

MANAGEMENT OF BISPHOSPHONATES INDUCED  
OSTEONECROSIS OF THE JAW- A SYSTEMATIC REVIEW

## Abstract

Bisphosphonate–Induced Osteonecrosis of the Jaw (BIONJ) adversely affects the quality of life, producing significant morbidity. Management of BIONJ has centered on efforts to eliminate or reduce severity of symptoms, to slow or prevent the progression of disease, and to eradicate diseased bone. The staging system adopted by the American Academy of Oral and Maxillofacial Surgeons (AAOMS) categorizes patients based on presence of exposed bone and severity of signs and/or symptoms. Specific management regimens have included medicinal management (chlorhexidine rinses, antibiotic therapy, hyperbaric oxygen, vitamin E, teriparatide and non-surgical sequestrectomy) and surgical debridement and/or resection of necrotic bone followed by reconstruction.

Keywords: osteonecrosis, Bisphosphonates, antimicrobials, surgery reconstruction

Date of Submission : 6/2/16

Date of Acceptance : 24/2/16

1. Vishal Mittal
2. Tejinder Kaur
3. Amit Dhawan
4. Jasmine Kaur
5. Ramandeep S Bhullar

1. Post graduate student, Department of Oral and Maxillofacial Surgery Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar.
2. M.D.S, Professor, and Head of the Department Department of Oral and Maxillofacial Surgery Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar
3. M.D.S, Assoc. Professor, Department of Oral and Maxillofacial Surgery Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar
4. M.D.S, Assoc. Professor, Department of Oral and Maxillofacial Surgery Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar
5. MDS Professor and Dean Academics Department of OMFS, Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar

Corresponding author:

Name: Dr. Tejinder Kaur

Address: Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar.

(M) :9814010528

e-mail: tkgumber@gmail.com

## INTRODUCTION

Osteonecrosis, which is also known as avascular necrosis of bone, aseptic necrosis, ischemic necrosis, is characterized by the death of bone as a natural consequence of a wide variety of systemic and local factors compromising the blood flow of the bone. This disorder can be caused by an injury or factors such as hemoglobinopathies, anticardiolipin antibodies, defects in the thrombotic and fibrinolytic systems, fat emboli, alcoholism, corticosteroids, radiation therapy and bisphosphonates.<sup>1</sup>

There are two principal groups of patients that are affected with this disorder. The first group suffers from

osteoradionecrosis. The clinical symptoms include pain, fistula, exposed bone, and even extended bone destruction and pathological bone fracture. Second type of osteonecrosis has been observed to involve the jaws during long term of antiresorptive bone treatment used routinely to decrease osteoclast-mediated bone loss in osteoporosis, multiple myeloma, Paget disease, and complications of metastatic disease. This type was first reported by Marx in 2003.<sup>2</sup>

According to the American Academy of Oral and Maxillofacial Surgeons (AAOMS), bisphosphonate-induced osteonecrosis of the jaw (BIONJ) is defined by three main characteristics: previous or current bisphosphonate

therapy, exposed necrotic bone in the maxillofacial region that has been persisted for more than 8 weeks, and no history of radiation therapy to the jaws. If these three conditions are present, the diagnosis can be confirmed clinically. It is important to exclude local malignancy, trauma, periodontal disease, and lingual-mandibular sequestration and ulceration.<sup>3</sup>

BIONJ treatment has been challenging from the beginning as there is no consensus regarding the clinical management of patients with BIONJ because of incomplete understanding of the etio-pathogenesis of the disease. The AAOMS 2014 Position Paper on Medication-Related Osteonecrosis of the Jaws states that the "Treatment objectives for patients with an established diagnosis of BIONJ are to eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone necrosis."

Different therapeutic approaches have been reported including anti-microbial rinses, antibiotics, local debridement and surgical resection, or a combination thereof. However, since several recent studies have shown durable disease-free status after surgical resection of lesions of BIONJ.

