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Outcome of tooth extraction in patients receiving bisphosphonate treatment - surgical protocol and risk factors

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Abstract

Bisphosphonate-associated osteonecrosis of the jaw (BAONJ) is a serious adverse reaction to the administration of drugs from the bisphosphonate group. It is a potentially painful and debilitating condition that can significantly affect patients' quality of life. Although the etiology and pathogenesis of the disease are still not fully understood, in the literature dentoalveolar surgical intervention is indicated as one of the main factors for its occurrence.

The aim of our study was to evaluate the outcome of tooth extraction in patients receiving bisphosphonate treatment, in a quadrant of the jaw without necrosis, investigating the risk factors for the development of the disease, following a clearly defined surgical protocol.

The study included 30 patients undergoing therapy with bisphosphonates (oral or intravenous), with indications for extraction of one or more teeth.

A total of 81 teeth were extracted applying a specific surgical protocol and an antibiotic prophylaxis. As a result, we found a relatively low incidence of BAONJ -it developed in 2 (6.7%) of our examined patients and 3 (3.8%) of our extracted teeth.

In conclusion, we can say that the combination of perioperative antibiotic prophylaxis, atraumatic surgical intervention, smoothing of sharp bone edges and closure of the extraction wound offers a safe and reliable strategy for tooth extraction in patients receiving oral and intravenous bisphosphonate treatment. Due to the limited sample size, however, to draw definitive conclusions regarding the role of various potential risk factors considered in the literature, further studies that include a larger number of patients will be needed.

Keywords: Bisphosphonate-associated osteonecrosis of the jaw (BAONJ), risk factors, tooth extraction

Introduction

Bisphosphonate-associated osteonecrosis of the jaw (BAONJ) is a multifactorial disease that affects the jaw bones and develops as a side effect of intake of drugs from the Bisphosphonate group. It is difficult to be treated and there is no agreement on the treatment method that leads to a complete healing in the literature. Bisphosphonates are widely used for the treatment of osteometabolic and malignant diseases. Dentoalveolar surgical intervention (tooth extraction) in these patients is one of the main risk factors for the development of the disease described in the literature (1,2). Applying certain surgical protocol when performing tooth extraction can lead to a reduction in the risk of developing BAONJ (3).

Aim

The aim of our study is to investigate the outcome of tooth extraction in patients on bisphosphonate therapy, in a quadrant of the jaw without necrosis, following a clearly defined surgical protocol.

Materials and Methods

The study includes patients undergoing bisphosphonate therapy (oral or intravenous), with indications for extraction of one or more teeth. This group includes a total of 30 patients. BF intake was due to malignant diseases in 14 patients (46.7%) and osteoporosis in 16 patients (53.3%). Of these, 13 patients (43.3%) received oral BF and 17 (56.7%) received intravenous BF. In these patients, there are no clinical data on the development of BRONJ, at the time of the primary examination in the quadrant in which the teeth to be extracted are located. In 7 (23.3%) of the patients examined by us with a need for tooth extraction, on BF therapy, necrosis was found in another quadrant. The intended extraction is in a quadrant without necrosis. The remaining 23 (76.7%) were patients requiring tooth extraction in an outpatient setting, without the development of necrosis to date, undergoing BF therapy.

We examined the following signs:

1. Demographic characteristics:

• Demographic information collected includes age at diagnosis and gender.
  - age - we divided the patients examined by us into six age groups, as follows - I group (30-40 years); II group (41-50 years); III group (51-60 years); IV group (61-70 years); Group V (71-80 years); VI group (81-90 years)
  - gender - women: men

• Primary disease - malignancy or osteoporosis

2. Regarding the bisphosphonates taken

• Type of bisphosphonate/bisphosphonates
  - Zoledronic acid
  - Alendronic acid
  - Ibandronic acid
  - Pamidronic acid

• Duration of BF therapy (in months)

• Mode of administration of BF-oral or intravenous.

We divided the group of 30 patients according to the outcome of the performed tooth extraction into two groups - patients who did not develop BRONJ and patients who developed BRONJ after the extraction. We

examined the distribution of the two groups of patients with regard to the following characteristics: Age, sex, main diagnosis, type of BF, method of introduction of BF, duration of introduction of BF, localization for the tooth intended for extraction (jaw, region), type of the administered antibiotic for antibiotic prophylaxis, duration of antibiotic treatment, presence of BRONJ before extraction in another quadrant and outcome of treatment.

