

OVERVIEW OF CLINICAL ISSUES ASSOCIATED WITH BISPHOSPHONATES IN GENERAL DENTISTRY AND ORTHODONTIC SPECIALITY

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ABSTRACT: Modern day general dental practice and orthodontic specialty practice is no longer limited only for healthy and younger individuals. Bisphosphonates (Bp) have gained much popularity with regard to treatment of calcium metabolic disorders. In every part of the world currently adult patients under bisphosphonate therapy are visiting dental and orthodontic clinics to resolve their problems. So far there is no contraindication for orthodontic patients who are under bisphosphonate therapy. Even though there is no contraindication for orthodontic intervention, few general dental procedures like surgical or invasive treatments are avoided as a precautionary measure. Considerable modifications of regular dental and orthodontic procedures should be enforced in their management. This article reviews the clinical implication of the patients under bisphosphonate therapy who are in need of dental and orthodontic procedures.

KEYWORDS: Bisphosphonates , Bisphosphonate associated osteonecrosis, General dental issues, Orthodontic issues.

INTRODUCTION

Numerous patients who are under medication for various health problems are in need of dental and orthodontic care on a daily basis. Among them some patients who are suffering from skeletal metabolic disorders like osteogenesis imperfecta, post menopausal osteoporosis, multiple myeloma, Paget's disease etc., are under Bp regime. These Bps play an important role in various clinical conditions for the management of dental and orthodontic problems. After the emergence of the first case report of osteonecrosis of the jaw (ONJ) in 2003 linking the usage of bisphosphonates¹, which alarmed the entire dental fraternity, as ample number of cases of ONJ / BON have been documented in the literature. Orthodontic tooth movement might be delayed / obstructed in Bp users due to anti-osteoclastic activity of Bps. In contrary, animal experimental studies of Bps related to orthodontics have shown beneficial effects [attaining retention as well as anchorage] on local administration.

Bisphosphonates

Bps are a group of drugs that are used to generate bone mass and are thus used to treat osteoporosis. Treatment with Bps causes early reduction in bone resorption and then a later reduction in bone formation. They bind strongly to bone mineral, and inhibit the bone

resorption and crystal dissolution. The integrity of bone is maintained by remodeling phenomenon i.e., addition of bone by osteoblasts and removal of bone by osteoclasts in a coordinated manner. These drugs are indicated in the prevention and treatment of osteoporosis, paget's disease, multiple myeloma, hyper parathyroidism, osteogenesis imperfect etc.,and contra indicated in pregnant woman , osteomalacia, chronic renal diseases etc.²

Bps are developed in the middle of 19th century. Before invading into in the medical field, their non medical use was to prevent the scaling in pipes by inhibiting calcium carbonate precipitation in the textile, fertilizer and oil industries³. Later they were introduced as an additive for tooth paste [anti tartar agent] to reduce dental decay⁴.

Bps shares a common chemical structure, in which two PO₃ (phosphate) groups are bonded to carbon atoms. Bps are analogs of inorganic pyrophosphate.^{5,6} but instead of central oxygen molecule , Bps contain carbon as a core molecule , which allows a great number of possible disparities . The long (R₂) side chain determines the potency of the drug, while the short (R₁) side chain influences the chemical properties and pharmacokinetics⁷. (Fig.1).

There are mainly '2' sub classes of Bps; they are Non-Nitrogenous Bps and Nitrogenous Bps. Non-nitrogenous Bps includes 1st generation (etidronate, clodronate) category. They incorporated into non-hydrolysable analogues of ATP, interfering with ATP-dependent pathways and resulting in osteoclast apoptosis.³

Nitrogenous Bps includes 2nd generation (pamidronate, alendronate) and 3rd generation (risedronate, zoledronate) sub groups. These are more potent than non nitrogen-containing Bps. They inhibit osteoclast farnesyl pyrophosphate synthase (FPPS) and prevent protein prenylation required for the formation of GTPases required by the osteoclast. Tiludronate is a Sulfur-containing Bps. The end result of all Bps is osteoclast apoptosis.⁸

