IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 4 Ver. VIII (Apr. 2016), PP 79-84
www.iosrjournals.org

Bisphosphonates Related Osteonecrosis of Jaw: Review and Upda te to General Dentist

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Abstract: *Bisphosphonates related osteonecrosis of Jaw (BROJ) is one of the serious complication caused by c onsumption of bisphosphonates mainly by intravenous routes which has been taken during the treatment of meta static diseases. Bisphosphonates are non-metabolized analogues of pyrophosphate that avidly attach to bone mi neral more or less resorbing osteoclasts and inhibit their function. As they are non-metabolized, high concentrat ions are maintained in bone for long periods of time disrupting osteoclast-mediated bone resorption without affe cting the bone density. There has been exponential rise in the literature of osteonecrosis and its complications b ut there is very few evidenced based literature present related to its management. In our article, we elucidate th e clinical implications of bisphosphonates and preventive aspects of BROJ to general dentist which will provide a better understanding the importance of its prevention along with line of treatment.*

Keywords: *Bisphosphonates, Osteonecrosis of Jaw, Bisphosphonates related osteonecrosis of Jaw, Risk Factor s, Prevention.*

I. Introduction

Bisphosphonate related osteonecrosis of jaws more colloquially expressed as "bis-phossy jaw". The ter m "bis-phossy jaw" is a derivative, and reflects a historical association with another painful and destructive cond ition confined to jaws, related to occupational exposure to white phosphorous of matchstick makers ('Lucifer "st rike anywhere" matches') of the 1830's, then termed "phossy jaw". The first case of BROJ was reported in 2003 by Marx as a painful exposure of bone in both maxilla and mandible[1], and after that many case series and report s published in literature. *Osteonecrosis* in simple words is death of bone due to reduced blood supply and Osteo necrosis of Jaw (ONJ) most commonly occurred in patients with head and neck cancer who have had radiation t herapy, is termed as *Osteoradionecrosis*. Historically middle of the 19th century, Gem diphosphonates or diphos phonates are the terms earlier used in the literature for bisphosphonates. Anti-tartar agents present in toothpastes like, pyrophosphates compounds are linked to bisphosphonates. Bisphosphonates are the drugs which act first a nd foremost to prevent resorption of bone and inhibit bone turnover. In early 1990s, bisphosphonates were used for diagnostic purposes in bone diseases and calcium metabolism[2]. Bisphosphonates mostly convey their effects on cell, tissues and molecular level[3]. In recent years, the use of bisphosphonates has dramatically increased in va rious bone diseases and cancer treatments in oral or intravenous preparations. American Association of Oral and Maxillofacial surgeons mentioned that Bisphosphonates related osteonecrosis of jaws is diagnosed, if oral woun d remains with an exposed necrotic bone for a period of minimum eight weeks who has taken or currently taking bisphosphonates even who has no history of radiation therapy[4]. This literature review is undertaken to enlighten the clinical implications of bisphosphonates, preventive aspects of bisphosphonates related osteonecrosis of jaw to general dentist which will provide a better understanding the importance of prevention and treatment options.

II. Epidemiology

The prevalence of bisphosphonate related osteonecrosis of jaw is very difficult to estimate because diff erent terminology has been mentioned in literature and some mild self resolving cases remained unidentified. It has been mentioned in literature approximately 95% of patients develop Osteonecrosis of Jaw who consumed bi sphosphonates. Intravenous bisphosphonates are more responsible than oral administration. It is more commonl y in mandible than maxilla because of reduced blood supply to bone[5]. The most recent available data indicates t hat Intravenous bisphosphonates for cancer therapy for extended periods related skeletal events, incidence varies from 0.8% to as high as 20% and concerning the incidence of bisphosphonate for age related and postmenopaus al osteoporosis is still limited, and may be under reported. Incidence of Oral bisphosphonates was 0.7/100,000 p erson/years of exposure mean 0.0007% of patients per year rising to 0.0021% by the third year of ongoing treat ment and in one survey of patients consuming oral medications, the risk of developing BROJ was approximately 0.1%[6].

