



# BISPHOSPHONATES IN DENTISTRY AN ASIAN PERSPECTIVE – EVIDENCE BASED REVIEW

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## ABSTRACT

Bisphosphonates are drugs with high affinity to bone, which accumulates in the bone matrix for a longer time and affects bone turnover. These are commonly prescribed in the management of malignant metastatic bone disorders and for several benign conditions such as osteoporosis and Paget's disease. The objective of this review is to provide a comprehensive report on the drug bisphosphonate, clinical applications and its potential adverse effects, with special focus on Asian literature. Frequencies of patients who are on bisphosphonates are increasing in dental clinics these days. However regarding the use of this drug and its clinical implication from Asian countries are sparse, presumably due to under-reporting of cases or possibly wrong diagnoses. Hence we have made an attempt to reinforce the existing knowledge about this topic in Asian context along with latest information for the readers.

**Key Words:** Bisphosphonates, osteonecrosis of the jaws, Asian perspective, Dental uses, Periodontitis.

## INTRODUCTION

Dental clinicians have a distinctive and obligatory responsibility to treat the patient as a whole, not just the dental concern. Hence thorough medical histories are of paramount importance, which allows the clinician to identify systemic diseases and take necessary precautions during dental treatment. Further it is a good routine to elicit drug history at every dental visit of the patient<sup>1</sup>.

Patients on bisphosphonates [BPs] are increasingly seen in the dental clinics<sup>2</sup>. These patients should be informed about the possibility of osteonecrosis of the jaws following any form of oral surgical procedures.

The reported cases of osteonecrosis from Asian countries are sparse. Is it because of inherent protection of population against osteonecrosis or under-reporting of the cases or wrong diagnosis? This review discusses comprehensively about the drug bisphosphonate and its pharmacotherapeutics, clinical uses and potential adverse effects with special focus on Asian literature.

## CLASSIFICATION OF BISPHOSPHONATES

BPs are classified as Nitrogen and non-nitrogen containing<sup>2, 3,4</sup>.

**Table 1: Classification of Bisphosphonates**

| Non nitrogen containing             | Nitrogen-containing                   |                             |
|-------------------------------------|---------------------------------------|-----------------------------|
|                                     | Alkyl-amino group                     | Heterocyclic Nitrogen group |
| Clodronate, etidronate, tiludronate | Pamidronate, alendronate, ibandronate | Risedronate, zoledronate    |

**Dosage:** Dosage of the drug depends on the route of administration and duration<sup>5,6</sup>

**Table 2: Oral Bisphosphonates**

| Drug        | Trade name *  | Daily | Weekly | Monthly |
|-------------|---|-------|--------|---------|
| Alendronate | Ralenost, zo-phost, restofos, poronil, denfos, osteofos, fosa-max | 10mg  | 70mg   | -       |
| Risedronate | Gemfos, actonel   | 5mg   | 35mg   |         |
| Ibandronate | Bonviva   | 2.5mg | -      | 150mg   |

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**Table 3: Intramuscular Bisphosphonates**

| Drug        | Trade name*    | Regimen                   |
|-------------|----------------|---------------------------|
| Clodronate  | Bonefos, Loron | 200mg 'twice a month'     |
| Neridronate |                | 25mg/12.5mg every 2 weeks |

**Table 4: Intravenous Bisphosphonates**

| Drug        | Trade name*                         | Regimen   |
|-------------|-------------------------------------|---|
| Ibandronate | Bonviva                             | 3mg every 3 months                                    |
| Pamidronate | Aredi, aredronet, bonapam, pamidria | 60-90mg over 2 to 4 hours per month                   |
| Zoledronate | Aclasta, zolasta, zobone, blaztere  | 4mg over 15 minutes, if necessary repeat after 7 days |

\*Available in India

Novel synthetic bisphosphonate: Disodium dihydrogen-4-[(methylthio) phenylthio] methane bisphosphonate [TRK-530]: has an antioxidant methylthio-phenylthio group in the R2 side chain and has both anti-resorptive and anti-inflammatory effect<sup>9</sup>.