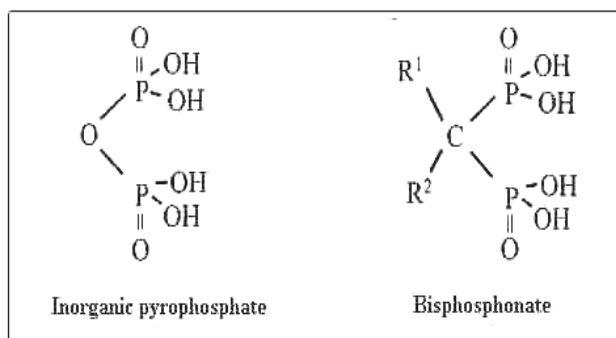


Fig.1. Structure Of Pyrophosphate and Bis Phosphonate

These drugs are given through various routes of administration. Orally administered Bps have very least bioavailability (1-10%), where as I.V administered have maximum availability (upto 50%). The available Bps in blood stream 30-70% is absorbed in the bone, rest excreted through kidney.⁹ The absorbed Bps are accumulated 10times greater in alveolar bones around the teeth when compared with other bones, this could be due to remodeling which occurs as a continuation process during mastication in jaws.^{10,11}

Bps play a very important role in general dentistry as well as in orthodontic discipline. The action of these drugs prove to have wide spread effect on oral structures there by resulting in conditions deterrent to effective dental treatment. To enumerate these side effects one has to scrutinize each system of dentistry in detail along with orthodontic speciality.

Bisphosphonate Associated Osteo Necrosis [BON]/ Osteonecrosis Of The Jaws [ONJ] / Bisphossy Jaw.

The highest risk of BON appears to be associated with duration (Monthly/Yearly), form of administration (IV Route) and dosage (High/Low) of the drug¹². The first report of osteonecrosis of the jaws [ONJ] linking with usage of bisphosphonate was documented in 2003¹. Bps has anti-angiogenic properties that inhibit endothelial growth factor which prevents angiogenesis, thereby, decrease capillary formation leading to poor healing

ability.¹³ Thus bone loses its vascularity and leads to a condition called BON. Predominantly BON is confined to the human jaws due to constant high level bone turnover when compared with other bones and these patients have compromised blood supply in their jaws due to occurrence of ischemic changes.^{14,15,16} The mandible is more commonly affected than the maxilla (2:1), and 69% of cases are preceded by dental invasive procedures. Other than oral surgical invasive procedures there are other potential co morbidities which may be affiliated in the formation of BON in bisphosphonate users. Mainly these co morbidities are steroid therapy¹⁷, uncontrolled diabetes mellitus and environmental factors like chronic smoking¹⁸. Generally maxillae get affected with multi focal or bilateral involvement and in the mandible, frequently lesions are found near the lingual aspect of mylohyoid ridge.¹⁹ American Society for bone and mineral research recently proposed a definition for BON i.e. "an area of exposed bone in the maxilla facial region that does not heal within 8 weeks after recognition by a medical practitioner in a patient who is under bisphosphonate therapy or has been exposed to a bisphosphonate and has not had radiation therapy to the cranio facial region."²⁰

About 94% of BON cases are associated with IV bisphosphonates and less common with oral administrations. Among these 85% of patients were being treated for multiple myeloma or metastatic breast cancer with IV bisphosphonate along with chemotherapy.^{21,22} Possible signs and symptoms include pain, swelling, paresthesias, suppuration, soft tissue ulceration, intra- or extraoral sinus tracks, and loosening of teeth.²³ BON may or may not be painful and may or may not be progressive. Many lesions do not heal or heal slowly; in few cases healing has been reported.²⁴

The tendency to develop BON may be investigated by analyzing fasting serum- CTX [C -terminal telopeptide] which reveals the risk of developing BON and categorized into 3 classes.; they are higher risk (serum -CTX less than 100 pg /ml) ; moderate risk (serum - CTX 100-150pg/ml) ; minimal risk (serum - CTX greater than 150 pg/ml)²⁵. These values may be used as indicator to commence any surgical invasive procedures. Before commencing any general dental procedures or orthodontic treatment it is suggested that serum - CTX levels should maintain towards minimal risk side and also "Drug holiday" (temporary cessation of bisphosphonate therapy) may be advised in such patients with the concern of a physician.

Management of BON

Till date there is no uniformly acceptable regime established for the treatment of BON in patients receiving Bp therapy. Surgical debridement, bone curettage, local irrigation with antibiotics and hyperbaric oxygen therapy are often employed^{26, 23}.

All these procedures have limited benefits to improve the condition and even temporary termination of Bp therapy may not improve the condition. The bacterial superimposition on necrotic bone leads to sequestra

formation. The surgical debridement and sequestrectomy along with antibiotic therapy are also not a satisfactory approach to improve the condition²⁷.

Various treatment protocols have been outlined, but trials and outcomes of treatment and long-term follow-up data are not yet available.²⁸

The policy "Prevention is better than Cure" can be applied for Bp users because the treatment response is unsatisfactory. So, preventive measures are to be followed to minimize/avoid the risk of developing BON.