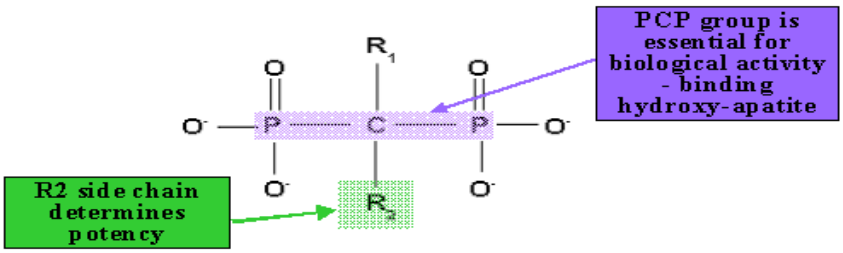
III. Bisphosphonates

Bisphosphonates are inhibitors of osteoclastic activity and can induce osteoclast cell death by Apoptosis, thereby significantly inhibit bone resorption. These are used for the clinical benefit in both the treatment and prevention of conditions associated with pathology secondary to bone resorption and turnover (Table 1). The chemical structure of bisphosphonates includes a P-C-P backbone that bestows a strong affinity for hydroxyapatite crystal on bony surfaces and provides potent inhibition of bone turnover both *in vivo* and *in vitro* with two side chains R_1 and R_2. R_1 chain usually a hydroxyl group enhances compounds the affinity for bone but has no antiresorptive effect while R_2 confers the antiresorptive potency of the compound and determines its efficiency[7,8].

TABLE 1: Indications for Bisphosphonate Therapy

INDICATIONS	COMMENTS
Osteoporosis	Post Menopausal, Corticosteroid Induced/Related, "Male" age related osteoporosis, Male Hypogonadism
Bony Metastasis from solid malignancies	Breast, Lung and Prostrate Cancer
Heterotopic Ossification	Prevention and treatment when associated with spinal cord injury.
Total Hip Replacement	1 Month Preoperatively, 3 Month Postoperatively
Hypercalcemia	
Multiple Myeloma	
Paget's Disease	
Other Rare Conditions	Osteogenesis Imperfecta, Reflex Sympathetic Dystropy (Complex Regional Pain Syndrome (CRPS))

Generic Bisphosphonates Chemical Structure



IV. Pathophysiology

In literature, to date there were several cases reported related to BROJ and it has shown that due to several anatomical and physiological factors responsible for propensity of jaws. The rapid bone remodeling occurs in jaws compared to the rest of the skeleton (the alveolar crest remodels at a rate ten-fold that of long bones), the added prospective for inflammation due to the dentition and the bacterial rich oral environment provide a realistic explanation for this[9].

The exact origin of BROJ is not known but many hypothesis seem to explain the pathogenesis under these three points,

a. On Bone Remodeling: It has been mentioned that bisphosphonates causes bone remodeling suppression. The jaw bones have high rate of remodeling than other bones hence rapid bone remodeling of jaw and suppression of remodeling leads to osteonecrosis.
b. On Osteocytes: In normal bone, osteocytes at the termination of their life cycle are removed and replaced with new ones. This process will be absent when bone remodeling is suppressed by bisphosphonate. The lacunae, where osteocyte resided will now be empty and can be demonstrated by fuchsin dye. Healthy osteocytes have canaliculi by which they communicate with adjacent osteocytes as well as exchange nutrients through blood supply. So, once the osteocytes die the nutrition is also cut-off leading to necrosis of bone. It is also noted that bisphosphonates attached to the bone act as cytotoxic agents to the osteocytes thereby leading to their death and later their necrosis.
c. On Antiangiogenesis: It is experimentally proved that bisphosphonate have antiangiogenic property as they curb capillary regeneration, epithelial growth factor and angiogenesis. The normal healing mechanism in jaw bone following extraction or invasive dental treatments is disturbed as the blood clot will not form due to angiosuppression by bisphosphonate. In addition to this, bone remodeling is inhibited as osteoclasts are suppressed by bisphosphonates leading to delay in wound healing process and BROJ ultimately[10].