Criteria for inclusion in the study

• Taking medicines from the group of bisphosphonates for the treatment of an underlying disease (osteoporosis, carcinoma, multiple myeloma)
• Age over 18 years
• Need for surgical treatment (extraction) of one or more teeth not amenable to conservative treatment
• Absence of exposed necrotic bone and absence of clinical and radiographic evidence of BRONJ in the extraction quadrant according to AAOMFS criteria (1, 2)
• they include a subgroup of patients with a need for extraction in a quadrant in which there is no necrosis, but necrosis is observed in another quadrant in connection with the intake of BF.

Exclusion criteria from the study:

• history of previous radiotherapy to the head and neck area
• presence of exposed necrotic bone and clinical and radiographic data or previous history of the presence of BRONJ in the quadrant in which the extraction will be performed.
• metastatic infiltration of the jaw bone

For each patient included in the study, a questionnaire prepared by the doctoral student was filled out, including detailed information on gender, age, underlying disease, type, route of administration and duration of bisphosphonate intake, clinical symptoms, stage of osteonecrosis, localization, performed dentoalveolar surgical intervention, results of microbiological, histological and radiographic examination, treatment carried out and result of treatment.

Methodology

The following surgical protocol was followed: 1. Gargling with chlorhexidine 0.2% 30 mL for 60 s; 2. Local anesthesia with 4% Articain (Ubistesin, Septanest); 3. Luxation and extraction of the tooth, carefully performed with a straight elevator and extraction forceps; 4. If necessary, the sharp bone edges are smoothed with bone forceps. 5. Removal of the pathologically changed tissues from the alveolus, using a curette; 6. Mobilization of adjacent tissues and maximal primary closure of the extraction wound, using single interrupted sutures.

The selected surgical protocol is in accordance with those published in 2006 (1) and 2009 (2) recommendations of the AAOMFS and the protocol published by the German Board of Oral and Maxillofacial Surgeons (3) regarding surgical interventions in patients on BF therapy. If extraction or surgical intervention on the bone is necessary, a tissue-sparing surgical technique is applied, and primary tissue closure is recommended. Surgery is followed by gargling with antiseptic chlorhexidine solutions and antibiotic prophylaxis at the discretion of the oral surgeon (1, 2).
All patients of the second group underwent surgical and medical treatment.
According to the recommendations of the American Dental Association, surgery is followed by gargling with antiseptic chlorhexidine solutions and antibiotic prophylaxis, at the discretion of the oral surgeon (4).

Antibiotic prophylaxis is also recommended by other authors (5, 6, 7, 8, 9). The antibiotic treatment we applied to the patients of the second group, in terms of type of AB and duration of AB intake, was in accordance with the published results and behavioral protocols for tooth extraction in patients on BF therapy (10).

The following therapeutic scheme was assigned:

- Antibiotic treatment with drugs from the group of Penicillins - the applied antibiotics are Duomox 1000/ Duomox 1000 and Augmentin 1000 mg (Amoxicillin 825 mg + clavulanic acid 175 mg). The daily dose is 2 grams (2000 mg), divided into two doses, orally, every 12 hours for 14-21 days. In patients with an allergy to Penicillin, we administered Clindamycin, 300 mg, a daily dose of 900 mg, divided into three doses, every 8 hours, for 14 days.
- Antiseptic solutions - gargling with 2% chlorhexidine solution twice a day - morning and evening, after brushing the teeth, lasting one minute (60 seconds).

Terms for reporting the results

The sutures are removed on day 7-10; the results are reported on day 14, day 30 and 6 months after the treatment (extraction under antibiotic prophylaxis).

The results were reported as follows:

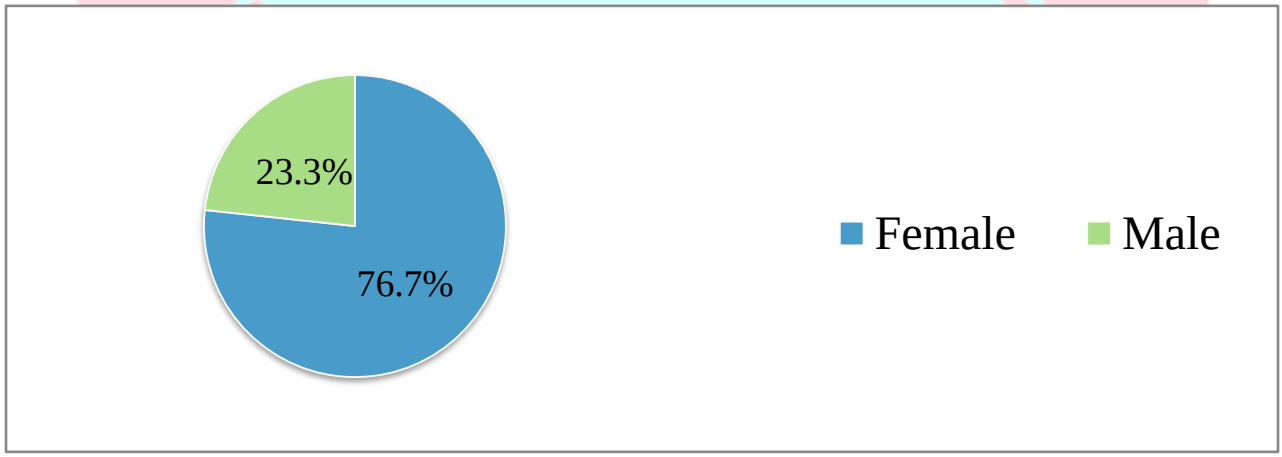
- normal healing process of the extraction wound - absence of clinical symptoms; the mucous membrane covering the extraction wound is intact, does not differ in color and consistency from the surrounding healthy one;
- progression of the disease - transition to the first group - clinical and radiographic data on the development of BRONJ

