

## Bisphosphonate-Related Osteonecrosis of the Jaw: An Enigma among Medical Practitioners

### Abstract

**Context:** Owing to the increasing number of cancer cases, and introduction of newer drugs like bisphosphonates (BP) for the management of metastatic bone disease, complications such as bisphosphonate-related osteonecrosis of the jaw (BRONJ) have come into light. However, several of the treating physicians are not fully aware of this adverse effect. **Aim:** This study aimed to assess the knowledge and awareness of physicians regarding BRONJ and practices related to bisphosphonate use. **Settings and Design:** A cross-sectional study conducted among health-care professionals in various medical institutions in Mangalore. **Subjects and Methods:** A questionnaire was developed to assess the knowledge and awareness of physicians about osteonecrosis of the jaw and practices related to bisphosphonate use, consisting of 21 questions, 12 – knowledge based and 9 – practice based. The questionnaire was validated and distributed among 113 doctors; their responses assigned scores, tabulated and assessed. **Statistical Analysis:** One-way analysis of variance and Tukey test. **Results:** More than 50% of the medical professionals had a score <40%, which shows a lack of knowledge about BP and BRONJ. About 45% of the medical professionals in the study group failed to identify the clinical features of BRONJ, and 67.26% were unaware of the risk associated with tooth extractions and oral surgical procedures in the development of the condition. **Conclusion:** Bisphosphonate-related osteonecrosis is almost exclusively seen in the jaws and hence, the diagnosis usually made by a dental practitioner. Lack of awareness of jaw osteonecrosis among the medical practitioners can result in delay in providing the right treatment.

**Keywords:** Awareness, bisphosphonate-related osteonecrosis of the jaw, bisphosphonates, osteonecrosis, physicians

### Introduction

Over the years, several developments in the field of oncology have dramatically changed the course of the disease and improved the survival and quality of life of patients, who were once considered incurable. The advances in the imaging modalities help in early detection of metastatic disease so that aggressive therapeutic regimens are instituted even in Stage IV disease. Several agents have been introduced to reduce the skeletal morbidity of metastatic bone disease, among which bisphosphonates (BP) play a major role. BP are antiresorptive agents that have been used for more than a decade, for the treatment of metabolic bone diseases, such as osteoporosis and osteopenia, and to control the skeletal complications associated with metastatic bone disease.<sup>[1]</sup> Despite their proven efficacy as antiresorptive

drugs, a devastating side effect, “bisphosphonate-related osteonecrosis of the jaw” (BRONJ), has been documented over the past decade.<sup>[2,3]</sup> Marx reported the first case in 2003,<sup>[4]</sup> following which several cases of osteonecrosis have been reported.<sup>[5,6]</sup> The American Association of Oral and Maxillofacial Surgery (AAOMS) in its position paper in 2014<sup>[7]</sup> recommended changing the nomenclature of BRONJ to medication-related osteonecrosis of the jaw (MRONJ) due to the growing number of reports of cases of osteonecrosis associated with other antiresorptive and antiangiogenic medications. AAOMS defined BRONJ as “exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than eight weeks in a patient with current or previous history of bisphosphonate therapy and no history of radiation therapy or obvious metastatic disease to the jaws.”<sup>[7]</sup>

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

**How to cite this article:** Krishnan S, Shetty V, Shetty J, Babu GS, Rajeev TP. Bisphosphonate-related osteonecrosis of the jaw: An enigma among medical practitioners. Indian J Med Paediatr Oncol 2019;40:257-64.