The aim of this review is to share different treatment approaches to patients with BIONJ. Fundamentally, treatment can be divided into medical and surgical therapies, although a combination is often used. For purposes of clarity, in this review we employ the staging system and treatment strategies (Table 1.) as described in the 2014 AAOMS position paper.

#### Management Strategies for Patients Treated with Bisphosphonates

Marx R E. et al (2005)<sup>5</sup> found a statistically significant, almost threefold reduction in the incidence of osteonecrosis in patients when preventive measures were applied. Treatment planning for patients who may be prescribed bisphosphonate therapy should include thorough examination of the oral cavity and a radiographic assessment. It is important to identify both acute infection and sites of potential infection to prevent future sequelae that could be exacerbated once drug therapies begin. Considerations during the clinical and radiographic assessment include:

- i. Patient motivation
- ii. Patient education regarding dental care
- iii. Fluoride application
- iv. Chlorhexidine rinses
- v. Periodontal disease
- vi. Presence of root fragments

vii. Caries

viii. Periapical pathology.

ix. Extraction of tooth with poor prognosis.

#### Treatment Goals<sup>6</sup>

The major goals of treatment for patients at risk of developing or who have Bisphosphonate-Induced Osteonecrosis of the Jaw are:

- Prioritization and support of continued oncologic treatment in patients receiving IV antiresorptive and antiangiogenic therapy. Patients having malignant disease can benefit greatly from the therapeutic effect of bisphosphonate therapy by controlling bone pain and reducing the incidence of other skeletal complications.
- Preservation of quality of life through:
  - a) Patient education and reassurance.
  - b) Control of pain.
  - c) Control of secondary infection.
  - d) Prevention of extension of lesion and development of new areas of necrosis.

#### MEDICAL MANAGEMENT

Treatment of BIONJ with medical therapy alone is most commonly employed for patients with less severe disease, those who decline surgery, or those whose comorbidities preclude them from surgery. Medical therapies currently in use include topical, oral and intravenous antimicrobials, other medications and hyperbaric oxygen (HBO).

#### ANTIMICROBIALS

- Topical antimicrobials

Chlorhexidine gluconate is a topical bactericidal and bacteriostatic agent that has been shown to be effective in treatment of patients with BIONJ. Although the pathogenesis of BIONJ remains unclear, there is evidence that the oral flora, and more specifically bio films, contribute to the disease process. The use of chlorhexidine is thus rationalized by its ability to decrease total bacterial counts, including potentially pathologic organisms.<sup>3,7</sup>

- Oral antimicrobials

Antimicrobials are a mainstay in the management of BIONJ. Antimicrobial therapy is based on clinical observation and scientific literature suggesting that pathogenic bacteria may contribute to BIONJ. Systemic antibiotics may decrease bacterial counts in the oral cavity, including pathogenic organisms. Selection of specific antibiotics should be based on patient tolerance, compliance, and prior antibiotic exposure. One should also consider therapies targeted against common colonizers of BIONJ lesions, including

Bacteroides scapillosus, Corynebacterium species, Fusobacterium nucleatum, Gemella species, Klebsiella pneumoniae, Parvimonas micra, Peptostreptococcus anaerobius, Porphyromonas accharolytica, Porphyromonas endodontalis, Porphyromonas gingivalis, Prevotella buccae, Prevotella disiens, Prevotella intermedia, Prevotella species, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus agalactiae, Streptococcus anginosus, Streptococcus constellatus, Streptococcus mitis, and alpha-hemolytic Streptococcus. Over the years penicillin remained the first treatment of choice, in patients allergic to penicillin alternatives are clindamycin, fluoroquinolones, metronidazole and newly introduced sitafloxacin. Although there is no data to clarify the most appropriate duration of antibiotic therapy for BIONJ, but it is advisable to prescribe a

2-week course for patients with persistent stage 1 disease and up to a 4- to 6-week course for more severe cases.<sup>7,8</sup>

