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The role of systemic antibiotics in tooth extractions in patients on antiresorptive therapy

Vloga sistemskih antibiotikov pri izdrtju zoba pri bolnikih na antiresorptivni terapiji

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Abstract

Basis: Antiresorptive drugs (ARZ) are used to treat osteoporosis and bone manifestations of certain malignancies. The drugs inhibit bone breakdown and consequently proper bone remodelling. During oral surgery in the oral cavity, such as tooth extraction, drug-induced osteonecrosis of the jaw may develop. The pathogenesis itself has not yet been fully elucidated, and an important factor in its development is inflammation. This could be treated with systemic antibiotics after the procedure. The main purpose of the study is to establish whether the use of antibiotics after tooth extraction in patients on ARZ treatment affects the incidence of osteonecrosis of the jaws.

Methods: We retroactively reviewed the documentation of 94 patients (83 women and 11 men) who had their teeth extracted between 2006 and 2015 at the Clinical Department for Maxillofacial and Oral Surgery and were treated with antiresorptive drugs. Extractions were performed according to a uniform protocol to prevent the development of jaw necrosis. A systemic antibiotic was administered to 22 patients after the procedure. Patients were monitored regularly. The results were statistically analysed.

Results: Osteonecrosis of the jaws developed in a total of 14 patients (14.9%). Five of 22 patients receiving systemic antibiotics developed jaw necrosis (22.7%), while the latter was observed in 9 of 72 patients (12.5%) who did not receive a systemic antibiotic. The overall incidence of osteonecrosis of the jaw when receiving a systemic antibiotic was 5.32%. The use of antibiotic protection and morbidity for MRONJ are not statistically significantly related ($p > 0.05$).

Conclusion: Additional systemic research is needed to confirm the pathogenesis of MRONJ development and the role of bacterial inflammation in it, so that the feasibility of systemic antibiotic use during oral surgery, especially in dental extractions in patients treated with ARZ, may be confirmed or refuted.

Izvleček

Izhodišče: Antiresoptivna zdravila (ARZ) se uporabljajo za zdravljenje osteoporoze in kostnih pojavov pri nekaterih malignih boleznih. Zdravila zavirajo kostno razgradnjo in s tem ustrezno kostno remodelacijo. Ob oralnokirurškem posegu v ustni votlini, kot je izdrtje zoba, se lahko razvije z zdravili povzročena osteonekroza čeljustnic. Sama patogeneza še ni povsem pojasnjena, pomemben dejavnik pa je vnetje. Nanj bi lahko vplivali s sistemskimi antibiotiki po samem posegu. Osnovni namen raziskave je, ali uporaba antibiotika po izdrtju zoba pri bolnikih na zdravljenju z ARZ vpliva na pojavnost osteonekroze čeljustnic.

Metode: Retrospektivno smo pregledali dokumentacijo 94 bolnikov (83 žensk in 11 moških), ki so jim med letoma 2006 in 2015 izdrli zob na KO za maksilofacialno in oralno kirurgijo in so se zdravili z antiresoptivnimi zdravili. Izdrtje je potekalo po enotnem protokolu za preprečevanje razvoja nekroze čeljustnic. Pri 22 bolnikih smo po posegu uvedli jemanje sistemskega antibiotika. Bolnike smo redno kontrolirali. Rezultate smo statistično analizirali.

Rezultati: Osteonekroza čeljustnic se je razvila pri skupno 14 bolnikih (14,9 %). Pri 5 od 22 bolnikov, ki so prejeli sistemski antibiotik, se je razvila nekroza čeljustnice (22,7 %). Pri 9 od 72 bolnikih, ki niso prejeli sistemskega antibiotika, se je razvila nekroza (12,5 %). Skupna pojavnost osteonekroze čeljustnice ob prejemanju sistemskega antibiotika je 5,32 %. Uporaba antibiotične zaščite in obolevnost za MRONJ nista statistično značilno povezani ($p > 0,05$).

Zaključek: Potrebne so še dodatne sistemske raziskave, ki bodo dokončno potrdile patogenezo razvoja MRONJ in pomen bakterijskega vnetja v le-tej. Nato se bo lahko dokončno potrdila ali ovrgla tudi smiselnost uporabe sistemskih antibiotikov ob oralnokirurških posegih, posebej pri izdrtju zob pri bolnikih, ki se zdravijo z ARZ.