Results

1. Results of the data according to the gender of the patients

Regarding the distribution of patients by gender, we found that 23 (76.7%) of the patients examined by us were women and 7 (23.3%) were men, and the difference between the sexes was statistically significant ($p<0.05$).

Fig. 1. Distribution of patients from the second group by gender



2. Results of the data according to the age of the patients included in the study.
Patients were divided into six age groups presented in Table 1.

Table. 1. Frequency distribution according to the variable Age in the group of 30 patients

Age group	Number of patients	Percent
30-40	3	10
41-50	1	3,333
51-60	4	13,333
61-70	15	50
71-80	6	20
81-90	1	3,333

From table 1, it can be seen that BRONJ occurs most often in the age between 61-70 years. There were 15 (50%) patients in this age group. The age between 71-80 years old patients is also highly represented (20%). The percentage distribution is lower in the age group 51-60 years (13.3%), followed by the group 31-40 years - 3 patients (10%). We observe 1 case (3.3%) of BRONJ in the 41-50 and 81-90 age groups. In the studied material, we did not find a case under the age of 30 years and over 91 years.

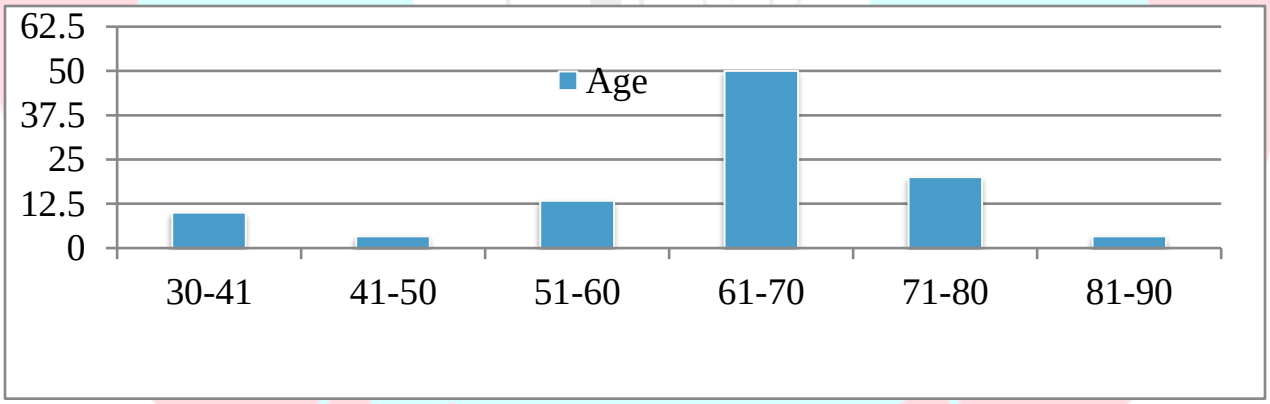


Fig. 2. Distribution of patients from the second group by Age

With regard to the age factor of patients with BRONJ, we found a minimum age of 30 years, a maximum age of 83 years, an average value of 63 years, with a standard deviation of 12.84.

3. Results of the data according to the main diagnosis of the patients
The present study showed that 16 (53.3%) of the patients had a primary diagnosis of malignancy. In 14 patients (46.7%), the intake of BF was indicated by an underlying disease of osteoporosis.

Fig. 3. Distribution of patients from the second group according to the main diagnosis

4. Data results according to the type of administered BF.

When examining the patients according to the type of BF administered, it was found that the BF with the highest frequency was Zoledronic acid - in 17 (56.7%) of the patients. Second place was taken by Ibandronic acid in 7 (23.3%) patients. Alendronic acid followed in 5 (16.7%) and Alendronic + Ibandronic acid in last place in distribution in 1 (3.3%) of the examined patients.