V. Adverse Effects And Risk Factors Of Therapy

In normal bone homeostasis, osteoclastic resorption is tightly linked to osteoblastic bone deposition and both functions are essential for repair of physiologic microdamage. Prolonged use of bisphosphonates may sup

press bone turnover to the point that such microdamage persists and accumulates[11]. Although Osteoblastic functi on is also reduced during bisphosphonate therapy, continued mineralization yields a hard, brittle bone with an in creased risk of fracture[12]. Generally, the side effects seen are hypocalcemia, skeletal bone or joint pain, constipat ion or diarrhea, tiredness, etc. Oral bisphosphonates can cause GI upset causing inflammation and erosions of es ophagus. IV infusion can give rise to fever and flu like symptoms after first infusions[13]. Risk factors those are re sponsible for development of BROJ can be grouped as: Drug related, Local risk factors, Preventive factors and d emographic/systemic factors (Table 2).

TABLE 2: Risk Factors responsible for BROJ

Drug Related Factors	Local Risk Factors	Preventive Factors	Demographic/Systemic Factors
a. Immunosuppressants b. Long duration of therapy c. Corticosteroid therapy	a. Dentoalveolar surgery b. Oral Infection (Periodontal and Dental Infections) c. Poor Oral Hygiene d. Intraoral Trauma e. Local Anatomy Mandible (Lingual tori and Mylohyoid Ridge). Maxilla (Palatal tori)	a. AAOMS taskforce on BROJ recommended that patients undergo dental evaluation prior to IV therapy	b. Age c. Systemic disease (renal failure, anaemia, obesity, diabetes) d. Smoking e. Alcohol Use f. Genetic Factor like single nucleotide polymorphisms in cytochrome P450-2C

VI. Clinical Presentation

The clinical presentation of bisphosphonates related osteonecrosis of jaw developed by the American Association of Oral and Maxillofacial Surgeons in a task force which released a position paper concerning BRO J in Sept. 2006: an Osteonecrosis of jaws that refers to a condition of exposed necrotic bone in the mandible or maxilla that persists for more than eight weeks in a patient who has taken or is currently taking a bisphosphonate and has no history of radiation therapy to the jaws[4]. The signs and symptoms for BROJ patients presents with lo calized pain, neuropathy, halitosis, exposed bone, erythema, gingivitis, mobility of teeth with suppuration and p us discharge[14]. There are some potentially confusing clinical conditions which may have a symptom similar to B ROJ include Alveolar Osteitis, Sinusitis, Periodontal Disease, Caries, Periapical Pathology and TMJ disorders. I n order to standardize the criteria for BROJ the American Association of Oral and Maxillofacial Surgeons has c ome up the three most important criterias:

- Current or previous treatment with bisphosphonate drug
- Exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks.
- No history of radiation therapy to the jaws[10].

Ruggiero et al suggested the following staging of BROJ at AAOMS in 2009 along with the treatment st rategies as per AAOMS recommendations. (Table 3,4.) One most important point to specify that HBO therapy h as no role in management of BROJ.

TABLE 3. Clinical Staging of BROJ as suggested by Ruggiero et al at AAOMS in 2009[10,,13,15,16.]

At risk Category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	No clinical evidence of necrotic bone but nonspecific clinical findings and symptoms
Stage 1	Exposed/Necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed/Necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bon e with or without purulent drainage
Stage 3	Exposed/Necrotic bone in patients with pain, infection and one or more of the following: Pathologic fracture, extraora l fistula or osteolysis extending to the inferior border.

TABLE 4. Treatment Strategy of BROJ as per the Recommendation of AAOMS in 2009[10,13,15]

At risk No special tre atment req	

uired; poss ibility of B ROJ and s ymptoms s hould be e xplained to patient	
Category	
Stage 0	Antibiotics should be administered if needed. Conservative treatment should be used for patient with dental caries an d periodontal problems. 0.12% chlorhexidine gluconate is effective in treatment at this stage. Surgery is not required.
Stage 1	Oral antibiotics and chlorhexidine mouthwash are used. Usually Penicillin is preferred, but if patient is allergic to it t hen quinolones, metronidazole, clindamycin, doxycycline, and erythromycin can be administered. Combination of O ral and intravenous antibiotics may be required.
S tage 2	Necrotic tissue is removed superficially without disturbing underlying soft tissue. Necrotic bone is removed. Systemi c antibiotics have to be given along with anti-inflammatory drugs.
Stage 3	Oral antiseptic mouthwashes are recommended.

