Mode of Actions of Bisphosphonates in Dental Implant Procedure: An Overview

Krishna Nanda[1], Gopal Krishna Choudhury[2], Rasmita Kumari Samantaray[1], M. Krishna[1], Sneha Bharadwaj[1]

[1]Post Graduate Trainee, [2]Professor and Head, Department of Prosthodontics, Crown & Bridge, Institute of Dental Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India

Abstract

Bisphosphonates (BP) are the most commonly used drug forthe past few years for the treatment of various types of bone disorders and malignancies**.** Osteonecrosis of the jaw (ONJ) is most devitalizing but still not has been properly acknowledged as of now. These drugs suppress bone turnover by decreasing osteoclastic activity**.** This article points in featuring the key and pharmaco-physiological system of activity of both N2 and non N2 bisphosphonates on bone and activity of bisphosphonates on dental implants, particularly their commitment in success of the implant and the present suggestions and rules for implant treatment in patients who are on bisphosphonate therapy**.** This article also includes the prevention and management for decreasing the cumulative IV bisphosphonate dose, stoppage of bisphosphonates before any invasive dental treatment, and in ONJ using serum beta-CTX-1 in assessment of risk. "Drug Holiday" for the invasive dental procedure is incorporated as well.

Keywords: *Bisphosphonate, Dental implants, osseointegration, osteonecrosis, BRONZ.*

Introduction

"Bisphosphonates (BP)",since years is been used to treat diseases such as "osteoporosis, Pagets' disease, hypercalcemia in malignancy, osteolytic lesions of multiple myeloma and bone metastasis associated with breast, prostate, lung and other soft tissue tumours". Their mode of action is osteoclastic inhibition and synthetic biochemical modification of bone resorption.[1]

There are two method of drug intake, oral and intravenous route. Systemic administration i.e. (Intravenous) bisphosphonates, is more potent than orally administered. The potency of the drug does not depend upon the mode of delivery rather depends upon the existence of the N-H group to the basic P-C-P structure. Due to the good binding affinity to the minerals, they are appropriate therapy for skeletal disorder where bone metabolism is high. It decreases osteoclastic actions by stimulating osteoblasts and afterward suppresses bone remodeling and turnover. N2 containing and non N2 containing are the two varieties of BP.[2]

According to some hypothesis, action of BP on the oral mucosa, specifically to the oral epithelium, keratinocytes, macrophages and fibroblasts is impaired oral wound healing.[30-35] Ill-fitting dentures cause BRONZ of the jaw without any surgical injuries, which further hinder angiogenesis continuing to avascular necrosis.

Many side effects are also reported due to long term use of BP, which may be a matter of concern regarding the safety issue of the drug. Patients, who are prescribed with BP may require implant therapy. Therefore it is necessary to know the effects of these drugs on osseointegration and implant survival & success rates.[3,4]

History of BP: BP was used in the textile, fertilizer and oil industries when it was synthesized in Germany

Corresponding Author:
Dr. Krishna Nanda
Post Graduate Trainee, Department of Prosthodontics, Crown & Bridge, Institute of Dental Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India
e-mail: krishnananda09@gmail.com

in 1865. In an in vitro study,Herbert Fleisch and colleagues found the role of inhibition of inorganic pyrophosphates (PPi) for the dissolution of calcium phosphate in plasma and urine. Severe mineralization defects of the skeleton were found in 1964 due to high PPi levels in urine. An in vivo study has shown that the compound prevented ectopic calcification; it did not have any effect on resorption of bone and normal mineralization. Pyrophosphate used in scintigraphy and dental calculus as therapy. Bisphosphonates have empathy for mineralization of bone, it additionally represses the arrangement and conglomeration of calcium phosphate crystals as PPi.Early studies indicate that bisphosphonates also can inhibit the dissolution of hydroxyapatite crystals. It is discovered in the early 1990s the potency of the drug is mainly depend upon the Nitrogen compound present in its structure.[5]

Chemical Confugaration Nitrogen Containing BP: The drug potency is increased by the alteration in the chemical structure that is the peripheral or side chain of the central carbon atom and N2 group in the R2 position and it is also done by adding alkyl and amine groups to R1 side chain for chain elongation. This helps to maintain the calcium-binding affinity through the OH group in the R1 position.When hydroxyl or amino group present in one side chain, it increases Ca binding affinity, due to tridentate conformation.[6]

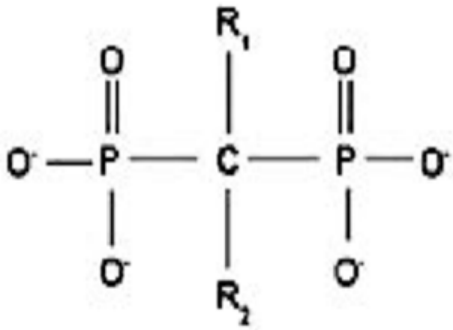

Figure 1. Bisphosphonate

Mechanism of actions: Osteoclastic bone resorption is inhibited by osteoclast-mediated BP internalization due to which there is decreased osteoclastic activity. Two types of mechanisms are there, one is cellular, and the other is biochemical. They help in decreasing skeletal resorption and turnover.

