Article published online: 2021-06-03

Original Article

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

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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.[1] 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.[2,3] Marx reported the first case in 2003,[4] following which several cases of osteonecrosis have been reported.[5,6] The American Association of Oral and Maxillofacial Surgery (AAOMS) in its position paper in 2014[7] 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."[7]

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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.

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Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_20_18

Quick Response Code:

BRONJ is a relatively new entity, and the treating physicians and even the dental professionals may not be very much aware of this complication in patients on BP. A history of bisphosphonate use for osteoporosis or metastatic cancer should make the dentists wary about the risk of osteonecrosis of jaw (ONJ). The physicians prescribing BP for osteoporosis, metastatic bone disease, or hypercalcemia may not be very observant about the oral health[8] of these patients and complications such as jaw osteonecrosis may go undetected. At the same time, details of bisphosphonate use may not come to the notice of the treating dental professionals, either due to incomplete history or the patient himself being ignorant of the drug, and its possible side effects due to which the history is not contributory. Pathophysiology of BRONJ is still unclear, but poor oral hygiene and oral health and invasive dental procedures have been proposed as risk factors.[9] Hence, good knowledge of the drug, its indications and adverse effects are essential for possible prevention, early detection, and management of this not so common complication. This would help them to identify patients at risk, and educate them about the prevention and management of BRONJ and thus make them aware of the associated signs and symptoms.

In cancer patients, receiving intravenous bisphosphonate therapy, ONJ can be easily mistaken for a metastatic lesion due to its clinical presentation and imaging characteristics.[10] The practicing oncologist, the radiologist, the nuclear medicine specialist, and the dental specialist must all be aware of BRONJ as an entity mimicking bone metastasis. Early recognition will facilitate early diagnosis, minimize the need for biopsies, and multiple unnecessary imaging studies, and most importantly, allow appropriate treatment measures to be initiated. Other health-care professionals such as orthopedicians and general physicians prescribe BP and other antiresorptive agents for osteoporosis and hypercalcemia and hence should be aware of the adverse effects of the drug and the risk factors. The ear-nose-throat (ENT) surgeons and the dental professionals share a common work area, the oral cavity, and hence should be able to identify exposed, necrotic bone or stages leading to it; so that early diagnosis, intervention, and patient education are possible. Our study aimed to assess the knowledge and awareness of physicians regarding BRONJ and practices related to bisphosphonate use.

Subjects and Methods

A questionnaire tool* was developed to assess the awareness of physicians about BRONJ and practices related to bisphosphonate use. The questionnaire consisted of 21 questions, of which 12 were knowledge based and 9 were practice based. Of the 12 knowledge-based questions, three were on BP, and nine on BRONJ. Each question had three to four options and each option had a "Yes" or "No" response.

The questionnaire was assessed by three experts separately for evaluation of its content validity. Each validator was provided with a criteria checklist for validation, where they would rate each question on a scale of "0" to "5," "0" being the least score suggesting inappropriateness of the question and "5" being the best score suggesting it to be most appropriate.

0 1 2 3 4 5

(Inappropriate) (Most appropriate)

The modifications suggested were incorporated and the tool was finalized for the main study.

A pilot study was then conducted among five physicians. The responses were given scores, "1" for correct response and "0" for wrong response in case of the questions pertaining to knowledge assessment; and the responses to the practice-based questions were scored as "1" for "Yes" and "2" for "No."

To calculate the reliability of the knowledge questionnaire, Cronbach's alpha was used. The following formula was used for the calculation:

$$\alpha = \frac{k}{k-1}\left(1-\frac{\sum s_i^2}{s_T^2}\right)$$

Where k is the number of items (37).

S_i^2 is the variance of the "i"th item ($S_i^2 = 7$).

S_T^2 is the variance of the total score formed by summing all the items ($S_T^2 = 55.8$).

Cronbach's alpha = 0.898 (0.9) was obtained which proved the tool to be reliable.

The results of the pilot study conducted were used to calculate the sample size. It was observed that 40% of the physicians in the pilot study had good knowledge (Score ≥29) regarding BP and ONJ. The sample size was then computed using the technique of estimation of proportion:

$$n = \frac{Z^2_{1-\alpha/2}\, P(1-P)}{d^2}$$

Where, α = level of significance = 5%.

- d = precision = 15%
- p = anticipated knowledge = 40%.

The calculated sample size was 41. The questionnaire was distributed among 113 health-care professionals in various tertiary care hospitals in Mangalore; their responses assigned scores, tabulated, and their awareness, knowledge, and practices regarding BP and BRONJ were assessed. The results obtained were subjected to statistical analysis.

Results

The scores were assigned as "0" for wrong response and "1" for correct response. Thus, the maximum possible score in the section on knowledge assessment was 36. The

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	*n*	Mean score	SD	*t*	*P*
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	*n*	Mean score	SD	*F*	*P*
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	*P*
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.[11] 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.[12] 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.[11]

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.[13]

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.[14]

Al-Mohaya *et al*.[15] 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.[16]

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.[17]

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.[18]

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[19] 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.[20]

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.

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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