### Mechanism of action of bisphosphonates

Bone is a dynamic hard tissue undergoing constant remodelling. During bone resorption, bone morphogenetic protein and insulin growth factors are released which direct the migration, differentiation and osteoid production of new bone from local and circulating stem cells.<sup>10</sup>

Most commonly used BPs is nitrogen containing, which are extremely bone selective. The basic action of BPs is to inhibit bone resorption, turnover and renewal, thus reducing serum calcium levels. They bind to the mineral crystals on bone surfaces and a repeated dose accumulates in the bone matrix. During the bone remodelling BPs are released from the bone surface and are internalized by osteoclasts. This affects the protein prenylation which is important for the activity and survival of osteoclasts, subsequently leading to apoptosis.<sup>5,11,12</sup>

## THERAPEUTIC USES

### MEDICAL APPLICATIONS

The earliest medical applications of bisphosphonates were in the treatment of Fibrodysplasia ossificans progressiva, in patients who had undergone total hip replacement surgery and for bone imaging. Subsequently

**Table 5: Summary of Mechanism of Action of Bisphosphonates**

|                 |   |
|-----------------|---|
| Tissue level    | 1. In bone metabolic units, there is positive focal bone balance – formation exceeding resorption and thus reduction in bone turnover   |
| Cellular level  | 1. Decrease in the recruitment and number of osteoclasts<br>2. Osteoclasts inactivation<br>3. Shortening of life span of osteoclasts through apoptosis<br>4. Increase in the number and differentiation of the osteoblasts<br>5. Stimulation of osteoblasts to produce osteoclast inhibitory factor<br>6. Decrease in the release of cytokines by macrophages |
| Molecular level | 1. Inhibits mevalonate pathway resulting in apoptosis of the osteoclasts<br>2. loss of osteoclastic activity due to disruption of the function of post-translational prenylation of key regulatory proteins such as guanosine triphosphate [gtp] binding proteins[rab, rho, rac]<br>3. Down regulation of MMPs  |

it became treatment of choice in various bone diseases, such as Paget's disease, osteolytic bone diseases, osteoporosis,<sup>13,14,15,16</sup> hypercalcemia of malignancy and in metastases of malignant tumours, further this was applied in paediatrics in the management of brittle bone disorders and osteogenesis imperfecta.<sup>13</sup> Finally interesting observations such as antiparasitic and analgesic effects are found with BPs.

## PERIODONTAL APPLICATIONS:

The potential dental applications of BPs have been explored not only for the treatment or prevention of periodontal bone loss but also as a diagnostic aid to detect bone loss associated with periodontal disease and cessation of bone loss following treatment. However this application did not come into routine use for reasons possibly related to cost, accessibility and full-body irradiation due to intravenous administration.<sup>3</sup>

The anti-resorptive effects of systemic<sup>3,8,17-23</sup> and topical<sup>24-30</sup> BPs have been applied in the management of periodontitis.<sup>31-33</sup> Takaishi Y et al 2001 reported clinical effect of etidronate 200 mg daily for two weeks, followed by off-periods of 10 weeks or more for 2-3 years and suggested marked improvement in the appearance of gingival tissue, depth of periodontal pockets and radiographic

appearance of alveolar bones. They concluded that the effect may be owing to the anti-resorptive and the anti-inflammatory action of etidronate.<sup>34</sup> On the contrary Graziani F 2009 conducted a study to determine the efficacy of adjunctive short term intramuscular neridronate in non surgical periodontal therapy and found no additional short term improvements in periodontal conditions of chronic periodontitis patients when compared to periodontal treatment alone.<sup>8</sup>

A Chinese report in 2011 summarized the mechanism of bone regulation and local delivering system of BPs in the management of peri-implant bone loss and suggested that calcium phosphate ceramics, polylactic acid, fibrinogen film and collagen membrane can be used as BPs carriers<sup>35</sup>