VII. Prevention

Prevention of BROJ is still not completely understood, given there as yet no existence, or evidence bas ed published guidelines. Prevention is mainly based on the following principles:

a. Identification of at risk patients.
b. Knowledge and recognition of the limited number, that is later generation potent, nitrogen containing, bisphosphonate agents associated with BROJ.
c. Treatment planning for patients identified as being at risk for BROJ requires common sense approach, and flexibility to exploit preventive measures to reduce the opportunity for infections, and minimize the invasiveness of treatment proposed.
d. Intervention for BROJ is based on as yet unproven, but clinically derived understanding of the critical risk factors for aetiology and pathogenesis of BROJ, namely the type, duration, and route of bisphosphonate administration; minimizing wound exposure to bacteria at the time of tooth extraction/surgery; and gentle, atraumatic surgical technique.

However, patients who is at risk for BROJ should planned properly as completion of all necessary dent al treatment before the commencement of second or third generation bisphosphonates and treatment occurring a s soon as possible following commencement of bisphosphonates, ensuring that treatment is completed within the "window" period (Table 5) for specific bisphosphonate agents. The window period applies from the commence ment of the therapy and is the time in which dental procedures, including extractions, may be undertaken with a relatively lower risk of BROJ occurring. There are three risk categories, minimal, medium or significant (Table 6,7) which will assist the clinicians in determining if the use of recommended protocol, using protracted antibiot ic prophylaxis pre and post treatment is advised. Since treatment for BROJ is limited, prevention remains imper ative. This is because even in patients discontinue uptake of bisphosphonates, the effect of discontinuation is sub tle due to characteristics of bisphosphonates in that it remains in the bone for several years. The apparently low r isk of BROJ given among patients receiving oral bisphosphonates for osteoporosis, maintainance of good oral h ygiene and the same level of dental care as for general population need to be implemented. The use of an antibio tic regimen to lessen the risk of BROJ from occurring in patients at high risk for BROJ is controversial, and exp ert opinion is divided on the appropriateness of this approach. While not well defined, bacterial infection is note d in the existing literature as having some role in the aetio-pathogenesis of BROJ, so use of antibiotic prophylaxi s does seem logical. Hence the centre for oral Health strategy has been given some preventive regimens for dent al procedures (Table 8,9) for minimizing the risk of BROJ.

VIII. Conclusion

Osteonecrosis of the jaws is a recognized condition reported in patients treated with bisphosphonates, i n particularly potent amino-bisphosphonates. These commonly developed in patients with multiple myeloma or metastatic cancer, but the condition has also been identified in osteoporosis patients. In all these general dentist has the most important role in diagnosing this condition. According to recent consensus, regular dental checkup is the best way to minimize the risk of it. To identify the patients at increased risk of developing BROJ, no valid ated diagnostic tool available till date. There are very few cases reported on ongoing problems of BROJ, and de bridement of necrotic bone seems to be helpful, and the conservative treatment should always be the first choice for management however positive outcomes not guaranteed.

TABLE 5. "Window Periods" for specific Amino-Bisphosphonate Agents in which invasive dental procedures can be undertaken with a lower risk of BROJ occurring			
Generic Name	**Route of Indication Administration**		**Window Period: Months from commencement of Bisphosphonate therapy**
Zoledronic Acid Ibandronate Disodium Pamidronate Ibandronate	Intravenous Intravenous Intravenous Oral	Malignancy – Related Skeletal Events	6 9 24 24
Disodium Etidronate	Oral	Pagets disease, heterotopic ossification with spinal cord injury, total hip replacement	36
Zoledronic Acid Disodium Pamidronate Risedronate Alendronate	Intravenous Intravenous Oral Oral	Osteoporosis (treatment/ prophylaxis)	Undefined

TABLE 6. Risk Stratification Categories and Protocol Recommendation	
Risk Stratification Group	**Referral Recommendation**
MINIMAL	✓ No special precautions indicated. ✓ Use of recommended protocol, using protracted antibiotic prophylaxis pre and post treatment NOT indicated ✓ Proceed with all routine non invasive dental care, and any routine dental extractions or oral surgery.
MEDIUM	✓ Consider use of protocol involving protracted antibiotic prophylaxis pre and post procedure. ✓ Consult with immediate (local) senior clinician or contact appropriate specialist.
SIGNIFICANT	✓ Use of protocol, involving protracted antibiotic prophylaxis pre and post procedure RECOMMENDED