Extractions - Extractions are very common procedures done in the dental office on a regular basis but a patient undergoing long-term Bps therapy is more prone to develop BON due to decreased vascularity in their jaws and also compromised healing which may get infected following extraction and may progress into osteomyelitis and later into BON^{29,30}. In such conditions extractions should be avoided. If at all extraction is unavoidable prophylactic antibiotic therapy is recommended. Extraction could be done by vertical splitting of tooth thus minimal open extraction wound is left out³¹. Also, instead of forceps extraction, slow extraction technique has been advocated by using separating elastics for few weeks to enhance atraumatic exfoliation with minimal wound opening³².

Periodontics - Bps have paradoxical effects in the oral cavity; having potential beneficial effects on periodontal bone, whilst also increasing the risk of BON³³. The significant alveolar bone reduction and improved periodontal clinical parameters have been demonstrated in clinical cases of Bp users.^{34,35} Contrastly two clinical studies are reported with no improvement in periodontal clinical parameters.^{36,37} Thus the effects of Bps on periodontium are somewhat inconclusive whether beneficial or not. But the periodontal diseases which are in demand of invasive procedures may increase the risk of rising BON.

Implants - Implants and its usage is gaining popularity and rapidly growing in modern dentistry which needs to be understood effectively. There are two schools of thought. In one study Bps have shown positive effect by forming adequate bone volume around the implant,^{38,39} whereas another study has shown failure of osteointegration.⁴⁰ Topical application of Bps enhanced implant base and increased bone volume.⁴¹ However, the present ideology is to avoid implants in patients with long term bisphosphonate therapy in order to reduce the risk of BON.

Prosthodontic Issues - In general noninvasive prosthodontic (removable partial/complete denture) treatment procedures are preferable for patients who are associated with bisphosphonate therapy, in need of prosthetic appliances. These non invasive methods may also provoke the formation of BON, because the pressure or injury caused by sharp edged dentures or ill fitting dentures may cause laceration of the oral mucosa in which these patients have already compromised blood

supply in their jaws.⁴² In order to overcome these risks irregular/ sharp edged dentures are smoothen or immediately replaced with new dentures or in few instances advised to avoid dentures or they should be fabricated precisely and seated in the oral cavity without any disturbance.

Clinical Issues of Orthodontic Specialty

The prime importance of Bps comes into play in the field of orthodontics because now a day's adult orthodontic treatment is widely practiced and day-by-day all over the world the demands for such treatments are raising among the general population. It is therefore highly essential for an orthodontist to know how these drugs would react to tooth movement and its overall influence on orthodontic treatment outcome. These drugs may have favorable effects and unfavorable effects on orthodontic tooth movement, few studies have put into perspective about the pro's and con's of these drugs.

Unfavorable Orthodontic Issues - The most important orthodontic problem encountered with this drug is hindrance of tooth movement. Patients suffering from Osteoporosis have reduced alveolar bone height, therefore the centre of resistance of the tooth shifts apically and there by the movement increases.⁴³ Yamashiro et al stated that there is increase velocity of tooth movement in osteoporotic induced rats.⁴⁴ Therefore patients with Osteoporosis may have greater relapse tendency, conversely patients who are on Bp therapy may have the opposite effect. In experimental rats with Bp therapy along with orthodontic intervention was observed that there is 40% retarded tooth movement for a period of three weeks.⁴⁵ Increased duration of orthodontic tooth movement and limited bodily tooth movement were also reported in bisphosphonate users under orthodontic treatment.⁴⁶ In these patients extreme difficulties may be encountered during retraction of teeth followed by extraction space closure, because Bps have antiosteoclastic effect which may obstruct orthodontic tooth movement; this was explained by radiographs with radio opaque sclerotic lines around the roots of teeth close to extraction sides.⁴⁷ Thus space closure is achieved by tipping instead of bodily movement.

Favorable Orthodontic Issues - Following the principle of 'Necessary Evil', Bps though retard tooth movement could be affectively utilized in a favorable manner by inhibiting undesirable tooth movement which is essential in orthodontic anchorage. This drug has a positive role when induced locally where the tooth is meant for anchorage there by creating an effective anchorage system. It could also be used to prevent relapse tendency followed by orthodontic correction.^{48,49} In young patients with Bp therapy so far sign of BON was not reported. In these subjects therapeutic extractions for orthodontic treatment may not be contraindicated.⁵⁰ Bps may be used for peri-implant defects to promote osseointegration,⁵¹ this may be favorable attempt for placement of micro implants utilized for enhancing orthodontic anchorage, but still very less data is available to substantiate this issue.

