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Knowledge of dentistry students on bisphosphonate-related osteonecrosis of the jaw

Conhecimento de alunos do curso de Odontologia sobre osteonecrose dos maxilares relacionada ao uso de bisfosfonatos

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ABSTRACT

Objective: Bisphosphonates are anti-resorptive drugs used in the control and treatment of calcium and bone metabolism disorders. Despite their high clinical efficacy, these drugs have been associated with bisphosphonate-related osteonecrosis of the jaw. The goal of this study is to evaluate the knowledge of final year undergraduate dentistry students on bisphosphonate-related osteonecrosis of the jaw. **Material and Methods:** A sample of 100 students from private institutions in the state of São Paulo was invited to complete a questionnaire relating to bisphosphonates and the risk factors associated with the development of osteonecrosis of the jaws. **Results:** 66% of the students did not recognize any bisphosphonate ($p=0.0019$) and 79% did not recognize their trademark names ($p<0.0001$). 60% of the students recognized osteonecrosis of the jaws as a side effect of bisphosphonates ($p<0.0001$) and 56% identified at least one risk factor associated with the drug that may contribute to the side effect ($p<0.0001$). 66% of the students stated that their course did not provide any lectures on the topic ($p<0.0001$). **Conclusion:** The knowledge of dentistry students about bisphosphonates and bisphosphonate-related osteonecrosis of the jaw is variable. This may be related to an inadequate discussion of this topic during their undergraduate studies.

KEYWORDS

Bisphosphonates; Osteonecrosis; Dentistry students.

RESUMO

Objetivo: Os bisfosfonatos são medicamentos antirreabsortivos utilizados no controle e tratamento de desordens do cálcio e do metabolismo ósseo. Apesar da elevada eficácia clínica, a terapia com estes medicamentos tem sido associada a uma importante complicação denominada de osteonecrose dos maxilares relacionada ao uso de bisfosfonatos. O objetivo deste estudo é avaliar conhecimento sobre a osteonecrose dos maxilares relacionada ao uso de bisfosfonatos entre os alunos do último ano do curso de graduação de Odontologia. **Material e Métodos:** Uma amostra de 100 alunos de instituições privadas do estado de São Paulo foi convidada a responder um questionário sobre as principais informações dos bisfosfonatos e fatores de risco associados com o desenvolvimento da osteonecrose dos maxilares. **Resultados:** Os 100 questionários foram respondidos: 66% dos estudantes não reconheceram algum bisfosfonato ($p=0,0019$), 79% não reconheceram seus nomes de marcas comerciais ($p<0,0001$); 60% dos alunos reconheceram a osteonecrose dos maxilares como um efeito colateral dos bisfosfonatos ($p<0,0001$) e 56% apontaram pelo menos um fator de risco associado com o medicamento que pode causar o desenvolvimento do efeito colateral ($p<0,0001$); 66% dos estudantes afirmaram que o curso não forneceu alguma aula abordando esta temática ($p<0.0001$). **Conclusão:** O grau de conhecimento dos alunos de Odontologia sobre bisfosfonatos e osteonecrose dos maxilares relacionada ao uso de bisfosfonatos é variável e está relacionado com a pouca discussão deste tema durante a graduação.

PALAVRAS-CHAVE

Bisfosfonatos; Osteonecrose; Estudantes de Odontologia.

INTRODUCTION

Bisphosphonates (BPs) are a class of drugs that are widely used in the control and treatment of osteoporosis, Paget's disease, osteogenesis imperfecta, osteopenia, multiple myeloma, and malignant hypercalcemia due to bone metastases of some neoplasms[1,2].

BPs are synthetic analogs to pyrophosphate. Pyrophosphate presents as two phosphate groups attached to a central carbon atom which renders the molecule more resistant to enzymatic degradation[2,3]. The R1 and R2 side chains linked to the central carbon define its affinity for bone crystals and antiresorptive acrivity[2,3]. Basically, BPs act by inhibiting the function of osteoclasts, resulting in the suppression of bone remodeling and an increase in bone density[4].

Despite the benefits of BPs, there has been an increasing number of cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in the literature since 2003[5,6]. Several hypotheses have been proposed to explain the pathogenesis of BRONJ, including changes in bone remodeling and the resultant bone sclerosis and ischemia, and the possibility of a toxic effect on oral epithelial keratinocytes[4,6]. Dentoalveolar surgery is considered the main local risk factor for the development of BRONJ, while periodontal diseases and the use of poorly adapted prostheses are considered potential secondary local risk factors[6,7]. The duration of therapy, type of BP, and route of administration are considered risk factors related to BRONJ[7]. Recently, a new nomenclature of medication-induced osteonecrosis of the jaws was adopted due to the increasing number of cases of BRONJ associated with other antiresorptive and antiangiogenic therapies[7]. Among these cases, BPs represent the most important group due to their widespread use. For this reason, we will refer to BRONJ in this study.