Sharma A and Pradeep A R 2012 conducted series of studies with the objective of assessing the clinical efficacy of 1 % alendronate gel as local drug delivery agent in adjunct to mechanotherapy in the treatment of chronic periodontitis, chronic periodontitis with diabetes mellitus, aggressive periodontitis, and in the treatment of degree II furcation involvement. The results of these studies indicated probing depth reduction, attachment gain and improved bone fill.<sup>24,25,28,30</sup>

Basma Mostafa et al 2012 conducted a study to evaluate the combined effect of systemic bisphosphonates, calcium and vitamin D supplements along with surgical periodontal therapy on the alveolar bone in osteoporotic post menopausal females with chronic periodontitis. They found that this combination showed better improvement in treatment outcomes as in clinical and radiographic parameters.<sup>36</sup>

**Bisphosphonate coating on dental implant surface:** The BP coated implants have been studied to investigate its effects on osseointegration.<sup>37-40</sup> Yoshinari M<sup>41</sup> 2002 conducted a study to evaluate the bone response to titanium implants coated with thin calcium-phosphate followed by bisphosphonate and they concluded that there was highest percentage of bone contact with these test implants group compared to the control group, suggesting the promotion of osteogenesis on surfaces of dental implants

Despite the listed applications in dentistry the usage of BPs is not popular, possibly because of the major adverse effects as osteochemonecrosis. Although the local delivery of BPs in the management of periodontitis and peri-implantitis are reported, these needs to be interpreted with caution as there are very few reports to support this mode of delivery and also there were no reports on short and long term soft and hard tissue adverse effects, besides most of the data are from few centres. Hence

further long term, multicentre, multiethnic, prospective studies should be encouraged.

The comparison of Asian studies<sup>24, 28, 30, 22</sup> with that of western studies<sup>23, 42,19,39,40, 43</sup> are outlined in table 6, which focuses only on human studies.

## TOXICITY:

Bps have been reported to cause several adverse effects such as skeletal and non skeletal. Although skeletal adverse effects as BRONJ has drawn major attention, there are non skeletal effects such as oesophagitis like symptoms, oesophageal cancer, fever, flu like symptoms, potential renal failure, risk of atrial fibrillation, cardiovascular and valvular calcifications with iv and oral bisphosphonates. However few of these non skeletal adverse effects have not been reported in Asian literature.

The most sinister skeletal adverse effect of BPs is BRONJ, bisphosphonate related osteonecrosis of the jaws. Patients may be considered to have BRONJ if they have exposed bone in the maxillofacial region for atleast 8 weeks are currently on or have taken bisphosphonates and have no history of radiotherapy to the jaws<sup>44</sup>

The risk factors for developing BRONJ can be systemic and local. The systemic factors such as malignancy, patients on long term concurrent corticosteroid therapy, reduced immunity as in diabetics and smokers. In addition the route of administration, dose and potency of BPs predisposes the patient to develop BRONJ.

Further the local risk factors as dentoalveolar surgeries with osseous modifications in areas of thin mucosa overlying tori and mylohyoid ridge and patients with dental abscesses who are on iv bisphosphonates are susceptible to BRONJ.

## Incidence of BRONJ:

Patients undergoing oral bisphosphonate therapy are at a considerably lower risk for BRONJ than oncology patients on monthly IV bisphosphonates. The incidence of BRONJ in patients on oral BPs varies from 0.01 to 0.04%<sup>45</sup> the incidence of BRONJ in patients with IV bisphosphonates is about 0.8-12%<sup>45</sup>.

The incidence of BRONJ in Asian population was unknown till 2010. The first few reported cases of BRONJ in Asia were from South Korea. W.Park.N et al 2010<sup>46</sup> reported 5 cases of BRONJ caused by oral BPs in Asian population. Authors concluded that irrespective of race elderly women undergoing steroid therapy have an increased incidence of BRONJ even with oral BPs. Another