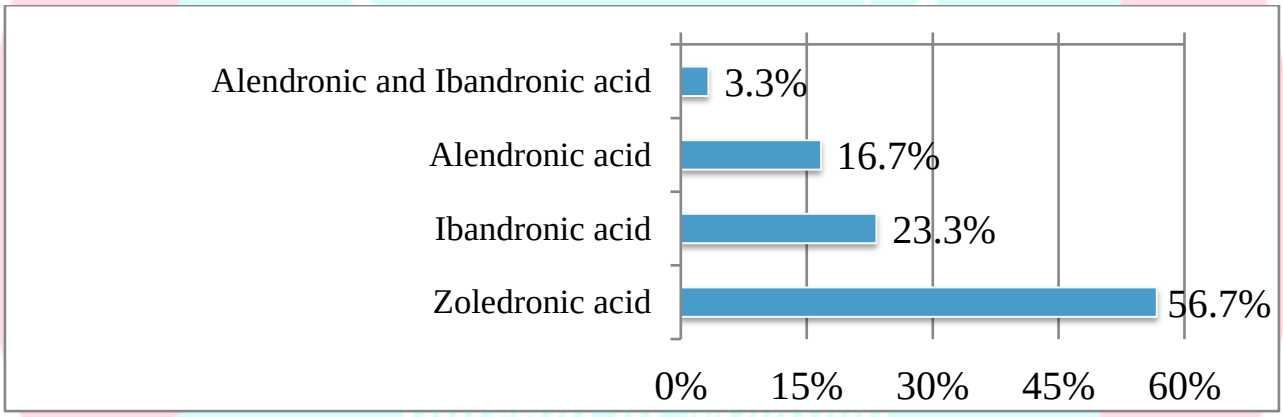


Fig. 4. Distribution of patients from the second group according to the type of BF

5. Data results according to the method of intake of BF

According to the method of introduction of BF into the body, we found close distribution values - BF was introduced intravenously in 17 patients (56.7%), compared to 13 of the patients (43.3%), in whom BF was introduced orally.

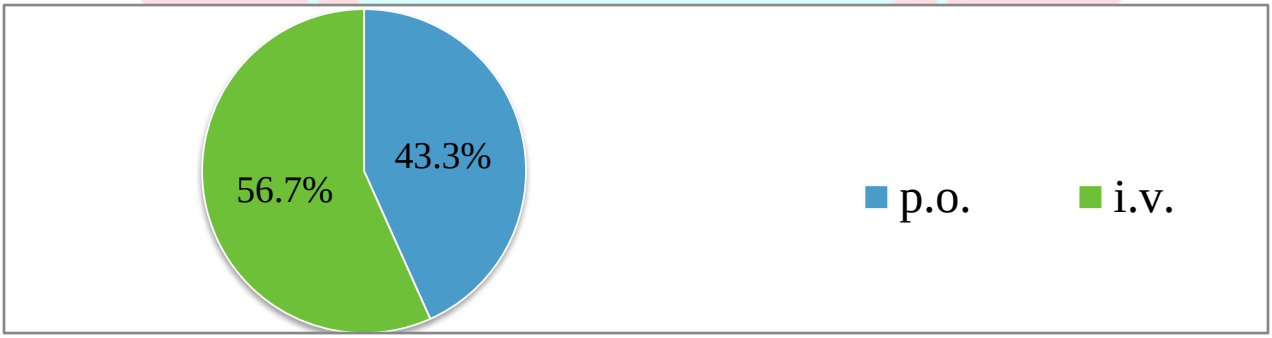


Fig. 5. Distribution of cases from the second group according to the method of introduction of BF

6. Data results according to duration of BF intake

Our study showed a maximum value of the duration of BF intake 157 (in months), a minimum - 2 months, an average value - 42.23 months, with a standard deviation of 41.47 months. The distribution is shown in the table below:

	Mean	Minimum	Maximum	Standard Deviation
Duration	42,23	2	157	41,47

Table 2. Distribution of cases according to the duration of BF reception

7. Results of the data according to the presence of BRONJ before extraction.

7 (23.3%) of the patients had a BRONJ involving another quadrant before extraction and 23 (76.7%) of the patients had no BRONJ before the extraction.