Prior to commencing BPs, patients should undergo a detailed dental evaluation followed by the adoption of appropriate dental treatment to decrease the risk of BRONJ[2]. To minimize complications, it is important for dentists to have extensive knowledge of BPs and their potential side effects. Although the first reported case of BRONJ was published more than 10 years ago, only one study in Brazil evaluated the knowledge of dentists and dentistry students on this matter8. This study aimed to evaluate the knowledge of Brazilian students from private dentistry schools on BPs and BRONJ.

MATERIAL AND METHODS

This quantitative-based cross-sectional study was conducted from August to October 2016 with undergraduate dentistry students at the Braz Cubas University (UBC), University of Mogi das Cruzes (UMC), and Cruzeiro do Sul University (UNICSUL) in the state of São Paulo, located in south-eastern Brazil. The study was approved by the Research Ethics Committee of the University of Mogi das Cruzes (opinion number: 1.602.514).

Inclusion criteria were final year undergraduate dentistry students at UBC, UMC, or UNICSUL. Final year students were selected as they should have attended the relevant curricular unit on the topic. A convenience sample of 100 students who voluntarily agreed to participate in the study was asked to sign the informed consent form.

A questionnaire, modified from a reference questionnaire used by other researchers, was used for data collection[8]. The questionnaire consisted of three parts. In the first part, there were questions related to the characterization of the sample, such as the university attended, date of birth, sex, and the period he/she attended. The second part of the questionnaire consisted of 14 objective questions and multiple choices relating to BPs, such as drug names, trademarks, medical indications, and the main actions of BPs. In addition, there were questions that evaluated students' knowledge about the characteristics, risk factors, and prevention strategies of BRONJ. The third part of the questionnaire was used to evaluate the questionnaire per se including the clarity of the questions, the time provided, and the ease of response. The questionnaire was applied by a single researcher and the interviewees were not authorized to consult any source of information during the study.

The data obtained were analyzed. The frequency of the variables investigated in the study was calculated in Excel (Microsoft ™, San Francisco, USA). First, the data were submitted for descriptive analysis. The data obtained from the questions with more than two possible answers were grouped into the categories "correct answer" and "incorrect answers/cannot answer". For each question, the answers were analyzed as means using the chi-square test and a "p-value"

was assigned, indicating whether the frequency of the response was statistically significant. The significance level was set at 5% for all analyses.

RESULTS

Initially, 152 students who met the inclusion criteria were selected. Of these 152 students, 100 agreed to participate in the study, representing 65.75% of the initial population. Among the 100 participants, 75 (75%) were female and 25 (25%) were male. Data relating to the date of birth was not available for 11 (11%) of the students (not provided the information or improperly filled out the date). The average age of 89 (89%) students was 27.64 years, ranging from 20 to 50 years of age.

The results are shown in Tables 1-3.

Table 1 - Knowledge of dentistry students on bisphosphonates and their relevance in anamnesis, the medical indications, and the main mechanism of action

Variable n (%)		Total sample	p-value
Do you know the class of medicines called bisphosphonates?	Yes	59 (59.0)	0.081
	No	41 (41.0)	
Choose the bisphosphonates you know:	CA	34 (34.0)	0.0019*
	DN	66 (66.0)	
What are the trademark names of bisphosphonates you know?	CA	21 (21.0)	<0.0001*
	DN	79 (79.0)	
In the anamnesis, do you consider it important to take into account the patient undergoing bisphosphonate treatment?	Yes	89 (89.0)	<0.0001*
	No	11 (11.0)	
In the anamnesis, do you consider it important to take into account the patient who underwent treatment with bisphosphonates in the past medical history?	Yes	90 (90.0)	<0.0001*
	No	10 (10.0)	
Do you know the medical indications for bisphosphonates?	CA	59 (59.0)	<0.0001*
	IA/DN	41 (41.0)	
Do you know the main mechanism of action of bisphosphonates?	CA	56 (56.0)	<0.0001*
	IA/DN	44 (44.0)	

CA: Correct answer, IA: Incorrect answer, DN: I don't know; *Statistically significant.