**Table 6: Periodontal applications – Asian and Western literature**

| Year - published                            | Type of evidence | Type of bisphosphonate | Duration  | Dosage and route    | Dental application  | Reported adverse events | Randomization and Blinding                                    | Number of cases                   | Advantages  | Disadvantages   |
|---|------------------|------------------------|---|---------------------|---|-------------------------|---|-----------------------------------|---|---|
| ASIAN<br>Anuj Sharma and A R Pradeep - 2012 | Type I           | Nitrogenous            | Single application – evidence of drug in GCF till one month | 1% alendronate gel  | Local drug delivery in intrabony defects as an adjunct to mechanical therapy in generalized aggressive periodontitis patients | Nil                     | Randomization-computer generated system<br>Double blind study | 17 cases – 52 intrabony defects   | Highest level of evidence. Systemic administration of antibiotics - avoided. Clinical and radiographic parameters are assessed  | Short term follow up, Single centre study, No bone turnover bio-marker was assessed                                       |
| ASIAN<br>Anuj Sharma and A R Pradeep - 2012 | Type I           | Nitrogenous            | Single application  | 1% alendronate gel  | Local drug delivery in intrabony defects as an adjunct to mechanical therapy in chronic periodontitis                         | Nil                     | Randomization -   | 73 patients -66 intrabony defects | Highest level of evidence. Clinical and bone fill parameters are assessed 'concept of bio adhesion or muco adhesion ' was suggested Drug release profile in GCF was checked           | 6 months follow up Single centre study, no bone turnover marker was assessed.   |
| ASIAN<br>A R Pradeep et al - 2012           | Type I           | Nitrogenous            |   | 1 % alendronate gel | Local drug delivery as an adjunct to mechanical therapy in patients with chronic periodontitis with diabetes mellitus         | Nil                     | Randomization?<br>Double blind                                |                                   |   | Authors suggest adverse effects were recorded at recall intervals, however the nature of adverse events are not mentioned |
| ASIAN<br>Pradeep A R et al 2013             | Type I           | Nitrogenous            | Single application  | 1%alendronate gel   | Local drug delivery as an adjunct to SRP in class II furcation defects  | Nil                     | Randomization – computer generated tables.<br>Double blind    | 69 class II furcation defects     | Highest level of evidence<br><br>Local delivery of drug<br>Clinical and radiographic parameters assessed<br><br>Follow up of one year<br>Adverse effects recorded at recall intervals | Single centre   |

Table 6: (Continued)

|         | Year - published                              | Type of evidence                             | Type of bisphosphonate | Duration                                   | Dosage and route   | Dental application             | Reported adverse events          | Randomization and Blinding          | Number of cases  | Advantages   | Disadvantages   |
|---------|---|--|------------------------|--|--|--------------------------------|----------------------------------|-------------------------------------|--|--|---|
| ASIAN   | Reddy GT et al 2005 [only abstract available] | Combination of in vitro and in vivo          | Nitrogenous            | In vivo study was carried out for 6 months | Alendronate gel in 3 different concentration                         | Local drug delivery            | Not available                    | Information not available           | Information not available  | Combination of in vitro and in vivo study<br><br>Pharmacokinetics of the drug was assessed   | Single centre   |
| Western | Jeffcoat MK et al 2007                        | Type I                                       | Nitrogenous            | Two years                                  | 70 mg once weekly  | Systemic (oral) administration | No adverse effects were reported | Randomization – Double blind        | Total 335 cases randomly assigned to bisphosphonate or placebo group | Highest level of evidence<br><br>In patients with lower mandibular bone mineral density at baseline: BP significantly reduced bone loss compared to placebo<br><br>Authors reported no BRONJ and upper gastrointestinal disturbances | Single centre<br><br>Systemic administration of BPs for long duration |
| Western | Lane N et al 2005                             | Type I – Randomized placebo controlled study | Nitrogenous            | 12 months                                  | Alendronate 10 mg per day and Risedronate 5 mg per day for 12 months | Systemic (oral) administration |                                  | Randomization - Double masked study | Total 70 patients randomly assigned to test and placebo group        | Highest level of evidence<br><br>Bone mass was assessed with dental radiographs using fractional analysis and digital subtraction radiography  | Single centre<br><br>Systemic administration of BPs for long duration |