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1 Introduction

Medication-related osteonecrosis of the jaw (MRONJ) occurs with patients who were treated with antiresorptive drugs (ARD), such as bisphosphonates or denosumab, and drugs that are used for treating oncology patients and affect the blood supply of the so-called angiogenesis (1). In addition to therapy with ARD, a condition for setting the MRONJ diagnosis according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) from 2014 is an exposed bone lasting more than 8 weeks, and no radiation therapy of a head or neck malignant growth (2). Their full pathogenesis is yet to be explained. Five main mechanisms have been proposed: partial bone remodelling, inhibited angiogenesis, local toxicity, immunomodulation, inflammation (3). The most frequent triggers mentioned are local and systemic factors. Besides ARD therapy, local risk factors for the development of MRONJ include dental extraction and other oral surgery procedures that cause microtrauma or microfractures. Because of inhibited remodelling and other effects of ARD, these are entry points for the microorganisms of mouth flora. Other local factors mentioned include unsuitable prosthetics fits, peeling and smoothing of roots, and spontaneous growths at points of predilections, such as bone tori covered by thinner mucosa with poor blood supply (Figure 1).

The presence of dental and soft tissue related inflammatory processes is the reason for the decline of local pH, which results in increased release of accumulated bisphosphonates in bones and an increase of their local concentration and toxicity. A concurrent secondary infection from a rich mouth flora can lead to the onset of MRONJ (4).

The main systemic factor is a primary disease, treated with ARD. The method of intake, the dosage and concentration of ARD are indirectly related to the onset of MRONJ. Osteoporosis patients usually re-

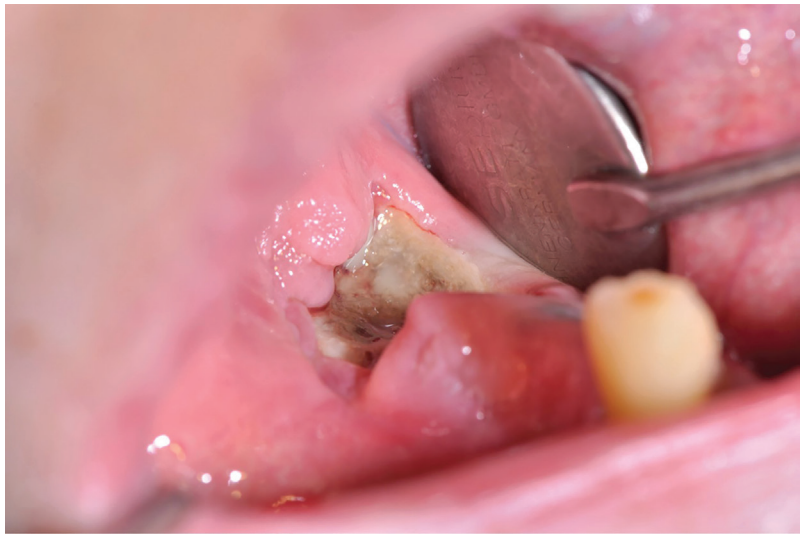

Figure 1: Exposed osteonecrotic bone in the mouth of a patient receiving anti-resorptive drugs.

ceive ARD orally, in lower doses and over longer intervals (low-risk patients) than oncology patients (high-risk patients). With the latter, the intake is usually intravenous, in larger doses and more frequent intervals. The availability of the therapy differs up to 140-fold between oral ingestion and intravenous delivery. Another risk for an increase is concurrent chemotherapy or corticosteroid therapy (3).

Most protocols for MRONJ prevention and patient care emphasise dental care before introducing ARD therapy. In spite of this, there is often a need for dental extraction and other oral surgery procedures after the start of the therapy. Recommendations differ especially regarding whether it is sensible to use systemic preventive antibiotics as factors for decreasing the onset of MRONJ (Figure 2).

