dexamethasone 2 yrs for multiple myeloma	Stopped zoledronic IV treatment, augmentin md 30 tabs, PO, TID and chlorhexidine rinse BID after which patient stated that pain was gone but the exposed necrotic bone remained. Subsequently rinsing with a phosphate buffer-stabilized 0.1% chlorine dioxide containing mouth rinse for 30 seconds, 3 times/day	4
Soolari et al, 2011 ¹¹	3×3×2 mm lesion at palatal aspect of tooth #1 that was diagnosed 3 months after extraction of tooth #1	38 yr-old F zoledronate - 7 yrs for breast cancer	Augmentin 500 mg TID for 10 days, chlorhexidine rinse BID for 30 seconds, after which patient stated that pain was gone but the exposed necrotic bone remained. Zoledronic acid was discontinued. Subsequently rinsing with a phosphate buffer-stabilized 0.1% chlorine dioxide containing mouth rinse for 30 seconds 3 times/day	5

visits and instructing the patient to rinse with a phosphate buffer-stabilized 0.1% chlorine dioxide containing mouthrinse for 30 seconds, 3-4 times/day. The authors¹⁰ found great success in lesions that were less than 3 mm of exposed bone, in which the lesions healed uneventfully after 1-3 months' use of the medicated mouthrinse.

Two case reports involved a 64-year-old male with multiple myeloma and a 38-year-old female with breast cancer, both treated with 4 mg IV zoledronic acid once per month developed MRONJ after extractions were performed. The patients were initially prescribed a systemic antibiotic (Augmentin 500 mg) and 0.12% chlorhexidine gluconate mouthrinse. However, there was a lack of soft tissue closure over the exposed necrotic bone and persisted even when zoledronic acid was stopped after a medical consultation.¹¹ This makes biological sense, as bisphosphonates accumulate in the bone long after medication discontinuation, and no differences were found on healing of MRONJ lesions with and without discontinuation of anti-resorptive medications.^{12,13} The authors decided to put the patient on a phosphate buffer-stabilized 0.1% chlorine dioxide containing mouthrinse for 30 seconds, three times/day. After 4-5 months, complete soft-tissue coverage was attained over the MRONJ lesion.¹¹

Discussion

The inability of chlorhexidine gluconate to allow complete soft tissue closure can be partly explained by the cytotoxicity of chlorhexidine to gingival fibroblasts. In a study by Tsourounakis et al,¹⁴ an undiluted 0.12% chlorhexidine gluconate induced near complete cell death 24 hours after only a 60-second treatment in human gingival and periodontal

ligament fibroblasts in vitro. Even at 5% of the prescribed concentration, there was near complete gingival fibroblast death 7 days after the exposure.¹⁴ Chlorhexidine was able to decrease gingival fibroblast proliferation and migration in a dose-dependent manner.¹⁵ Alternatively, another in vitro study¹⁶ found that chlorine dioxide did not induce significant apoptosis of human gingival fibroblasts at any concentrations that were examined. Phosphate buffer-stabilized 0.1% chlorine dioxide mouthrinse may have similar or increased efficacy against removing periodontal pathogens compared to chlorhexidine rinses.¹⁷ The efficacy of using chlorine dioxide as a mouthrinse was studied as far back as 1989, when the chlorine dioxide mouthrinse was able to reduce dental biofilm by more than 30% compared to the placebo in a month-long study, and no complications were noted.¹⁸

Marder et al¹⁰ attributed the preference for using chlorine dioxide as the primary mouthrinse for treatment of MRONJ lesions because it is not only bactericidal, but it has also been proven to be fungicidal and viricidal.¹⁹ There is evidence that the biofilms of MRONJ lesions are complex, and studies^{4,20} have identified not just bacteria, but also fungi and viruses. It is also important to note that some of the authors¹⁰ of the case reports instructed the patients to continuously use the phosphate buffer-stabilized 0.1% chlorine dioxide mouthrinse for life as a preventive measure against recurring MRONJ lesions. Patient compliance becomes a problem when a medication has to be taken long term. Many patients dislike the flavor of chlorhexidine, and it also increases staining and calculus formation as well as causing taste changes, all of which deter the patient from following the prescribed regimen. A study²¹ showed that patients preferred the taste of

chlorine dioxide mouthrinses, and experienced fewer taste alterations. In a small observational study²¹ it was noticed that even some Down-syndromic patients who were not initially compliant with their oral health care regimen were able to use a chlorine dioxide rinse twice a day for long periods of time. Not only was there a significant increase in compliance, but oral conditions such as gingival inflammation, halitosis, burning tongue and plaque retention were improved or resolved.^{21,22}

Conclusion

In today's evidence-based dentistry, it is important for a clinician to provide sound scientific rationale for recommending a treatment, and while these case reports were successful in treating MRONJ with a phosphate buffer-stabilized 0.1% chlorine dioxide mouthrinse, it is essential that additional research be done in this area to find the most appropriate mouthrinse to treat MRONJ and prevent its progression to Stage 2 or Stage 3 types of lesions, leading to significant morbidities. The case reports discussed in this article suggest that additional studies be conducted on the role of a phosphate buffer-stabilized 0.1% chlorine dioxide mouthrinse on healing of MRONJ lesions and, possibly, wound healing post periodontal or implant surgical procedures.

Dr. Myneni Venkatasatya is Assistant Professor, Director of Periodontal Research; Ms. Alluri is Research Assistant, Department of Periodontology, Stony Brook University, Stony Brook, NY, USA. Dr. Wang is Resident; Dr. Ciancio is Distinguished Service Professor and Chair, and Director, Center for Clinical Dental Studies, Department of Periodontics & Endodontics, School of Dental Medicine, University at Buffalo Buffalo, NY, USA.

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