Table 6: (Continued)

|         | Year - published    | Type of evidence                             | Type of bisphosphonate    | Duration       | Dosage and route   | Dental application   | Reported adverse events | Randomization and Blinding      | Number of cases | Advantages  | Disadvantages                         |
|---------|---------------------|--|---------------------------|----------------|--|--|-------------------------|---------------------------------|-----------------|---|---------------------------------------|
| Western | Reddy MS et al 2003 | Type I – systematic review                   | Information not available | Not applicable | Not applicable   | Systemic administration  | Not available           | -                               | -               | Highest level of evidence<br>This review focused on 2 groups:<br>Effects of host modulation agents in patients with periodontal diseases<br>Effects of host modulation agents on dental implant success | -                                     |
| Western | Abtahi J et al 2010 | Pilot study                                  | Nitrogenous               | Not applicable | Coating of dental implants with bisphosphonate in a fibrinogen matrix      | Pamidronate and ibandronate coated dental implants                                     | No complications        | Not applicable                  | 5 cases         | First human study assessing the stability of bisphosphonate coated dental implants  | This is a pilot study                 |
| Western | Abtahi J et al 2012 | Type 1 - Randomized clinical trial           | Information not available | Not applicable | Coating of dental implants with two bisphosphonates in a fibrinogen matrix | bisphosphonate coated dental implants  | No complications        | Randomization - double blinding | 16 cases        | Paired dental implant placement in maxilla<br><br>Better Implant stability quotient [ISQ] levels were shown in this study for coated dental implants  | Single centre<br>Short term follow up |
| Western | Rocha et al 2001    | Type I – randomized placebo controlled trial | Nitrogenous               | 6 months       | 10 mg daily systemic (oral)  | In type 2 diabetics with periodontal disease along with mechanical periodontal therapy | Not reported            | Randomization –double blind     | 40 cases        | Biochemical marker for bone resorption and digital radiographic were assessed   | Single centre<br>Short term study     |

retrospective study conducted by Hong JW 2010,<sup>47</sup> suggested the prevalence of BRONJ to be 0.05 to 0.07%. The authors concluded that the prevalence of oral BRONJ in Korea is similar to that reported previously in Western populations.

The BRONJ is clearly an uncommon complication of oral BP administration, however the sheer volume of prescriptions of this drug throughout Asia may mean that many cases are likely to present in future.

The summary of incidence of BRONJ in Asian literature<sup>46-49</sup> and comparison with that of western literature is outlined in table 7. Although the reported incidence of BRONJ in western literature<sup>50-54</sup> is more, we have outlined only a few, as it is beyond the scope of this review to list them all

### Aetio-pathogenesis of BRONJ:

The incidence of BRONJ is more in jaw bones compared to rest of the skeleton owing to its vascularity. However this view has been challenged by Bauss F and Pfister T, 2008<sup>55</sup> suggesting similar uptake of ibandronate by spine, femur and jaw bones. Hence the aetiology for BRONJ remains unclear. The alternative explanation could be the initiation of BRONJ is in the mucosa rather than in bone. This view has been supported by Landesberg 2008,<sup>56</sup> who showed pamidronate inhibits oral keratinocyte wound healing. Further Kim et al 2011<sup>57,58</sup> in their in vitro study showed that BPs can cause aging of keratinocyte and result in defective re-epithelialisation inside the mouth and they hypothesised that this could be contributing factor towards poor mucosal healing.

Primarily the action of BP is said to be on bone cells<sup>3</sup>. However few reports suggests bps inhibit angiogenesis by hampering vascular endothelial growth factor and also endothelial proliferation, thus reduced capillary tube formation, vessel sprouting and loss of blood vessel resulting in avascular necrosis. However the anti angiogenic property of BPs has been challenged by a histological study who reported normal vascularity in bones exposed to BPs<sup>4,59,60</sup>

**CLINICAL FEATURES:** BRONJ can be presented in various forms such as unexplained pain, numbness, altered sensation to frank necrosis of the bone depending on the severity of the condition. The procedures such as placement of dental implants, minor oral surgical procedures, periodontal non surgical and surgical procedures and ill-fitting dentures can lead to BRONJ.<sup>6</sup>

Frequently non healing sockets presentation following extraction is common.<sup>6</sup>