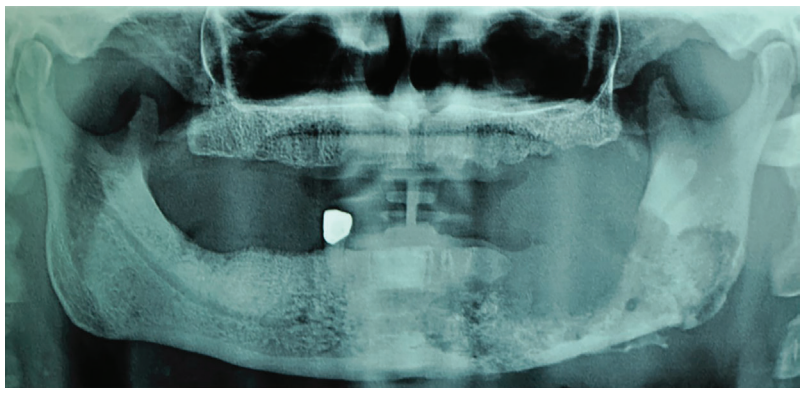

Figure 2: Drug-induced osteonecrosis, visible in an orthopantomogram.

The use of systemic antibiotics for prevention of potential complications following extractions and other oral surgery procedures still largely depends on personal preferences and experiences of the maxillofacial surgeon. General preventive use of antibiotic protection is not sensible for all oral surgery procedures, as there is no evidence that such inhibition or limitation of bacteraemia resulting from the procedure significantly reduces the onset of complications in a healthy individual (5). The guidelines of the American College of Cardiology from 2017 confirm the findings from recent years and significantly limit the prophylactic use of antibiotic therapy (6). This is limited only to preventing infectious endocarditis and with some other exceptional conditions. The final group includes some systemic diseases and the general systemic stress resulting from an odontogenic infection. General, especially non-critical use of systemic antibiotics leads to bacterial resistance, which is a major medical issue of modern times.

This latter issue was also the main objective of our retrospective review of our patients and their care.

The main objective of the study was to establish whether the use of an antibiotic after dental extraction on a patient undergoing ARD therapy has an effect on the onset of osteonecrosis of the jaw.

2 Material and methods

The Clinical department for maxillofacial and oral surgery of the Ljubljana University Medical Centre treated 94 patients (11 men and 83 women) between 2006 and 2015, who were receiving ARD therapy and needed a dental extraction of one or more teeth. The age of the patients at the time of the procedure was between 39 and 91 years (average age of 72.01 years

and a standard deviation of 9.40 years). Patients were treated by various maxillofacial surgeons according to standardised procedures. We did not influence the decision on using an antibiotic with any individual patient.

In addition to epidemiological data, we also gathered data on the patients' primary disease that required ARD therapy, the type of ARD, method of ingestion, dosage, and duration of the therapy. We also obtained data on comorbidities and additional therapies.

After completing the clinical review and assessing x-ray images, we set a working diagnosis. Next, we assessed the indications and contraindications for dental extraction. We selected the technique individually, based on anatomically-morphological particularities of a tooth and the roots, according to the primary disease for which the patient was receiving ARD therapy, taking into account its duration and the risk for the onset of osteonecrosis. The completed extractions included simple extractions, surgical extractions or extrusion extractions using orthodontic elastics. With all patients, except those with an extrusion extraction, we performed a curettage of the alveolus, removed the sharp bone edges, additionally lowered the alveolar walls, and tightly sutured the wound by bringing local tissues together.

With 22 patients, we introduced antibiotic therapy after the procedure. We used an antibiotic from the penicillin group, i.e., amoxicillin with clavulanic acid. Antibiotic therapy lasted 5 to 30 days. Patients with an allergy to penicillin preparations received clindamycin. For the remaining 72 patients we did not institute antibiotic therapy after the procedure.

The patients returned for control examinations 14 days, one month, three months, and six months after the procedure. At control examinations the physicians monitored the complete course of healing of the extraction wound, the onset of early complications after dental extraction and a potential onset of MRONJ.

In the retrospective review of the collected data that we analysed for this study, we divided patients into two groups. The first group included those who received antibiotic therapy, and the second one those who did not.

We statistically processed the results. The methods we used to analyse the results were the median and standard deviation values of the obtained values. We used the chi-squared test to calculate statistical significance.

The study was approved by the Committee for Medical Ethics of the Republic of Slovenia on 2 November 2017 (decision no. 0120-480/2017/3).

3 Results

With 77 patients (2 men, 75 women) the reason for ARD therapy was osteoporosis, and with 2 female patients it was osteopenia. 15 patients were treated for bone metastases (see Table 1 for details). One patient suffered from osteoporosis as well as breast carcinoma.