**Shalini Krishnan,  
Vijith Shetty<sup>1</sup>,  
Jayarama Shetty<sup>2</sup>,  
Gogineni Subhas  
Babu<sup>3</sup>,  
TP Rajeev<sup>4</sup>**

Departments of Oral and Maxillofacial Surgery and <sup>3</sup>Oral Medicine and Maxillofacial Radiology, A. B. Shetty Memorial Institute of Dental Sciences, Nitte University (Deemed to be), Departments of <sup>1</sup>Medical Oncology and <sup>4</sup>Urology, <sup>2</sup>Professor and HOD of Radiation Oncology, K. S. Hegde Medical Academy, K. S. Hegde Charitable Hospital, Nitte University (Deemed to be), Mangalore, Karnataka, India

### Address for correspondence:

Dr. TP Rajeev,  
Department of Urology, K. S. Hegde Charitable Hospital, Nitte University (Deemed to be), Mangalore - 575 018, Karnataka, India.  
E-mail: rajeevtp@yahoo.com

### Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo\_20\_18

### Quick Response Code:





study population consisted of medical professionals, 68 consultants and 44 residents (one person did not mention his designation), from the specialties of oncology (7), orthopedics (28), urology (13), ENT (11), general medicine (39), and general surgery (15).

The years of experience in the specialty ranged from 1 month to 35 years, with a mean of 5.17 years and a standard deviation of 5.89. The maximum score attained in the knowledge section of the questionnaire was 33 out of 36, and the minimum score obtained was 5. The average score attained was 16 (44.4%) with a standard deviation of 6.17.

In more than 50% of the doctors, the responses to 22 out of 36 items were either wrong or no response marked, which showed lack of knowledge about BP and BRONJ. About 53% of the doctors obtained a score of >50% in the questions on the drug BP, but in the section of BRONJ, 71% of them scored <50%. With regard to BP, 51.3% and 53.1% doctors did not know their use in the treatment of hypercalcemia and bone metastases, respectively. About 63% of the physicians did not know BRONJ as a complication in patients on oral BP, and 76% did not know that BRONJ could occur in patients with a history of BP therapy. BRONJ was considered, as a self-limiting condition by 76% and 83.2% believed that it regresses after stoppage of BP therapy, and 60.2% did not consider it to be a challenging condition to treat. BRONJ could be treated medically alone was the assumption of 77% of the physicians. 45% of the medical professionals in the study group failed to identify the clinical features of BRONJ, and 67.26% were unaware of the risk associated with tooth extractions and oral surgical procedures in the development of the condition.

Based on the response to the practice-based questions, it was found that among the doctors who see 5–10 patients/month on BP, 69.2% got a score <50% and only one secured >80%. Majority of them got a score <40%; four out of seven doctors who see more than 10 patients/month on BPs secured <50%.

The comparison of the scores obtained by the consultants and residents was done using the unpaired *t*-test, the significance set at the level of 0.05. *P* value obtained was 0.046, and therefore, it was found that there was a difference between the knowledge scores of consultants and residents at 5% level of significance [Table 1].

The mean scores in each specialty were obtained, and comparison of the scores in each specialty was performed using the one-way analysis of variance [Table 2]. The results showed that the highest mean score obtained was by the oncologists (23), followed by the urologists (20), orthopaedicians (18), general surgeons (13.7), general physicians (13.69), and the ENT surgeons attained the least score (12).

The comparison of the specialties, with respect to the scores attained in the knowledge questionnaire, was carried out using the Tukey test, with the significance set at 0.05 [Table 3]. There was no significant difference between the scores obtained by the urologists and the oncologists. It was found that there was a significant difference between the scores obtained by the specialists in urology, and the specialties of ENT (*P* = 0.004), general medicine (*P* = 0.002), and general surgery (*P* = 0.018). A significant difference was also noted between the knowledge scores of oncology, and that of ENT (*P* = 0.001), general medicine (*P* = 0.001), and general surgery (*P* = 0.004). There was also a significant difference between the mean scores of the orthopedicians and the ENT surgeons (*P* = 0.027), and the specialists in general medicine (*P* = 0.017).

Questions based on practice revealed that osteoporosis and metastatic cancer were the indications for BP in the patients seen by these professionals, intravenous was the most common route of administration, and cancer chemotherapy was the concomitant drug therapy in the majority of them.