#### Intravenous antimicrobials

Intravenous antimicrobials may be of benefit in patients with pathogenic organisms resistant to oral agents and may provide greater tissue penetration in certain cases. When all available oral agents have been exhausted and no less invasive option exists, it is mandatory to employ long-term intravenous antimicrobials (6 weeks). In the future, it is conceivable that antimicrobial therapy may be more effective in BIONJ treatment when combined with developing delivery mechanisms most capable of penetrating biofilms.<sup>7</sup>

#### Other Medications

Table 1. Staging of and treatment strategies for bisphosphonate-induced osteonecrosis of the jaw (BIONJ) according to the American Association of Oral and Maxillofacial Surgeons (AAOMS).<sup>3,4</sup>

BIONJ Stage	Clinical Conditions	Treatment strategies
At Risk	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment indicated Patient education
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms	Systemic management, including the use of analgesics and antibiotics
Stage 1	Exposed and necrotic bone in asymptomatic patients without evidence of infection	Oral anti-bacterial mouth rinse. Clinical follow-up on a quarterly basis, patient education and review of indications for continued BP use.
Stage 2	Exposed and necrotic bone associated with infection as evidenced by pain and erythema in the region of exposed bone, with or without purulent drainage	Symptomatic treatment with oral antibiotics, oral anti-bacterial mouth rinse, and pain control Superficial debridement to relieve soft tissue irritation.
Stage 3	Exposed necrotic bone in patients with pain and erythema and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, such as the inferior border and ramus in the mandible, or maxillary sinus or zygoma in the maxilla, resulting in pathological fracture, extraoral fistula, or oral-antral/oral-nasal communication, or osteolysis extending to the inferior border of the mandible or to the maxillary sinus floor.	Oral anti-bacterial mouth rinse, antibiotic therapy and pain control Debridement/surgical resection for prolonged relief of pain and infection.

#### · Pentoxifylline and vitamin E

The combination of pentoxifylline and vitamin E has been used successfully in the treatment of jaw osteoradionecrosis and BIONJ. Pentoxifylline, a xanthine derivative with an excellent safety profile decreases inflammation and reduces blood viscosity by increasing erythrocyte deformability. Vitamin E decreases tissue inflammation and fibrosis, and is a scavenger of free radicals capable of cellular injury. Numerous reports supporting the role of both inflammation and decreased vascularity as contributors to BIONJ make the use of this relatively well tolerated drug combination a rational choice. The duration of treatment has not been clarified, but literature suggests that the benefits may plateau after 2 to 3 years of use. The recommended dose of pentoxifylline is 400 mg sustained release twice daily and 1000 IU vitamin E daily.<sup>7</sup>

#### · Teriparatide

Teriparatide is a subcutaneously administered drug used primarily in the treatment of osteoporosis. It retains the anabolic effects of endogenous parathyroid hormone, including promotion of bone remodeling. Teriparatide is thought to stimulate effectively osteoblast function and proliferation, increase osseous cells signaling and activate osteoclasts. The safety, side effects, dosing, and duration of therapy for the management of BIONJ are not known. Currently, this agent is not frequently used in practice for treatment of BIONJ and it is important to note that teriparatide is contraindicated in patients with metastatic bone disease or osteosarcoma. Certainly, promising results have been observed with this therapy and, given the limited options available for treatment of BIONJ, its use should be considered and studied further.<sup>7,9,10</sup>

#### · Hyperbaric Oxygen Therapy

HBO therapy has been used for management of osteoradionecrosis of the jaw for many years and more recently has been applied to treatment of BIONJ. HBO provides greater oxygen to tissues with impaired vascularization reverses impaired leukocyte function and also supplies reactive oxygen. All of these effects theoretically contribute to improved wound healing and bone turnover. HBO is seldom used as a singular treatment modality, but is more commonly used as a surgical adjunct. The clinical utility of HBO for management of BIONJ remains unclear and it deserves further study.<sup>7</sup>