Orthodontic Recommendations for patients on Bp therapy

It is highly in the interest of an orthodontist to understand what are the protocols need to be followed when selecting, dealing and treating a patient on bisphosphonate therapy. So far there is no clinical scientific data that has been announced where a patient under Bps therapy associated with orthodontic intervention has emerged with BON. But still an orthodontist should always monitor such patients with conscientious follow-ups in order to avoid the risk of BON. For these patients who are in demand of orthodontic therapy, we are proposing few recommendations based on the previous available scientific literature and also the potential risk factors of Bps.

Majority of these recommendations are not evidence based but definitely, perhaps these could be taken as preventive measures which may be helpful to orthodontic practitioners when they come across Bps users for orthodontic intervention.

1. The orthodontic treatment is initiated only after thorough counseling of patient and discussion with Oncologist or Physician in order to reduce the risk and enhance the benefit to the patient. Strictly the risk of BON should be intimated to Bps users, who are ready for orthodontic intervention.
2. In mild to moderate crowding cases, inter proximal disking might be preferred as a method of gaining space instead of extraction. It is healthier to discourage extraction orthodontic therapy in these cases. If at all extraction is unavoidable, it may be cautiously permissible in younger patients but to be avoided in adult patients. Extraction therapy may be considered in adults under oral Bps therapy but not at all in patients under I.V therapy.
3. Adjunctive orthodontic minor surgical procedures [Ex: frenectomy, exposure of impacted tooth etc] and major surgeries [Ex: orthognathic surgeries] should be avoided. If at all minor surgery is compulsory, it may be considered for oral bisphosphonate users and not for I.V users.
4. If any delayed orthodontic tooth movement is observed, then check radio graphically for sclerotic areas/ hyper mineralized areas and also periodontal status which should be monitored clinically. If at all sclerotic areas are encountered 'DRUG HOLIDAY' [temporary discontinuation of drug prior to three months of appliance placement and or throughout the duration of orthodontic treatment] may be considered. In some circumstances treatment may be discontinued.
5. If at all fixed appliance is needed in these subjects few modifications may be advisable in routine orthodontic procedures in order to keep the mucosal intact without disruption., they are
 - During molar banding, the band material may impinge the gingiva. Molar bands are avoided

and bondable tubes may be beneficial to prevent any sort of injury to mucosa.

- Minimize or avoid the usage of ligature wire, instead elastic modules or elastic threads are chosen for ligation.
 - Lingual appliance may not be advisable because of the difficulty in oral hygiene maintenance and associated gingival inflammation.
 - Avoid usage of TPA and Nance palatal arch in these cases because these components may injure palatal mucosa.
6. Children under Bps therapy suffering from osteogenesis imperfecta, requiring functional correction, activator and/or bionator therapy may not be viable because these appliances may cause pressure on palatal and lingual mucosal surface. So, functional correction may be discouraged and camouflage management may be executed.
 7. During retention phase Hawley's or Begg's retainers may be discouraged for these patients even though fabricated passively. Irritation or trauma from these appliances on mucosal tissue of the palate and lingual mandibular surfaces may intensify the risk of BON. Lingual bonded retainers or invisible retainers may be reasonable for these patients.
 8. Placement of micro implants for the purpose of orthodontic anchorage may be discouraged in order to avoid the potential risk of BON. If at all placement of micro implant is obligatory it can be carried out in patients consuming oral Bps but not in patients on I.V Bps. Micro implants may be denied in elder patients and may be considered in younger patients.
 9. Generally orthodontic patient should be reviewed every month for follow ups. But orthodontist should pay additional attention for these patients and review at least twice in a month to monitor the tooth movement whether proceeding normally or delaying and also customarily monitor the periodontal status clinically as well as radiographically.

CONCLUSION

It is highly evident that the number of adult patients suffering from various bone disorders will be on a rise and these patients seeking orthodontic treatment will be a major consideration to tackle by clinicians. Thus there are few major key points that one should be aware. The principle of "conservative approach" should always be advocated in general dentistry practice when treating such patients.

Clinically when these patients approach an orthodontist, a thorough examination should be done during the very first visit itself. The clinician should bring out the most viable orthodontic treatment modality under the consultation of a physician as well as to modify the treatment plan when ever required. 'Drug Holiday' policy may be enforced at least during the period of orthodontic treatment.

Finally various experimental procedures are being conducted on different animal models regarding the quality

of anchorage that is developed by using Bps and other drugs like NSAID's^{52,53} when administered locally. However lots of research needs to be carried out in this field before preceding effective and safe human trials.

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