Non-N2 containing bisphosphonates (Cellular Mechanism): First-generation BPs (clodronate and etidronate) resembles to the PPi. They reverse the activities of aminoacyl-tRNA synthases through metabolically incorporated into nonhydrolyzable cytotoxic ATP analogs as pyrophosphate. The derived metabolites which should consist of β, γ-phosphate groups of ATP, but it contains P-C-P structure, which is non-hydrolyzable. These metabolites get accumulated intercellularly, which inturn hinders the functions of osteoclast. They interrupting with mitochondrial ATP-translocases resulting in osteoclastic cell mortality. So the cell death of osteoclast due to BP causes resorption of bones.[7]

N2-containing bisphosphonates and "Mevalonate biosynthetic pathway" (Biochemical): In the mevalonate pathway, farnesyl diphosphate and geranylgeranyl diphosphate proteins are biosynthesized. The amide group-containing BPs are inhibitors of the biosynthetic pathway. In the case of post-translational prenylation of small GTPases such as Rho, Rac, RAS, the above proteins are required. The Rho and Rac proteins are activated through geranylgeranylation, so that it helps organize the cytoskeleton and ruffling of the cell membrane. The "ruffled border" is important because it helps in the attachment to bones and destroys the bone tissue. When the ruffled border diminished, then automatically it turns into osteoclastic cell death. Ultimately there is a reduction in bone turnover. N2 containing bisphosphonates create disruptions in osteoclastic functions, the morphology of cells and cytoskeleton, which fails in the sealing zone and ruffling of membrane, apoptosis and also trafficking of vesicles.[8]

According to **Elliott Ballantyne** Sealing zone consists of

1. Ruffled border
2. The basolateral domain
3. The functional secretory domain

Prolonged Effects of BPs: BPs has long-term effects on decreasing bone turnover. Some BPs (eg. alendronate and zoledronate) act more prolonged than others (etidronate and risedronate). The rate of resorption and fracture is less even after the discontinuation of the drug for a longer period. Also the disadvantages of the drug may take a long duration to go away. BPs are inserted in the skeleton, which are liberated in future cycles of resorption. It implies prolonged and steady removal of all BPs from the bones. Some study reveals that the elimination of alendronate in humans is so slow that it can take up to 12 years. [9,10]