**Table 1: Comparison of knowledge scores obtained by consultants and residents**

Designation	<i>n</i>	Mean score	SD	<i>t</i>	<i>P</i>
Consultants	68	16.8824	6.73492	2.018	0.046
Residents	44	14.6364	5.01667		

SD – Standard deviation

**Table 2: Comparison of mean knowledge scores according to specialty by using one-way analysis of variance**

Specialty	<i>n</i>	Mean score	SD	<i>F</i>	<i>P</i>
Oncology	7	23.0000	7.09460	8.050	<0.001
Urology	13	20.3846	6.34479		
Orthopedics	28	18.0714	5.27698		
General surgery	15	13.7333	3.36933		
General medicine	39	13.6923	5.76356		
ENT	11	12.0909	3.75379		

SD – Standard deviation; ENT – Ear-nose-throat

**Table 3: Multiple comparison of knowledge by using Tukey test**

Specialty	Specialty	Mean difference	<i>P</i>
Urology	ENT	8.29371	0.004
Urology	General medicine	6.69231	0.002
Urology	General surgery	6.65128	0.018
Orthopedics	ENT	5.98052	0.027
Oncology	ENT	10.90909	0.001
Orthopedics	General medicine	4.37912	0.017
Oncology	General medicine	9.30769	0.001
Oncology	General surgery	9.26667	0.004

The mean difference is significant at the 0.05 level.

ENT – Ear-nose-throat

## Discussion

Physicians should inform the patients, in whom bisphosphonate therapy is to be initiated, about the benefits and risks of therapy, including BRONJ. If the systemic condition permits, treatment with BP should be delayed until the dentist evaluates the patient.<sup>[11]</sup> It is recommended that dental surgeons evaluate and treat patients scheduled to receive an intravenous BP, similar to those patients scheduled to initiate radiotherapy to the head and neck. Once bisphosphonate therapy is initiated, the maintenance of good oral hygiene and dental care is of paramount importance in preventing a dental disease that might require dentoalveolar surgery. Stopping BP before invasive dental surgery does not seem to decrease the chance of developing BRONJ given the very long half-life in bone.<sup>[12]</sup> Moreover, oncology patients benefit greatly from the therapeutic effects of BP, because they control bone pain and incidence of pathological fractures and discontinuation of BP at this stage does not offer any short-term benefit.<sup>[11]</sup>

A recent study conducted among Lebanese physicians showed an alarmingly deficient knowledge regarding BRONJ. It was observed that they were unaware that ONJ could be a bisphosphonate-related undesirable event, which is similar to the findings in our study. They had confused ideas regarding the clinical features, diagnosis, and management of the condition. It was recommended that more research should be conducted to better establish the level of knowledge in different settings, and also that international studies with different groups of physicians might help understand, how medical education can be compared in different physician cohorts around the world with regard to this devastating complication.<sup>[13]</sup>

The knowledge of dental professionals and dental students about BP: and BRONJ has been found to be poor as evidenced in a study on Brazilian dentists. They were unable to identify the drugs belonging to the class of BP, their medical indications, and also the risk factors for BRONJ. The findings reflect the lack of awareness and recognition of the importance of awareness.<sup>[14]</sup>

Al-Mohaya *et al.*<sup>[15]</sup> in their questionnaire survey found that physicians and dentists have low awareness and deficient knowledge regarding BRONJ, although most of them do prescribe BP to their patients. Less than one-third of the participants (31.5%) were aware of ONJ. In our study, conducted among medical professionals alone, 71% of the doctors scored <50% in the questionnaire section on BRONJ.