### Clinical features of BRONJ:

- Pain
- Swelling
- Evidence of infection: purulent discharge
- Ulceration
- Extra and intra oral sinus tracts
- Possible Involvement of anatomical structures such as maxillary sinus, zygoma, ramus and inferior border of the mandible
- Mobility of teeth
- Denuded bone
- paraesthesia

**Box 1:** Clinical Features of Bronj:<sup>4,61,44,46, 62</sup>

### Diagnosis of BRONJ:

Several investigative procedures are available for detecting early BRONJ [see box 2], yet there are no confirmatory tests available till date. The lab based investigation such as tissue biopsy is useful to rule out the possibility of metastatic malignant lesions. In addition panoramic radiographs may also be useful in cases of suspected metastases, though they are non specific. If there is a sequestrum shown on the radiograph this could help to differentiate from metastatic lesions.

### Investigations:

#### Lab based:

- CTX-1 [carboxy-terminal cross linked telopeptide of type 1 collagen
- Tissue biopsy

#### Panoramic radiographs

#### Imaging techniques:

- CT
- CBCT
- MRI

#### Functional/physiological tests:

- Technetium -99 radioisotope scintigraphy
- Positron emission tomography

**Box 2:** Investigations

**Table 7: BRONJ: Asian and Western literature**

|         | Year - published  | Type of evidence   | Type of bisphosphonate | Duration              | Dosage and route                | Type of dental treatment performed | Prevalence     | Randomization and Blinding | Number of cases                                       | Advantages   | Disadvantages  |
|---------|---|--|------------------------|-----------------------|---------------------------------|------------------------------------|----------------|----------------------------|---|--|--|
| ASIAN   | Hong J W et al 2010 – South Korea [only abstract available] | Type II – Retrospective review   | Not available          | 5 to 120 months       | Oral route dosage not mentioned | Not mentioned                      | 0.05 to 0.07 % | NA                         | 24 Cases  | Superior hierarchy of evidence<br>Retrospective observational study<br>First report in Asia                      | Not the highest level of evidence, the type of bisphosphonate used was not available |
| ASIAN   | W.park et al 2010 –South Korea                              | Type IV – Report of 5 cases  | Nitrogenous            | 5 to 10 years         | Oral route                      | Extractions, dental implants,      | NA             | NA                         | 5 cases   | Details of location of the BRONJ and concurrent medication such as prednisolone was mentioned                    | Not the highest level of evidence  |
| ASIAN   | Kwon T G et al 2012 – South Korea [only abstract available] | Type III – Two groups: patients with BPs before and after dental implant placement | Not available          | Not available         | Not available                   | Placement of dental implants       | NA             | NA                         | 3 cases of BRONJ out of 16 patients who were on BPS   | Histological features of the lesions are mentioned such as “en block sequestration of bone with implant          | Not the highest level of evidence.<br>Concurrent medications were not mentioned      |
| ASIAN   | Yamazaki T et al 2012 – Japan [only abstract available]     | Type II – cohort   | Not available          | Not available         | Intravenous route               | Extractions                        | 3.9%           | NA                         | 5 cases BRONJ out of 126 patients who were on BPs     | Good level of evidence   | Concurrent medications were not mentioned  |
| Western | Assaf AT et al 2013 -Germany [only abstract available]      | Type II - retrospective  | Not available          | 80 months             | Intravenous route               | Not mentioned                      | 8.9%           | NA                         | 15 cases of BRONJ out of 169 patients who were on BPs | First of its kind to address the existing comorbidities and medications, underlying disease and specific therapy | Type of dental intervention was not mentioned  |
| Western | Ulmner M et al 2013 – Sweden [only abstract available]      | Survey – 2007 and 2008   | Not available          | Not known             | Oral bisphosphonates            | Not known                          | -              | NA                         | 69 cases BRONJ out of 100,000 patients -year          | Large sample size  | Not the highest level of evidence.   |
| Western | Edy Braun, Vincent J Lacono, 2006 - USA                     | Case report – type IV evidence   | Nitrogenous            | Approximately 8 years | Intravenous zolendronate        | Non surgical periodontal therapy   | NA             | NA                         | Single case report                                    | This report suggested even non surgical periodontal therapy can be a potential risk for developing BRONJ         | Not the highest level of evidence.   |