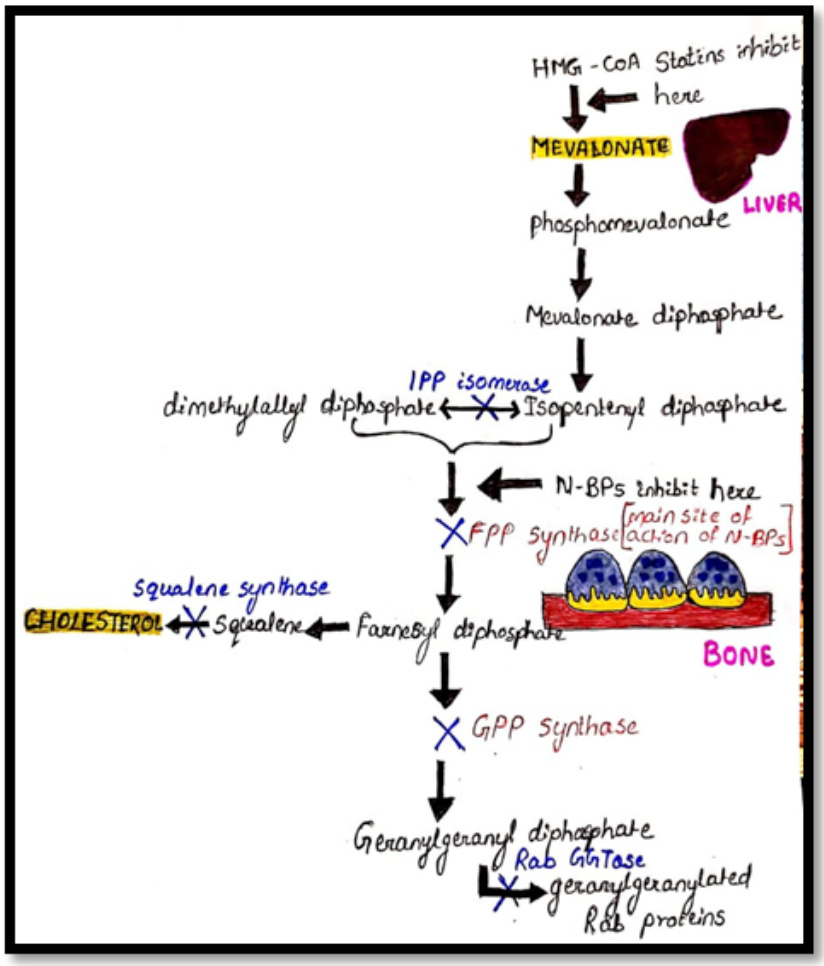

Figure 2. Mevalonate biosynthetic pathway

Why BP Deposition is higher in Jaws: Bisphosphonates are useful for metabolism in bones of the body however in the event of BRONZ of the jaw the most common site is in the maxilla and mandible. It is said that the thinner the mucosa over the bone, the higher the rate of deposition of the drug. So, jaws containing less than 5mm mucosal layer are more favourable than the other bones of the body.

As indicated by certain investigations that the alveolar crest get remodeled at a higher rate of 10 times quicker than the tibia, 5 times quicker than the inferior border of the mandible and 3 - 5 times the rate of the mandible at the Inferior Dental canal and jaws and collect a higher rate of concentration of bisphosphonates because of the alveolar ridge remodeling at rapidly.[11]

Effects of BP in "Angiogenesis and vasculogenesis": For the local immunity, tissue homeostasis and regeneration, sufficient blood supply and new vascularisation is fundamental. The veins in bones and the cells in the endothelium are significant in bone development and resorption. The Angiogenesis and vasculogenesis both are different.

Angiogenesis is defined as "the sprouting from pre-existing vessels of mature endothelial cells". Vasculogenesis is "the formation of new primordial vessels from bone marrow-derived, circulating endothelial progenitor cells". [12]

Some studies concluded that the N containing bisphosphonates like zoledronate inhibits angiogenesis. In some in vitro studies after using human umbilical cord vascular endothelial cells (HUVEC) it is found that zoledronate inhibits the production of HUVEC and it is dose depending upon the dose. Zoledronate inhibits integrins (α5β3 and α5β5), which helps in the

formation of a blood vessel by endothelial cell adhesion and migration.

In some in-vitro studies, it is mentioned that the endothelial cell proliferation and migration are become impaired after administration of zoledronate. RANKL is suppressed resulting in deterioration cellular mechanism by bisphosphonates. [13]

Tissue healing around the implant: Fundamentally wound healing process around dental implants is significant and important for implant to survive. It involves delicate tissue recuperating and hard tissue mending around the implants.After osteotomy and placement of an implant, the delicate soft tissue ought to be sutured appropriately with the goal that it must seal the blood coagulation and save the zone from bacterial colonization. There should not be any tension present in soft tissue during primary wound closure. A series of processes goes on during healing at the implant site like the development of blood clot, fibroblast, macrophage activity, and epithelial proliferation which is associated with primary osteoid formation, called primary stability of the implant. [14]

As there is suppression of endothelial cell proliferation and interruption in angiogenesis and vasculogenesis the tissue healing around the implant becomes delayed after administration of BP.Primary stability is one of the key factors for the survival of the implant.That is why in case of a patient taking BP the survival of the implant is a questionable matter. [15]

Failure of implant: Failure of an implant can be defined as "the first instance in which the performance of an implant fails to meet the criteria for success". The indication like implant mobility, vertical bone loss greater than 0.2 mm, bleeding pockets that are greater than 5 mm are observed when evaluated clinically. Implant failure is further classified as early or late failures, depending on whether they occur before or at abutment connection or after occlusal loading following the prosthetic restoration. Early implant failure results due to the inability of the implant to establish an intimate bone contact. Evidence says BP interrupts in osseointegration by the formation of fibrous connective tissue around the implant results in early failure. Late failures occur during functional loading and cause periimplantitis. BP has a significant role in late failures as well as it is compromising the wound healing.[2]

Laboratory Marker: During bone formation, resorption and turnover C-telopeptides (CTx) fragments of collagen are liberated. Because BPs decrease CTx levels, it is also well believed that evaluating serum CTx levels is a reliable indicator for risk assessment. The "CTx test, also known as C-terminal telopeptide and collagen type 1 C telopeptide is a serum test obtained in laboratories or hospitals.[16]

Oral Bisphosophonate Use >3 Years

1. Physician approval to discontinue bisphosphonates 3 months before sugery and 3 months after sugery ("drug holiday").
2. Determine serum CTx levels during initial consultation and immediately before surgery; CTx levels must be >150 pg/mL before proceeding with surgery.
3. Detailed informed consent for bisphosphonate-associated osteonecrosis.