The results of our study are in concordance with a similar study carried out in the North East of England during the same period among general practitioners and pharmacists. There was uncertain knowledge among the participants about BRONJ, its prevalence, the risk factors for its development, and also had limited exposure to the condition.<sup>[16]</sup>

Another questionnaire survey conducted in North Wales among general practitioners and pharmacists, describing their attitudes toward, their perceptions of, and their roles in preventive strategies for BRONJ reported awareness of the side effects of BP; however, only 11.8% of general practitioners (GPs), and 9.7% of pharmacists specifically identified osteonecrosis as a potential unwanted effect of therapy.<sup>[17]</sup>

A recent study was conducted to review legal databases in the USA to research judicial processes against doctors as a consequence of misconduct in the diagnosis and treatment of oral cancer, in addition to inadequate practices with regard to oral side effects caused by oncological treatment and antiresorptive therapies, including BRONJ. The data revealed that one of the highest recoveries was \$10,450,000, which was paid to a patient with breast cancer, who had been under treatment with BP, and the professional failed to recognize the risk for BRONJ. Thus, to minimize the possibility of such processes and financial indemnifications, dental and medical professionals must be trained to identify the oral side effects of certain medications with emphasis on BP. Lack of prevention, recognition, and management of oral complications can lead to medico-legal action.<sup>[18]</sup>

Because ONJ is associated with drugs like bisphosphonate which decrease bone turnover by inhibiting osteoclast, any new inhibitors of osteoclast differentiation and function that enter the pharmacologic armamentarium for the treatment of diseases, with increased bone turnover must be closely studied and observed for potential ONJ as a side effect. Few drugs have been added to the class of drugs associated with ONJ such as denosumab, a human monoclonal antibody which inhibits receptor activator of nuclear factor kappa-B ligand (RANKL), used in the treatment of postmenopausal osteoporosis and metastatic bone cancers; bevacizumab, a vascular endothelial growth factor inhibitor; and tyrosine kinase inhibitors such as sunitinib and sorafenib. Several cases of ONJ have been reported in patients on these drugs. Data are emerging to show that BP or denosumab in combination with targeted antiangiogenic therapies<sup>[19]</sup> increase the likelihood of Medication Related Osteonecrosis of the Jaw (MRONJ). The risk of ONJ in patients on oral BP used for the management of osteoporosis, namely alendronate, ibandronate, and risedronate, is less compared to that with intravenous BP and is estimated to be around one in 10,000/year of use.<sup>[20]</sup>

## Conclusion

The medical practitioners in our study reported uncertain knowledge about the side effects of BP and BRONJ in particular. This could be attributed to BRONJ being a new and rare disease entity, described in the past decade due to the increasing use of BP. Moreover, in this era of subspecialization, the involvement of the primary physicians in advanced cancer care seems to be limited. As dedicated oncology departments are getting established

in most centers in recent years and are involved in upfront chemotherapy, the role of other specialists in managing cancer is limited to the diagnosis and initial management. Lack of tumor board discussions and multispecialty interactions could be a contributing factor to the low level of understanding of this rare side effect of a standard drug therapy.

Bisphosphonate-related osteonecrosis is almost exclusively seen in the jaws and hence the diagnosis usually made by a dental practitioner. Lack of awareness of jaw osteonecrosis among the medical practitioners can result in delay in providing the right treatment and has in a few instances resulted in unnecessary investigations, and biopsies due to misdiagnosis of the condition as a metastatic bony lesion. Hence, a good knowledge of the probable causes and the clinical features can help in the prevention, early diagnosis and prompt management of a not so common complication. Better interaction between the medical and dental fraternity and continuing medical education programs may play a major role in enhancing the knowledge and awareness among medical professionals.