#### SURGICAL MANAGEMENT

Focus in the surgical treatment of BIONJ is directed toward stage-specific therapeutic options. Patients with stage 0 and stage 1 disease generally do not warrant surgical intervention. In general practice, surgical treatment is

offered when disease progresses to the point where symptoms are not controlled with medical therapies.<sup>11</sup>

A wide spectrum of disease is often seen with stage 2 BIONJ, ranging from focal minimally symptomatic exposed bone to severely painful widespread bone necrosis. It is thus difficult to recommend a single surgical treatment approach in these patients. Rather, the decision regarding operative intervention depends on the patient's medical status, comorbidities, pain level, their treatment goals, and the extent of disease.<sup>7,12,13</sup>

#### Treatment modalities for stage 2 BIONJ

Debridement, marginal resection and segmental resection are terms commonly seen in the literature describing surgical treatment of BIONJ. Debridement and marginal resection both refer to removal of necrotic bone, primarily in the alveolus, with the goal of maintaining an intact inferior border of the mandible. Segmental resection, on the other hand, refers to en-bloc removal of involved bone, including the inferior border of the mandible, with a resulting continuity defect. Success rate vary widely in response to local debridement/marginal resection ranging from 15% to 100%.

Success of debridement or marginal resection may also be limited by the difficulty in differentiating healthy bone from diseased bone. Inadequate removal of affected bone has been found to increase BIONJ recurrence. Because the extent of the osteonecrosis is often greater than what is seen clinically, preoperative imaging with CT or cone beam CT, bone scintigraphy, and/or MRI can also aid in determining the type and extent of surgery and assist in identifying bony margins. Intraoperative fluorescence-guided debridement has been suggested to assist in differentiating necrotic from viable bone.

Tetracycline is used as a bone label for this purpose because it is incorporated into sites of bone remodeling and thus will only be seen in viable bone. The technique involves preoperative administration of doxycycline (100 mg twice a day 10 days before surgery). A fluorescent light source is applied to the affected region during debridement and areas of necrotic bone are seen to fluoresce as a pale bluish-white color whereas viable bone appears brightly fluorescent.<sup>14</sup>

During surgical debridement, extraction of any involved teeth is also indicated. It is better to debride diseased tissue adequately, including removal of adjacent potentially involved teeth, than leave the area inadequately treated to preserve teeth. Any sharp bony spicules should be removed and extraction sockets and bony margins should be free of sharp edges to aid in achieving tension-free primary closure. All resected hard and soft tissue should be sent for histopathological examination and culture sensitivity to

allow directed postoperative antibiotic therapy.

Adjunctive treatments, including platelet-rich plasma<sup>15</sup>, low-level laser therapy<sup>17</sup> Hydroxyapatite composite<sup>18</sup>, have been used in conjunction with surgical debridement to improve postoperative healing. A systematic review of the literature on platelet concentrates concluded that it promotes gingival healing and acts as a barrier membrane between the alveolar bone and the oral cavity. Hydroxyapatite composite focuses on the bone formation and the angiogenesis by the grafting material, dual releasing simvastatin and bone derived fibroblast growth factor for the further prevention of BIONJ. Low-level laser therapy stimulates bone healing by increasing vascularity and osteoblastic differentiation, has been used in conjunction with surgical debridement of osteonecrosis. However, rates of healing after surgical debridement with and without low-level laser therapy are comparable and further research is needed to determine the value of low-level laser therapy. In summary, in cases of stage 2 BIONJ when debridement and marginal resection is determined to be the indicated treatment, the following principles should be applied:

1. Appropriate preoperative imaging to assess the extent of disease.
2. Removal of all necrotic bone and any involved teeth to achieve disease-free bony margins.
3. Removal of any sharp bony edges and spicules.
4. Achievement of a layered tension-free primary wound closure whenever possible.
5. Culture-directed postoperative antibiotic therapy until mucosal healing is seen.
6. Restraint from wearing any oral prosthetic devices until complete mucosal healing is seen.<sup>7</sup>