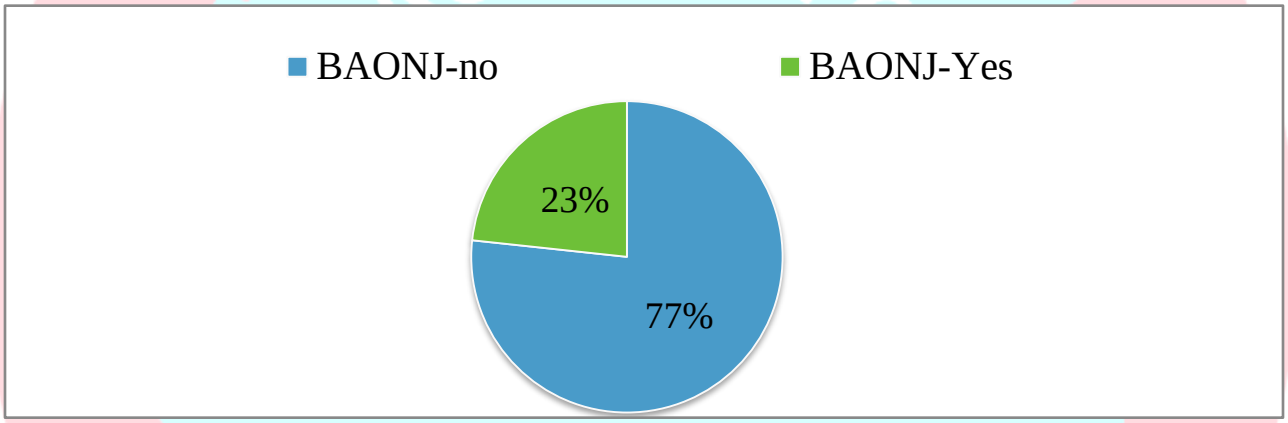


Fig. 6. Distribution of cases according to the presence or absence of BRONJ before tooth extraction

8. Data results according to the diagnosis of the tooth to be extracted.

In the largest percentage of cases - 21 (70% of patients) the diagnosis of the tooth subject to extraction is Periodontitis chronica granulomatosa diffusa/localisata. Next is the diagnosis of Parodontitis chronica generalisata - 7 of the patients (23.3%), in 1 patient (3.3%) - Dens semiretinens, as well as 1 patient with a diagnosis of Cysta radicularis (3.3%).

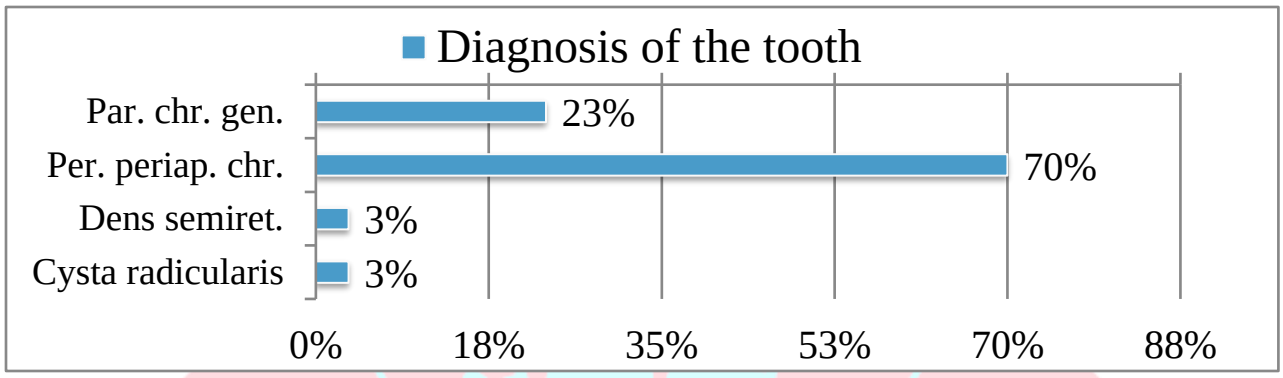


Fig. 7. Distribution of cases according to the diagnosis of the tooth subject to extraction

9. Data results according to the jaw on which the teeth to be extracted are located.

According to the jaw on which the teeth subject to extraction are located, the distribution is as follows: in 8 patients (26.7%) the teeth are located in the lower jaw, in 17 patients (56.7%) in the upper jaw and in 5 patients (16.7%) were extracted teeth of the lower and upper jaw.

