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Review Article

Bisphosphonate-Related Osteonecrosis of the Jaws: A Review

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Abstract

Bisphosphonate drugs can be used to prevent and treat osteoporosis and to reduce symptoms and complications of metastatic bone disease. However, they are associated with a rare but serious adverse event: osteonecrosis of the maxillary and mandibular bones. This condition is called bisphosphonate-related osteonecrosis of the jaw or BRONJ. Various articles have been reviewed on different treatment modalities used along with bisphosphonates, their side effects, and management. In this review article, data from different studies with different treatment modalities were carefully analyzed and drafted.

Keywords: *Bisphosphonates, osteonecrosis, medical management, surgical management*

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INTRODUCTION

Bisphosphonates (BP) are synthetic analogs of the endogenous substance pyrophosphate (a normal constituent of the bone matrix), which inhibit bone resorption and thus have a hypocalcemic effect. They are an extremely effective treatment for reducing symptoms and complications of metastatic bone disease and for preventing and treating osteoporosis. Bisphosphonates are drugs very similar to pyrophosphate (a normal substance found in bone). They are used to lessen symptoms and complications due to the spread of cancer to the bones, and to prevent and treat fragile bones in osteoporosis (a condition where tiny holes in the bones make them brittle). These drugs can cause a rare but serious condition called bisphosphonate-related osteonecrosis of the jaw or 'BRONJ' [1,2] .

EPIDEMIOLOGY

Since Marx et al. first reported BRONJ, this condition has been known as a complication in patients receiving tooth extractions during BP therapy, despite the general systemic benefits of these drugs. BPs also inhibit other cell types such as osteogenic cells, endothelial cells, human fibroblasts, and macrophages and reduce the viability of oral keratinocytes, with associated impairment in mucosal wound healing. The true incidence of BRONJ is unknown with reported rates ranging from 0.028% to 18.6% [3].

PATHOGENESIS

The pathogenesis of MRONJ has not yet been fully elucidated and remains an active area of research. It is probably multifactorial [4]. In addition, inhibition of angiogenesis has been observed with zoledronic acid and may contribute to the pathogenesis of MRONJ, because reduced blood vessel formation can impair post-interventional healing. MRONJ has also been reported in patients with cancer receiving other agents with anti-angiogenic effects, such as bevacizumab and sunitinib. Preclinical data also suggest that bisphosphonates may exert a toxic effect directly on the oral mucosa, which may also contribute to MRONJ pathogenesis [5]. However, it is unknown whether these effects are achieved in clinical practice.

DIAGNOSIS AND STAGING

According to a position paper published by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014, MRONJ is defined by the presence of all of the following: current or previous treatment with bisphosphonates or denosumab or anti-angiogenic therapy; an area of exposed jawbone or bone that can be probed through at least one intraoral or extraoral fistula that has persisted for more than 8 weeks; and no history of radiation therapy to the jaw or obvious metastatic disease of the jaw. The most widely used staging system for MRONJ is that described by the AAOMS [6]. It is divided into many stages which reflect disease presentation and can assist in the appropriate stratification of patients. In addition to the stages requiring specific management approaches, an initial stage 0 is described, in which there is no clinical evidence of necrotic bone, and yet patients present with non-specific symptoms or clinical and radiographic findings. The treatment strategy in such cases is systemic (e.g. pain medication and, if appropriate, antibiotics) [7].

MANAGEMENT [8-10]

• Conservative treatment:

1. Disinfectant mouth rinses

2. Antibiotic therapy

3. Anti-fungal therapy.

• Surgical techniques:

1. Surgical debridement, sequestrum removal, surgical sinus drainage procedures
2. Extraction of teeth
3. Bone resection;
4. Surgical wound closure, reconstructive surgery, grafts;
5. Laser-assisted surgery and
6. Fluorescence-assisted surgery.

• Adjuvant non-surgical treatment strategies:

1. Hyperbaric oxygen therapy;
2. Pentoxifylline and tocopherol (vitamin e);
3. Ozone therapy;
4. Low-level laser therapy (lllt)
5. Platelet-rich plasma;
6. Parathyroid hormone and teriparatide; and
7. Bone morphogenetic protein (bmp).

CONCLUSION

BRONJ has been known as a complication in patients receiving tooth extractions during BP therapy, despite the general systemic benefits of these drugs. BPs also inhibit other cell types such as osteogenic cells, endothelial cells, human fibroblasts, and macrophages and reduce the viability of oral keratinocytes, with associated impairment in mucosal wound healing. Dentoalveolar surgery is often a precipitating factor for BRONJ symptoms. Hence, preventive measures include maintaining good oral hygiene and undertaking all necessary dental treatment before beginning a course of intravenous bisphosphonate treatment. Some clinical guidelines recommend that people at risk of BRONJ should take a three-month break from oral bisphosphonates before and after dental treatment.

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