#### Treatment modalities for stage 3 BIONJ

Patients with stage 3 BIONJ who present with extensive maxillofacial involvement may benefit from wide local debridement or segmental resection of necrotic bone. This treatment is reserved for those with severe symptomatic disease when other modalities have failed. Segmental resection for treatment of stage 3 osteonecrosis of the jaw followed by reconstruction has shown generally favorable outcomes with up to a 90% success rate. As with stage 2 disease, evidence of osteomyelitis at one of the resected margins is a predictor for recurrent disease. Experiences with segmental resection in cases involving both the maxilla and mandible has overall been positive with successful long term resolution of BIONJ without recurrence. The same treatment principles outlined for stage 2 BIONJ also apply to patients with stage 3 disease.<sup>7, 19</sup> Reconstructive procedures for Bisphosphonate-Induced Osteonecrosis of the Jaws have

been divided into 4 basic categories by Marx R.E:

1. Resections with immediate rigid plate fixation:  
Indicated where reconstruction is required beyond a primary closure or more commonly in case of a continuity resection. Rigid plate fixation in this group should be precise and be placed with the intent on long-term use.<sup>20</sup>
2. Resections with delayed rigid plate fixation:  
Indicated in cases with high risk of secondary infection, high degree soft tissue loss and patient's debilitation from the malignancy. In such cases, it is very reasonable to accomplish the required resection in a shorter focused surgery and plan to place a rigid plate later if and when the patient's local tissue health and systemic conditions improve.<sup>20</sup>
3. Resections with or without rigid plate reconstruction but requiring soft tissue replacement:  
Indicated in cases with a significant loss of either mucosal lining and/or skin due to the antiangiogenesis effect of the bisphosphonate.<sup>20</sup>
4. Delayed bone graft reconstruction (free fibula).<sup>20,21</sup>

#### Future Perspectives

Treatments modalities like hematopoietic cell transplantation, Adipose-derived stem cells, plasma rich in growth factors, ozone and vitamin D supplementation have been advocated for the management of BIONJ, but all these modalities are under trial and need further research to ensure as an optimal patient treatment protocol of BIONJ.

#### Conclusion

Management of BIONJ presents a challenging clinical dilemma. Mucosal coverage is the main goal of BIONJ treatment in order to prevent secondary infection. The management of BIONJ remains controversial, and there is no definitive standard of care for this disease. Non-surgical, conservative, and minimally invasive treatment regimens for BIONJ are considered useful to control the disease, leading to predictable good results in cases of lower stages of BIONJ. Further research is indicated particularly for higher stage BIONJ (refractory stage 3 lesions). BIONJ may also be approached with new adjunctive treatments such as laser therapy, HBO, growth factors or hydroxyapatite composite in order to ensure an optimal patient treatment protocol. The application of adjunctive treatments remains an opinion-based approach rather than an evidence-based one. Controlled studies or clinical trials should be performed to evaluate these adjunctive treatments for BIONJ patients.