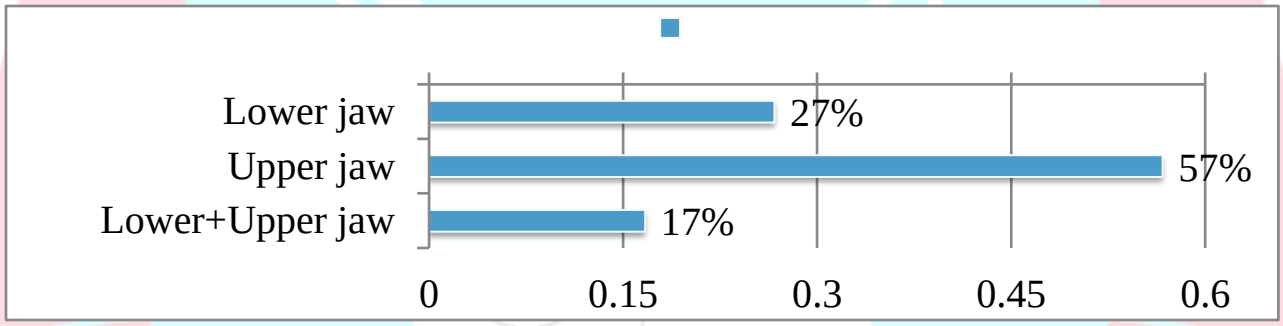


Fig. 8. Distribution of cases according to the jaw on which the teeth subject to extraction are located.

10. Results of the data according to the area of the jaw on which the teeth subject to extraction are located.

According to the area of the jaw in which the teeth subject to extraction are located, we found the following distribution: in 9 of the patients (30%) teeth located in frontal and distal region of the jaw, in 6 of the patients (20%) the extracted teeth were in the frontal region and in 15 (50%) in the distal region of the jaw.

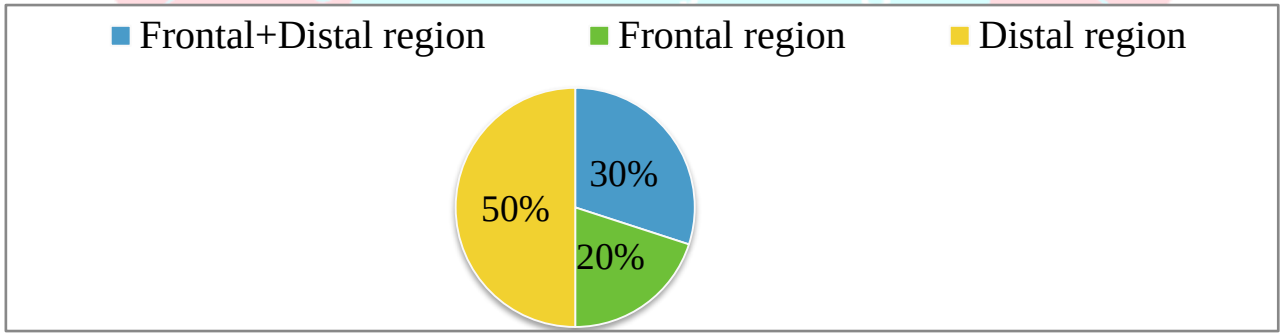


Fig. 9. Distribution of cases according to the area of the jaw in which the teeth subject to extraction are located.

11. Results of the data according to the type and duration of the antibiotic taken during the antibiotic prophylaxis.

Only 3 of the patients (10%) received Lincosamide and a significantly greater percentage of the patients-27 (90% of the patients) received Penicillin.

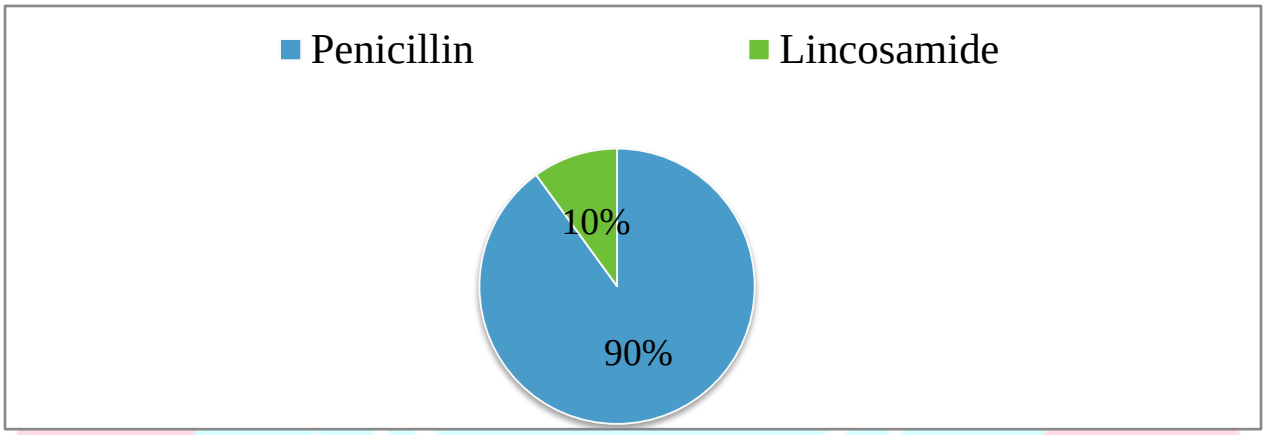


Fig. 10. Distribution of cases from the second group according to the type of antibiotic taken for antibiotic prophylaxis.