Table 7: (Continued)

|         | Year - published            | Type of evidence                                     | Type of bisphosphonate | Duration | Dosage and route                  | Type of dental treatment performed | Prevalence | Randomization and Blinding | Number of cases    | Advantages   | Disadvantages                                    |
|---------|-----------------------------|--|------------------------|----------|-----------------------------------|------------------------------------|------------|----------------------------|--------------------|--|--|
| Western | Bedogni A et al 2010 -Italy | Case report –type IV evidence                        | Nitrogenous            | 6 years  | Oral bisphosphonate - Alendronate | Placement of dental implant        | NA         | NA                         | Single case report | In addition to panoramic radiograph, the technetium Tc 99m scintigraphy labeled granulocytes was utilized as a part of investigation               | Not the highest level of evidence                |
| Western | Wang H L et al 2007         | Case report and literature review – type IV evidence | Not known              | >10 yrs  | Oral bisphosphonate               | Placement of dental implant        | NA         | NA                         | Single case        | This case report discusses the management of osteonecrosis using systemic antibiotics, local microbial mouthrinse and aggressive defect management | Single case<br>Not the highest level of evidence |

Table 8: Staging of Bronj

| Stage | Symptoms  | Clinical Findings   | Treatment   |
|-------|---|---|---|
| 0     | <b>Non specific symptoms:</b> Unexplained pain in the jaws, radiating to TMJ and maxillary sinus wall, not related to odontogenic cause.<br><br>Altered neurosensory function | <b>Non specific findings:</b><br>1. Mobility of teeth unrelated to periodontitis<br><br>2. Periapical/periodontal fistula unrelated to caries   | Conservative symptomatic management with special focus on caries and periodontal disease                                    |
| 1     | Asymptomatic  | Exposed bone with no infection  | Chlorhexidine gluconate 0.12%, No surgical intervention indicated   |
| 2     | Painful presentation  | Erythema around the exposed necrotic bone with or without evidence of infection   | 0.12% chlorhexidine gluconate with systemic antibiotics based on microbial culture and sensitivity results.<br>Pain control |
| 3     | Symptomatic –painful  | Exposed necrotic bone with evidence of infection with one or more of the following:<br>1. Exposed bone extending to involve surrounding anatomical structures such as maxillary sinus, zygoma, inferior border and ramus of the mandible, consequently pathological fractures of the jaws.<br><br>2. Extra-oral fistula<br><br>3. Oro-antral fistula<br><br>4. Oro-nasal communication<br>5. Osteolysis extending into maxillary sinus or inferior border of the mandible | 0.12% chlorhexidine gluconate, systemic antibiotics, debridement or resection may offer long term palliative care           |

**Table 9: Dental Management of Patients Who are Starting or Who are Already Receiving Bisphosphonate Therapy**

| Procedures             | Oral bisphosphonate therapy   | Intravenous bisphosphonate therapy   |
|------------------------|---|--|
| NON-INVASIVE: ACCEPTED | <ol style="list-style-type: none"> <li>1. Comprehensive oral evaluation, preventive programs: caries control and oral prophylaxis.</li> <li>2. Orthograde root canal therapy</li> <li>3. Managing dental infections non surgically</li> </ol> | <ol style="list-style-type: none"> <li>1. Comprehensive evaluation and preventive programs: caries control and oral prophylaxis and patient education and motivation</li> <li>2. Orthograde root canal therapy</li> <li>3. Use of denture liners in denture wearers</li> </ol> |
| SURGICAL               | Unavoidable extractions can be carried out atraumatically, after informing the patient the risk of BRONJ and appropriate consent is obtained  | Elective dental procedures such as Periodontal surgery, dental implants, orthodontics, periapical surgery and extractions are not recommended.   |

**Differential diagnosis<sup>58</sup>:**

The diagnosis of potential BRONJ case needs the elimination of other possibilities such as Osteoradionecrosis, infectious osteomyelitis, neuralgia induced cavitation osteonecrosis, bone tumours, periapical pathology due to carious lesion, periodontal disease causing exposure of bone but with no history of bisphosphonate use, mucositis.