#### BIBLIOGRAPHY

1. Gutta R, Louis PJ. Bisphosphonates and osteonecrosis of the jaws: Science and rationale. *Oral surg Oral med Oral*

- path Oral radiolendod 2007; 104:186-93
2. Marx R E. Pamidronate (aredia) and zoledronate (zometa) induced avascular necrosis of The jaws: A growing epidemic J Oral MaxillofacSurg 2003; 61:1115-1118.
  3. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, et al. American association of oral and maxillofacial surgeon's position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral MaxillofacSurg 2014; 65: 369-376.
  4. R. Fliefel, M. Troitzsch, J. Kühnisch, M. Ehrenfeld, S. Otto. Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. Int. J. Oral Maxillofac. Surg. 2015; 44: 568–585.
  5. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-Induced Exposed Bone (Osteonecrosis/Osteopetrosis) of the Jaws: Risk Factors, Recognition, Prevention, and Treatment. J Oral MaxillofacSurg 2005; 63: 1567–1575.
  6. Yamashita J, McCauley LK. Antiresorptives and osteonecrosis of the jaw. J Evid Base Dent Pract 2012; S1: 233-247.
  7. Williams W B, O'Ryan F Management of medication-related osteonecrosis of the jaw Oral Maxillofacial SurgClin NAm 27 (2015) 517–525.
  8. Ikeda T, Kuraguchi J, Kogashiwa Y, Yokoi H, Satomi T et al. Successful treatment of Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) patients with sitafloxacin: New strategies for the treatment of BRONJ. Bone 73 (2015) 217–222.
  9. H. Kakehashi, T. Ando, T. Minamizato, Y. Nakatani, T. Kawasaki, et al Administration of teriparatide improves the symptoms of advanced bisphosphonate-related osteonecrosis of the jaw: preliminary findings. Int. J. Oral Maxillofac. Surg. 2015.07.018
  10. E. H. Dayisoğlu, F. C. Senel, C. Uğur, E. Tosun, M. C. Ankaya, et al The effects of adjunctive parathyroid hormone injection on bisphosphonate-related osteonecrosis of the jaws: an animal study. Int. J. Oral Maxillofac. Surg. 2013; 42: 1475–1480
  11. Bodem J P, Kargus S, Engel M, Hoffmann J. Value of nonsurgical therapeutic management of stage I bisphosphonate-related osteonecrosis of the jaw. Journal of Cranio-Maxillo-Facial Surgery (2015), j.jcms.2015.05.019
  12. Rupel K, Ottaviani G, Gobbo M, Contardo L, Tirelli G, et al. A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ). Oral Oncology 50 (2014) 1049–1057
  13. Reich W, Bilkenroth U, Schubert J, Wickenhauser C, Eckert A W, et al Surgical treatment of bisphosphonate-associated osteonecrosis: Prognostic score and long term results, Journal of Cranio-Maxillo-Facial Surgery (2015), j.jcms.2015.07.035
  14. Porcaro C, Amosso E, Scarpella R, Carini F Doxycycline fluorescence-guided Er:YAG laser ablation combined with Nd:YAG/diode laser biostimulation for treating bisphosphonate-related osteonecrosis of the jaw. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology (2014), j.o.oooo.2014.04.014.
  15. Soydan SS, Uckan S. Management of bisphosphonate-related osteonecrosis of the jaw with a platelet-rich fibrin membrane: Technical report. J Oral MaxillofacSurg 2014; 72: 322-326.
  16. S. Bocanegra-Pérez, M. Vicente-Barrero, M. Knezevic, J. M. Castellano-Navarro, E. Rodríguez-Bocanegra, et al. Use of platelet-rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw. Int. J. Oral Maxillofac. Surg. 2012; 41: 1410–1415.
  17. Vescovi P, Merigo E, Meleti M, Fornaini C, Nammour S, et al Nd:YAG laser biostimulation of bisphosphonate-associated necrosis of the jaw bone with and without surgical treatment. British Journal of Oral and Maxillofacial Surgery 45 (2007) 628–632
  18. Miyazawa A. Matsuno T., Asano K., Mataga I. Development of the HA composite for the prevention of BRONJ. AAOMS 2014; 195-196.
  19. Bodem J P, Schaal C, Kargus S, Saure D, Mertens C, et al. Surgical management of Bisphosphonate-related osteonecrosis of the jaw Stage II and III. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology (2015) j.o.oooo.2015.10.033.
  20. Marx RE. Reconstruction of defects caused by bisphosphonate-induced osteonecrosis of the jaws. J Oral MaxillofacSurg 2009; 67: 107-119.
  21. Nocini P.F., Bettini G, Ragazzo M, Blandamura S, Chiarini L, et al. Vascularized fibula flap reconstruction of the mandible in bisphosphonate-related osteonecrosis. EJSO 2009; 35: 373-379.