Table 2 - Knowledge of dentistry students on the side effects and risk factors associated with bisphosphonates

Variable n (%)		Total sample	p-value
Do you know of any side effects in the oral cavity caused by bisphosphonates?	CA	60 (60.0)	<0.0001*
	IA	00 (00.0)	
	DN	40 (40.0)	
What risk factors associated with bisphosphonate can cause the development of the oral side effect?	CA	01 (01.0)	<0.0001*
	PC	56 (56.0)	
	PC+IA/IA/DN	43 (43.0)	
What is the main dental procedure that may be a risk factor for the development of the oral side effect associated with the use of bisphosphonate?	CA	47 (47.0)	<0.0005*
	IA/DN	53 (53.0)	
What type of oral diseases can be a risk factor for the development of the oral side effect associated with the use of bisphosphonates?	CA	29 (29.0)	<0.0001*
	IA/DN	71 (71.0)	
What procedures can prevent oral side effects associated with the use of bisphosphonates?	CA	07 (07.0)	<0.0001*
	PC	53 (53.0)	
	PC+IA/IA/DN	40 (40.0)	

CA: Correct answer, PC: Partially correct, IA: Incorrect answer, DN: I don't know; *Statistically significant.

Table 3 - Evaluation of the curriculum on this topic and the last time dentistry students attended a lecture on oral medicine and pathology/stomatology

Variable n (%)		Total sample	p-value
Have you had any classes on this subject?	Yes	32 (32.0)	<0.0001*
	No	66 (66.0)	
	Didn't answer	02 (02.0)	
When was the last time you attended a lecture on oral medicine and pathology/stomatology?	Less than a year ago	25 (25.0)	<0.0002*
	1 year ago	16 (16.0)	
	More than 2 years ago	23 (23.0)	
	I've never attended but I'm interested	32 (32.0)	
	I've never attended and I'm not interested	04 (04.0)	

*Statistically significant.

DISCUSSION

After Marx's report in 2003[5], an increasing number of BRONJ cases have been published in the literature. Likewise, several studies have shown that preventive dental care and appropriate follow-up significantly reduce the chance of BRONJ[9]. Despite the advances in the pathophysiology and experience in the management protocols of this condition[7], the increasing number of patients exposed to these drugs signals the need for students and dentists to have extensive knowledge on the topic, to prevent the emergence of BRONJ.

Several studies have been published to verify the degree of knowledge of students[10,11], general practitioners[12,13,14,15] and experts[9,16] on this topic. In Brazil, only one study evaluated the knowledge of students on BPs and BRONJ[8]. In our study, we specifically recruited students who were in their final year from private dental schools. A total of 59% of respondents stated that they knew about BPs. In previous studies that evaluated the knowledge of Dentistry students, almost all of the interviewees (99%)[10,17], 77% of students[8], and 50% of those evaluated[14] have knowledge about this class of medicines.

When asked to identify the active principle of BPs, only 34% of the students answered appropriately. Published results are conflicting. In the study by Rosella et al.[10], most students are able to identify the drug, while only 25% of the participants assessed by Lima et al.[8], recognize them. Of the six active ingredients evaluated, zoledronic acid and alendronate are the best known[10,12]. When analyses were performed according to the students' year level (semester), the percentage of students with this knowledge increased progressively over time[12]. In our study, we evaluated only students who were in their final year. Our results were similar to those from Rosella et al.[10]. When presented with trademark names, 79% of the respondents did not recognize them. When questioning the users of BPs, the trade name is usually mentioned by the patient, and therefore, the lack of this knowledge among the professionals may lead to difficulty in clinical decision making[8]. The difference in the antiresorptive potency of the various drugs, either oral or intravenous, is well known[7]. An individualized risk stratification that guides the preventive and/or restorative dental procedures would fall short of the desired, which may increase the risk of developing BRONJ.

The mechanism of action of BPs is based on the inhibition of osteoclasts with a resulting decrease in bone remodeling. Increased bone density and inhibition of angiogenesis influence alveolar repair deficiency[7]. Our study showed that 56% of the participants were able to identify the main mechanism of action of the BPs. Similar results were observed regarding medical indications, with 59% of the interviewees identifying them correctly. Our understanding is that although the students have some knowledge about the indications and mechanism of action of BPs, they also have some difficulty in recognizing their various pharmacological presentations and commercial trade names. This suggests the need to approach the topic in a more specific way. Learning from teachers experienced in the management of the patient using BPs is important because one of the main risk factors for BRONJ is the varied antiresorptive potencies of the drugs. We agree with Lim[8], that one of the strategies to enhance student learning in this topic may include educational campaigns in

Dentistry schools and the involvement of specialty associations.