**“Concept of drug holiday”<sup>74,58,45,63</sup>**

Temporarily withdrawing BPs for the purpose of reducing the risk of BRONJ following dental extractions has been recommended. Drug holiday can be three months before and after the extraction, with physician’s approval. Besides the dental purpose this concept has place even to reduce the non skeletal adverse events.<sup>64</sup>

**Management of patients with established BRONJ:<sup>6,62,65</sup>**

The exposed and sharp edges of necrotic bone should be debrided under local anaesthesia, If associated with infection, such as erythematous tender areas with suppuration &/or sinus tracts, systemic antibiotics are administered.<sup>59,66</sup>

The management of these patients may range from pain control till surgical resection of the jaws. Teeth with extensive carious lesion should undergo endodontic therapy instead of extraction. The endodontically treated teeth can be used as an abutment for over denture.

Grade III mobile teeth can be extracted atraumatically and the patient should be followed up weekly for the first four weeks, then monthly until the sockets are healed and also there could be an indication for the empirical use of systemic antibiotics. Amoxicillin is the drug of choice, however the combination of amoxycillin & / clindamycin could offer extra benefit of bone penetration and wider spectrum of activity.<sup>60</sup>

**PRINCIPLES IN THE CLINICAL USE OF BISPHOSPHONATES:****Pre treatment evaluation**

Patient should be assessed by dentist before starting of the BP therapy. This requires communication between the physician/oncologist, patient and the dentist. As per the western literature about 41%<sup>45</sup> of physicians warn their patients about the risk of BRONJ and Asian literature does not provide any data on this issue.

**Benefits and risks:<sup>45,65,67</sup>**

The issue of BRONJ must be dealt with caution as we cannot ignore the beneficial effects of bisphosphonates, such as prevention of morbidity and mortality in osteoporotic patients. Besides in-vitro research has suggested the bisphosphonates may have anti-tumour effects in breast cancer, prostate and lung cancers via alteration of adhesion of malignant cells to the extracellular matrix.

Alternative bone modifiers may be considered, however their costs, potential adverse effects and the suitability influence the final decision

**Alternative bone modifiers:**

Denosumab<sup>58</sup> is a monoclonal antibody, acts on the RANK ligand system, thus inhibiting osteoclastic resorption<sup>68</sup>. Stopeck A T 2010<sup>69</sup> conducted a randomized double blind study and found that denosumab compared to zoledronic acid reduced events such as skeletal fractures.

Teriparatide [PTH 1-34]<sup>68</sup> is a synthetic parathyroid hormone with anabolic effects on the bone. Although the net effect of excess PTH is to induce bone resorption, in low and intermittent doses it promotes bone formation by indirectly involving insulin growth factor 1, without stimulating bone resorption.<sup>70</sup>

Raloxifene is a selective estrogen-receptor modulator, which retains the beneficial effects on bone without deleterious effects on breast and uterus. This is approved for treatment of osteoporosis<sup>68,71</sup>

Strontium ranelate is composed of an organic ion, ranelic acid, bound to two atoms of strontium. This acts by blocking osteoclast differentiation and induces apoptosis and thus inhibiting bone resorption<sup>68</sup>.

To conclude, there are plenty of evidence to suggest that bisphosphonates are used extensively by physicians and oncologists. In addition therapeutic application in dentistry have also been explored in invitro, animal and human studies. This review focussed on human studies alone. Available Asian literature based on randomized controlled clinical trials on the local drug delivery have shown promising results. However there is lack of evidence on the systemic use of bisphosphonates in the treatment of periodontal disease.

Further, there are very few Asian literatures regarding BRONJ. This could be due to lack of communication between dentists and medical specialists. In our view pre-treatment dental evaluation must be made mandatory and perhaps some guidelines by Asian authorities across the continent would be useful in assessing the incidence of BRONJ and prevention of the same

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