Regarding the duration of antibiotic intake, we found an average value of 14.7 days, a minimum duration of intake of 7 days and a maximum of 21 days.

12. Data results by treatment outcome

Regarding the outcome of the treatment, we found that in a significantly larger part - 28 of the patients (93.3%) after the extraction, a healing process occurred and in 2 (6.7%) of the patients, BRONJ developed.

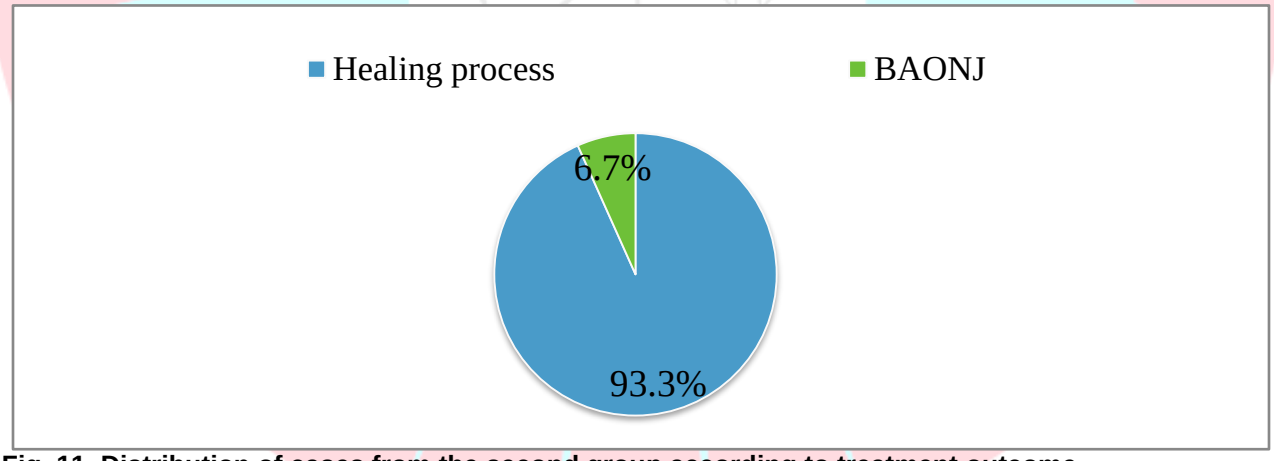


Fig. 11. Distribution of cases from the second group according to treatment outcome.

Discussion

The gender distribution of men: women is 1:3.3, and the difference between the sexes is statistically significant (p>0.05). In the two patients who developed BRONJ, the gender distribution was 1:1.

The largest number of patients examined by us are in the group of 61-70 years old. Both patients (100%) who developed BRONJ after extraction were in this group, with a mean age of 65.5 years. We found no cases under 30 years of age and over 91 years of age.

Some authors report a preferential involvement of female patients -73% (11), 87% (12) of all studied patients with BRONJ. According to the AAOMS, the higher rate of this complication in women is more likely a reflection of the underlying disease necessitating BF (e.g., osteoporosis, breast carcinoma) (2).

We also believe that the greater percentage of female patients and the age distribution is related to the frequency of occurrence of the underlying disease necessitating the use of BF in these groups.

In the literature, the risk factors for the development of BRONJ are divided into three main groups: 1) those related to the intake of BF 2) systemic factors and 3) local risk factors (2). In the present study, we found that in the two patients who developed BRONJ in relation to the administered BF, it was zoledronic acid administered intravenously, with a mean duration of administration of 84 months. Regarding the systemic factors in both patients, we established a primary diagnosis of malignancy (multiple myeloma), and taking into account the local risk factors in both patients - the diagnosis of the extracted teeth was Parodontitis chronica generalisata, the patients had developed BRONJ in another quadrant, before the extraction and the extracted teeth are located in the distal part of the jaw. Due to the limited sample size, however, to draw definitive conclusions regarding the role of various potential risk factors considered in the literature, further studies that include a larger number of patients will be needed.

The incidence of BRONJ in the extraction protocol applied by us is relatively low - 2 (6.7%) of the patients examined by us and 3 (3.8%) of the teeth extracted by us

In the majority of the patients the healing process was smooth, and there were no complaints at the time of the control check-up. Two patients developed complications in the healing process of the extraction wound.

The total number of extracted teeth was 78. Of these, 75 (96.2%) underwent a healing process and 3 teeth (3.8%) developed BRONJ.