Oral Bisphosophonate Use <3 Years without Clinical or Radiographic Risk Factors

1. Serum CTx level must be >150 pg/mL.
2. Proceed with surgery with detailed informed consent for bisphosphonate-associated osteonecrosis.
3. If serum CTx level <150 pg/mL, institute a physician approved "drug holiday"; continue monitoring every 3 months until CTx levels >150 pg/mL.

Oral Bisphosophonate Use <3 Years with Clinical or Radiographic Risk Factors

1. Physician-approved "drug holiday" for 3 months.
2. Serum CTx level must be >150 pg/mL to proceed with detailed informed consent for bisphosphonate-associated osteonecrosis.
3. If serum CTx level <150 pg/mL, continue monitoring every 3 months until CTx level >150 pg/mL.

Figure 3. According to Carl E Misch Protocol, suggestions and assessments for patient taking oral BP

CTx Value (pg/mL)	Risk for Osteonecrosis
300-600 (normal)	none
150-299	none to minimal
101-149	Moderate
< 100	High

Figure 4. Laboratory Risk Assessment

Discussion

A Review of this literature throws light on relative risk associated with the use of bisphosphonates and implant therapy**.** There are many case report and literature which expresses that utilization of bisphosphonate medication may promptly lead to failure of implant therapy in patients especially those accepting intravenous bisphosphonate treatment, while another review contemplates have shown that there might be a danger of osteopathology in patients getting oral bisphosphonates and dental implant treatment. According to **BRONJ** "it is a potential complication that may lead to implant failure. It is also important to distinguish that implant failure may occur without the presence of any clear pathology due to a loss of osseointegration in patients being treated with this group of drugs. This is believed to be the result of reduced bone turnover due to diminished osteoclastic activity".[17] "In the first reported case series it has found the occurrence rate of BRONJ was at about 70% after tooth extraction or other dentoalveolar surgical procedures such as periodontal surgery and dental implant placement."

According to **Vescovi et al**. "36.2% rate of incidence of BRONJ in a non-surgery triggered group compared to 63.8% rate of incidence in a surgery triggered group. [63] They also stated that intravenous bisphosphonate therapy for underlying malignant disease is an absolute contraindication for the placement of dental implants, whereas implants can be placed in patients receiving oral bisphosphonates for those treated for osteoporosis". [18]

According to **Elliott Ballantyne** "the association between oral bisphosphonate therapy and dental implant failure". [2]

In a systematic review by **Javier Ata-Ali et al**, it was discovered that the position of dental implants in patients treated with bisphosphonates doesn't decrease the implant success rate. On the contrary, it can't be said that such patients are not without difficulties and hazard evaluation. Therefore it is decided by the singular premise".[19]According to **Hom-Lay Wang et al** "bisphosphonates may play a role in wound healing and suggested that if there is compromised healing it can be successfully treated with systemic antibiotics, local microbial mouthrinse and aggressive defect management". [20]**Yip JK et al** 2012 did a study and found that the use of oral bisphosphonates at the time of implant placement was associated with dental implant failure. Specifically, the use of bisphosphonates among women were almost three times greater than other counterparts.[21]

According to **A Cheng et al** "placement of implants in patients on bisphosphonates does carry a small but defined risk. The long-term management strategy for the patient's underlying condition needs to be discussed with the patient's medical practitioner and informed consent of the risk needs to be provided. Patients with previously placed implants who subsequently are placed on the bisphosphonates need to be carefully monitored. Aggressive surgical salvage procedures are best avoided as these will probably decrease failure".Thought of bisphosphonate tranquilize occasion or elective clinical administration of their bone disorder ought to be talked about with the treating clinical expert and after that implant treatment ought to be effectively carried out. [22]

Conclusion

It is concluded that patients taking bisphosphonates by intravenous method should not be considered for the placement of dental implants. Patients under oral bisphosphonates can be chosen for the dental implants but before the surgery the protocol has to be followed.

Funding Statement: None

Conflict of Interest: None

Ethical Permission: Approved

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