### Acknowledgments

We would like to thank Prof. Dr. P. Venugopal, Emeritus Professor of Urology for his suggestions, comments, and insights. We would also like to extend our gratitude to Dr. Sanal T.S. for helping us with the statistical analysis of our research.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### References

- Coleman RE, McCloskey EV. Bisphosphonates in oncology. *Bone* 2011;49:71-6.
- Migliorati CA, Siegel MA, Elting LS. Bisphosphonate-associated osteonecrosis: A long-term complication of bisphosphonate treatment. *Lancet Oncol* 2006;7:508-14.
- Lenz JH, Steiner-Krammer B, Schmidt W, Fietkau R, Mueller PC, Gundlach KK. Does avascular necrosis of the jaws in cancer patients only occur following treatment with bisphosphonates? *J Craniomaxillofac Surg* 2005;33:395-403.
- Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115-7.
- Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. *J Oral Maxillofac Surg* 2004;62:527-34.
- Watters AL, Hansen HJ, Williams T, Chou JF, Riedel E, Halpern J, *et al.* Intravenous bisphosphonate-related osteonecrosis of the jaw: Long-term follow-up of 109 patients. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;115:192-200.
- Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, *et al.* American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw – 2014 update. *J Oral Maxillofac Surg* 2014;72:1938-56.
- Rabiei S, Mohebbi SZ, Patja K, Virtanen JI. Physicians' knowledge of and adherence to improving oral health. *BMC Public Health* 2012;12:855.
- Melo MD, Obeid G. Osteonecrosis of the jaws in patients with a history of receiving bisphosphonate therapy: Strategies for prevention and early recognition. *J Am Dent Assoc* 2005;136:1675-81.
- Bhatt G, Bhatt A, Dragu AE, Xiao-Feng LI, Civelek AC. Bisphosphonate-related osteonecrosis of the jaw mimicking bone metastasis. *Radiographics* 2009;29:1971-84.
- Abughazaleh K, Kawar N. Osteonecrosis of the jaws: What the physician needs to know: Practical considerations. *Dis Mon* 2011;57:231-241.
- Thumbigere-Math V, Michalowicz BS, Hughes PJ, Basi DL, Tsai ML, Swenson KK, *et al.* Serum markers of bone turnover and angiogenesis in patients with bisphosphonate-related osteonecrosis of the jaw after discontinuation of long-term intravenous bisphosphonate therapy. *J Oral Maxillofac Surg* 2016;74:738-46.
- El Osta L, El Osta B, Lakiss S, Hennequin M, El Osta N. Bisphosphonate-related osteonecrosis of the jaw: Awareness and level of knowledge of Lebanese physicians. *Support Care Cancer* 2015;23:2825-31.
- de Lima PB, Brasil VL, de Castro JF, de Moraes Ramos-Perez FM, Alves FA, dos Anjos Pontual ML, *et al.* Knowledge and attitudes of Brazilian dental students and dentists regarding bisphosphonate-related osteonecrosis of the jaw. *Support Care Cancer* 2015;23:3421-6.
- Al-Mohaya MA, Al-Khashan HI, Mishriky AM, Al-Otaibi LM. Physicians' awareness of bisphosphonates-related osteonecrosis of the jaw. *Saudi Med J* 2011;32:830-5.
- Sturrock A, Preshaw PM, Hayes C, Wilkes S. Attitudes and perceptions of GPs and community pharmacists towards their role in the prevention of bisphosphonate-related osteonecrosis of the jaw: A qualitative study in the North East of England. *BMJ Open* 2017;7:e016047.
- Masson D, O'Callaghan E, Seager M. The knowledge and attitudes of North Wales healthcare professionals to bisphosphonate associated osteonecrosis of the jaws. *J Disabil Oral Health* 2009;10:175-83.
- Epstein JB, Kish RV, Hallajian L, Sciubba J. Head and neck, oral, and oropharyngeal cancer: A review of medicolegal cases. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015;119:177-86.
- Fantasia JE. The role of antiangiogenic therapy in the development of osteonecrosis of the jaw. *Oral Maxillofac Surg Clin North Am* 2015;27:547-53.
- Khan AA, Morrison A, Kendler DL, Rizzoli R, Hanley DA, Felsenberg D, *et al.* Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the International Task Force on ONJ. *J Clin Densitom* 2017;20:8-24.