TABLE 7. Risk Stratification Definitions	
Lower Risk Patient	**Lower Risk Procedure**
Amino-Bisphosphonate Treatment for Osteoporosis • Alendronate • Any IV agent administered only once yearly (or less) eg. Zoledronic acid • Any bisphosphonate agent within designated window period	Routine office surgery • Routine dental extraction, done under local anaesthesia in dental chair (up to 3 contiguous teeth or 4 separate sites)
Higher Risk Patient	**Higher Risk Procedure**
1. Patient on long term bisphosphonate therapy beyond designated window periods 2. Bisphosphonate therapy related to malignancy ▪ Solid Cancer Metastases (breast cancer) ▪ Multiple Myeloma 3. Aged Patients ▪ 70 years of age or older 4. Immuno-suppression ▪ Recent (within 2 weeks) administration of cytotoxic chemotherapy (with resultant leucopenia) 5. Current or previous use of high dose systemic corticosteroid administration	1. Extensive oral surgery or number of dental extractions ▪ 5 teeth or more ▪ A dental quadrant 2. Surgical extraction of mandibular molar teeth, with risk of impinging lingual cortical plate/mylohyoid ridge 3. Surgery with risk of impinging of maxillary and mandibular tori

TABLE 8. Regimen for Minimising the Risk of BROJ			
Preoperative Regimen – Starting 5 days preoperatively (Day 1-5)			
Clindamycin	300 mg stat, then 300 mg by mouth QID daily	Chlorhexidine Mouthwash (ideally 0.12% aqueous)	10-15 ml swish up to 3 minutes and then spit out well after meals QID daily
Perioperative Protocol (Day 5) • Minimise local anaesthetic (Regional block if possible rather than local infiltration, use lower concentrations of vasoconstrictor) • Atraumatic technique • Encourage Bleeding (from socket – if possible) • Primary closure (reduce/ trim alveolar bone to ensure closure)			
Postoperative Regimen – Starting Day 5 (Days 5-11)			
Clindamycin	300 mg stat, then 300 mg by mouth QID daily	Chlorhexidine Mouthwash (ideally 0.12% aqueous)	10-15 ml swish up to 3 minutes and then spit out well after meals QID daily

<table>
<tr><td colspan="4">TABLE 9. Alternative Antibiotic Regimen to Clindamycin-containing Regimens (Amoxicillin/Metronidazole Combination)</td></tr>
<tr><td colspan="4">Preoperative Regimen – Starting 7 days preoperatively (Day 1-7)</td></tr>
<tr><td colspan="4">Indications:
1. Known allergy/hypersensitivity to clindamycin
2. Patient known to have previous clindamycin related diarrhea</td></tr>
<tr><td>Amoxicillin</td><td>500 mg stat, then 500 mg by mouth TID daily</td><td rowspan="2">Chlorhexidine Mouthwash (ideally 0.12% aqueous)</td><td rowspan="2">10-15 ml swish up to 3 minutes and then spit out Metronidazole</td></tr>
<tr><td></td><td>400 mg stat, then 400 mg TID daily
well after meals QID daily</td></tr>
<tr><td colspan="4">Perioperative Protocol (Day 7)
• Minimise local anaesthetic (Regional block if possible rather than local infiltration, use lower concentrations of vasoconstrictor)
Atraumatic technique
Encourage Bleeding (from socket if possible)
Primary Closure (reduce/ trim alveolar bone to ensure closure)</td></tr>
<tr><td colspan="4">Postoperative Regimen – Starting Day 7 (Days 7-14)</td></tr>
<tr><td>Amoxicillin</td><td>500 mg stat, then 500 mg by mouth TID daily</td><td rowspan="2">Chlorhexidine Mouthwash (ideally 0.12% aqueous)</td><td rowspan="2">10-15 ml swish up to 3 minutes and then spit out well after meals QID</td></tr>
<tr><td>Metronidazole</td><td>400 mg stat, then 400 mg TID daily</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>

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