Regarding side effects, 60% of the students were informed about the side effects in the oral cavity caused by BPs. Only 1% demonstrated to know all the risk factors associated with BPs for BRONJ, while 56% of the students partially recognized them. Nevertheless, during the anamnesis, 89% of students regarded it as important to consider if a patient is being treated with BPs. For patients who documented the use of BPs in their medical history, 90% of students considered this information important. These findings are a cause for concern because students may value the information about drug use, but they have difficulties applying this information into clinical practice. It is crucial that future professionals are familiar with the risk factors and side effects of BPs.

The responses that did not point out the risk factors related to the BPs (type of BP, duration of drug therapy, and route of administration) were classified as partially correct. The incidence of BRONJ in patients using oral BPs varies between 0.01%–0.1%, while the risk is higher when BPs are used intravenously (1%-12%)[7]. In general, the longer the time of use, the higher the risk[7]. Regarding the local risk factors, 53% of students did not know any dental procedures that could contribute to the development of BRONJ, a result close to the 46% observed by Lima et al.[8] Moreover, 71% were not able to identify the oral diseases that contribute to the development of BRONJ. These results are perturbing, since the main local factor is dentoalveolar surgery, followed by periodontal diseases, periapical pathology of endodontic origin, and poorly adapted prostheses[6], which are all commonly seen in general dental practice. Regarding oral care and prevention strategies for BRONJ, 54% of the respondents partially pointed out steps relating to adequate oral care for the prevention of BRONJ and 7% of the interviewees pointed out all the steps. These figures also raise concern, since prevention is the best strategy to reduce the emergence of BRONJ and the harmful effects of BPs.

The results of this study reflect a certain contradiction between the desire to obtain more information and utilizing the knowledge effectively. In this study, 66% of the students stated that they had not attended a class on the topic. The insufficient coverage of this topic in the dentistry curricula is revealed as 41% of the students attended only one lecture on oral medicine and pathology in the period of up to one year, while 23% said they had attended one lecture within two years. Importantly, 36% of students never attended a lecture or discussed the topic. These answers reveal the precarious way in which this topic is taught. However, those who never attended (32%) showed interest in attending a future lecture on the topic. Some factors may explain these results: the graduation workload which favors technical knowledge more than topics that are linked to medicine; the interdisciplinary nature of the topic resulting it being presented to students sporadically from different perspectives and by teachers with diverse experiences. According to Dhima et al.[18], specialties related to oral pathology are the main sources of information on the topic, and therefore limited specialist contact with students may lead to a deficiency on this topic.

A study of Canadian dentists reported that the main source of information on BRONJ was obtained from scientific articles (56%), and only 20% obtained BRONJ knowledge at dentistry schools[13]. Several studies of general dentists also showed a lack of knowledge in this area[9,15,16]which may lead to problems in identifying risk factors in the growing population using BPs. In a study of Korean dentists, Yoo et al.[19] reported that 72% of the professionals did not identify dentoalveolar surgery as the main local risk factor. These results uncover the deficient knowledge and insufficient teaching on the topic in the undergraduate curricula. This, in turn, reflects the preparedness or the lack of future dentists. Given the relevance of the topic, this concern is important because it is expected that newly graduated professionals are trained in the identification and management of currently prevalent conditions.

Despite being a multicenter study, the study has some limitations. Only 65.75% of the eligible students answered the questionnaire. Students from public schools were not included in the study and we know that there are curriculum differences between public and private schools. Only students from a certain geographical region were included, therefore we cannot extrapolate the results and apply them to other regions of the country.

CONCLUSIONS

Our results suggest that dentistry students have limited and variable knowledge of BPs and BRONJ. We observed that students desire more knowledge on the topic, but they encounter a lack in their curricula. The topic should be included in the undergraduate curriculum and in a more organized manner. Further studies, including other groups of students, are necessary to support the implementation of strategies to solidly expand the knowledge of our future dental professionals, thereby improving the quality of care and management of patients using BPs.

Author Contributions

CYM: researcher and redactor. PSM: redactor. SCMR: redactor and statistician. MM: readctor and supervision.

Conflict of Interest

No conflicts of interest declared concerning the publication of this article.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of University of Mogi das Cruzes. The approval code for this study is 1.602.514.

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