The first patient who developed BRONJ was S.M. - male, 62 years old. with a primary diagnosis of multiple myeloma. He has been on monthly Zometa IV treatment for 60 months. The reason for the extraction of teeth 16 and 26 (upper jaw, distal region) was chronic generalized periodontitis. The patient was diagnosed with BRONJ in the fourth quadrant, distal section-II stage.

The second patient who developed BRONJ was D.S. -woman, 69 years old. She has been on monthly intravenous Zometa treatment for 108 months with main diagnosis Multiple Myeloma. She had an extraction of tooth 45 (lower jaw, distal section), the reason for the extraction was chronic generalized periodontitis. The patient was diagnosed with BRONJ in the third quadrant distal section-II stage.

After tooth extraction, antibiotic treatment with Augmentin 1g, 2g daily, divided into two doses, lasting 14 days in the first patient and 21 days in the second patient, was carried out in both patients. At the control examinations at the first and sixth month after the extractions of both patients, we found an unsatisfactory healing process, the extraction wounds were partially covered with epithelium and the presence of exposed necrotic bone was found. There were no complaints from the patients - they did not report the presence of pain, erythema, purulent exudate. In both patients, the development of BRONJ stage I was detected.

Several protocols have been published in the literature dealing with risk assessment and tooth extraction behavior of patients taking BF (1, 2, 3). However, the recommendations are somewhat contradictory. Therefore, the main purpose of this study was to prove whether the recommendations published by AAOMS and German the Oral and Maxillofacial Surgery Society, regularly applied in our clinical practice, are applicable and successful in this group of patients.

The results of this study confirm that the extraction protocol we used is reliable, with a low probability of developing osteonecrotic lesions, although 46.7% of high-risk patients with malignant underlying disease

receiving intravenous bisphosphonate treatment also included some patients with already developed BRONJ in other quadrants of the jawbones.

From the literature, we selected studies with an extraction protocol similar to ours in a second group of patients and found the following: Lodi et al. reported that of their study of 23 patients on BF treatment in whom 38 teeth were extracted, none developed OND during a follow-up period of 15 months (13). Schubert et al. performed extractions in 36 patients, 1 of whom (2.7%) developed ONH (14). Otto et al. extracted 216 teeth in 72 patients, of which 5 patients (6.9%) developed BRONJ (3.2% of extracted teeth) (15).

Kato et al. performed extractions on 20 patients in whom he extracted 62 teeth and reported the development of osteonecrosis in 4 of them (20% of patients and 6.4% of extracted teeth) (16).

Vescovi et al. studied 126 patients who performed extractions using the Nd:YAG laser in the treatment. Of the patients he studied and a follow-up period of >12 months, no patient developed ONH (17).

Sanchís et al. performed extractions on 34 patients in whom he extracted 62 teeth and reported the development of osteonecrosis in 9 of them (26.5% of patients and 14.5% of extracted teeth) (18).

Our results are close to those of a number of authors - Lodi et al. (13), Schubert et al. (14), Vescovi et al. (17) and Otto et al. (15).

Compared to the studies of Kato et al. and Sanchís et al., we obtain a lower rate of BRONJ development after a tooth extraction.

Tooth extractions and dentoalveolar surgical procedures in patients taking bisphosphonates are of increasing clinical importance in the field of dentistry, as well as in oral and maxillofacial surgery. Currently, dentoalveolar surgery is considered a major risk factor for the development of BRONJ. According to the AAOMFS, dentoalveolar surgery is a major risk factor for the development of BRONJ, citing studies with dental extraction performed in 52–61% of patients with BRONJ (2). A number of authors recommend that tooth extraction and other procedures that involve direct involvement of bone be avoided (1, 19, 20). Recently, however, the number of authors who define as the main risk factor for the development of BRONJ the infection of dental origin, and not the surgical intervention itself is increasing (21, 22, 23, 24, 25).

A number of authors recommend that teeth with a poor prognosis should be extracted to prevent the development of ONJ as a result of infection of dental origin (26, 20, 27).

Also, prolonged antibiotic treatment and complex dental rehabilitation may not be possible in cancer patients and in patients with compromised health (28).

Having in mind these considerations we apply the extraction prophylaxis in teeth, which cause infection in the jawbones and cannot be treated conservatively, assessing the risk of developing BRONJ.

Conclusion

Atraumatically performed surgical intervention, smoothing of the sharp bony edges and closure of the extraction wound, in combination with antibiotic prophylaxis lead to a smooth postoperative period in most of the cases and are the recommended approach for tooth extraction in patients undergoing oral or intravenous bisphosphonate treatment. Due to the limited sample size, however, to draw definitive conclusions regarding the role of various potential risk factors considered in the literature, further prospective multicenter studies that include a larger number of patients will be needed.

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