## Questionnaire\*

**Questionnaire:** Questionnaire tool used for study

**Specialty:** \_\_\_\_\_

**Designation:** \_\_\_\_\_

**Years of Experience in specialty:** \_\_\_\_\_

1) Bisphosphonates (BP) are drugs used to treat:

a) Hypercalcemia of malignancy  Yes/No

b) Osteopenia  Yes/No

c) Bone metastases  Yes/No

2) Which of the following drugs belong to the class of Bisphosphonates?

a) Zoledronic acid  Yes/No

b) Pamidronate  Yes/No

c) Ibandronate  Yes/No

3) How many patients do you see on bisphosphonates per month?

a) <5  Yes/No

b) 5–10  Yes/No

c) >10  Yes/No

4) What is the indication of BP therapy in these patients?

a) Osteopenia  Yes/No

b) Cancer  Yes/No

c) Osteoporosis  Yes/No

5) What is the route of administration of BP in these patients?

a) Oral  Yes/No

b) Intravenous  Yes/No

c) Both oral and intravenous  Yes/No

6) What are the other adjuvant medications in these patients?

a) Steroid  Yes/No

b) Chemotherapy  Yes/No

c) Others  Yes/No

7) Do you examine the oral cavity of patients on BP therapy?  Yes/No

8) Do you recommend dental checkup in patients before BP therapy?  Yes/No

9) Do you recommend regular dental checkups in patients on BP therapy?  Yes/No

10) Have you ever noticed exposed necrotic bone of the jaw among these patients?  Yes/No

11) Which of the following are the adverse effects noted with BP therapy?

a) Bone pain  Yes/No

b) Osteonecrosis  Yes/No

c) Flu-like symptoms  Yes/No

12) Bisphosphonate-induced osteonecrosis is known to occur in the:

- a) Spine  Yes/No
  - b) Jaws  Yes/No
  - c) Ribs  Yes/No
- 13) How many patients have you seen with osteonecrosis as a complication of BP therapy?
- a) 1-5  Yes/No
  - b) 6-10  Yes/No
  - c) >10  Yes/No
  - d) Nil  Yes/No
- 14) Bisphosphonate-induced osteonecrosis can occur in patients:
- a) On oral bisphosphonates  Yes/No
  - b) On intravenous bisphosphonate therapy  Yes/No
  - c) With past history of bisphosphonate therapy  Yes/No
- 15) The following drugs have been implicated to cause osteonecrosis of the jaws:
- a) Denosumab  Yes/No
  - b) Zoledronic acid  Yes/No
  - c) Sunitinib  Yes/No
- 16) The development of bisphosphonate-related osteonecrosis of the jaw maybe:
- a) Spontaneous  Yes/No
  - b) Following surgical procedures in the jaws  Yes/No
  - c) Following dental extractions  Yes/No
- 17) The signs and symptoms of osteonecrosis of jaws include:
- a) Pain  Yes/No
  - b) Exposed bone  Yes/No
  - c) Oro-cutaneous fistula  Yes/No
- 18) Diagnosis of osteonecrosis of jaws is mainly:
- a) Clinical  Yes/No
  - b) Radiological  Yes/No
  - c) Histopathological  Yes/No
- 19) Management of bisphosphonate-induced osteonecrosis of jaws includes:
- a) Medical management only  Yes/No
  - b) Surgical management only  Yes/No
  - c) Combination of medical and surgical therapy  Yes/No
- 20) Bisphosphonate-induced osteonecrosis of jaws:
- a) Is a self-limiting condition  Yes/No
  - b) Regresses after stoppage of bisphosphonate therapy  Yes/No
  - c) Is a challenging condition to treat.  Yes/No
- 21) Bisphosphonate-induced osteonecrosis of jaws can be prevented to a large extent by:

- a) Strict oral hygiene measures/practices  Yes/No
- b) Dental checkups/treatment before initiation of BP therapy  Yes/No
- c) Regular dental checkup  Yes/No