ARD therapy lasted a minimum of 2 months and up to 26 years. Patients were taking bisphosphonates and monoclonal antibodies (denosumab), and a combination of bisphosphonates and monoclonal antibodies. The average duration of ARD therapy was 5.12 years (standard deviation of 4.46 years). Tables 2 and 3 depict the ARDs that patients were taking.

There was a total of 220 extracted teeth, from 1 tooth and up to 12 teeth per patient, so an average of 2.34 teeth per patient (with a standard deviation of 2.17).

With 22 patients, the antibiotic was prescribed for the time after the procedure. The average period of taking an antibiotic was 9.32 days (with a standard deviation of 7.17). The most frequent reasons for introducing antibiotic therapy were the presence of an acute odontogenic infection, an extensive chronic odontogenic infection and the duration of the procedure.

After dental extractions, 14 of all the

Table 1: Division of patients to ARD and primary neoplasm.

Sex/ disease	Multiple myeloma	Lung cancer	Breast cancer	Prostate cancer	Follicular lymphoma
Men	3	2	0	4	0
Women	1	0	4	0	1

patients who were treated with ARD developed MRONJ (14.9%).

With 5 of 22 patients who received antibiotic protection, there was an onset of MRONJ, which is an incidence of 22.7%. With 9 of 72 patients who were not receiving antibiotic protection, there was an onset of MRONJ, i.e., an incidence of 12.5%.

With 5 patients who received antibiotic protection after tooth extraction and were taking ARD, MRONJ developed (incidence in the entire sample of 5.32%). The relation between the use of antibiotic protection and developing MRONJ is not statistically significant ($p > 0.05$) (Table 4).

Table 2: Distribution of ARD among patients.

Type of anti-resorptive therapy	Name	Number
Bisphosphonates (BP)	ibandronic acid	26
	alendronic acid	3
	pamidronic acid	2
	alendronic acid and cholecalciferol	19
	risedronic acid	5
	zoledronic acid	9
	clodronic acid	1
Denosumab (DEN)	prolia	2
	XGeva	1
ARD combination	BP + BP	8
	BP + DEN	12
	More BP	1
	More BP + DEN	2
	BP + DEN + strontium ranelate	2
	BP + strontium ranelate	1
		Total n = 94

Table 3: ARD with oncology patients.

ARD type	Number
Zoledronic acid	8
Pamidronic acid	1
Clodronic acid	1
XGeva	1
Zoledronic acid + XGeva	2
Zoledronic acid + aledronic acid	1
Zoledronic acid + ibandronic acid	1
	Total n = 15

4 Discussion

The sample we included in our study consisted of 94 patients. All of them were receiving ARD and needed a dental extraction. 79 patients (84%) were receiving ARD to prevent osteoporosis complications, while the remaining 15 (16%) were receiving it as additional treatment for bone metastases with a primary malignant disease. As evident from the literature, dental extraction is the reason for the onset of MRONJ in up to 70% of the cases (7,8). The main indicators for dental extraction were periodontal disease and chronic apical periodontitis. Inflammation is a common characteristic in both.

Table 4: Statistical significance of the onset of MRONJ with antibiotic therapy (chi-square test).

	Pearson's chi-squared test with Yates correction
Chi-squared value (c2)	0.701
Degree of freedom (df)	1
P-value	0.403

Regardless of whether the inflammation after local trauma of the bone and mucosa (e.g., after dental extraction) causes necrosis or is its result, it is clear that inflammation plays an important role in the pathogenesis of MRONJ. This is because a change of pH is, which is the result of a micro-organism activity and causes the release of otherwise bonded ARD, especially the bisphosphonates, is key. Another major negative impact also comes from other methods of therapy for the primary malignant disease, such as chemotherapy or corticosteroids (3). Bacterial infection is mentioned as crucial for the development or prolongation of MRONJ. Systemic antibiotics are mentioned as an important factor in the fight against MRONJ, as they could significantly contribute to lower incidence of the disease. Some of our participants also received a systemic antibiotic, which was not part of the general protocol of their therapy. It was used only after the general indication for use. The use of a systemic antibiotic in our patient sample did not result in lower incidence of MRONJ. Incidence of MRONJ among those patients who received the systemic antibiotic was 22.7% which is close to the values of incidence in the whole sample. The incidence among patients who did not receive the antibiotic was lower, at 12.5% Statistical analyses did not prove a statistically significant link between using antibiotic therapy and the onset of MRONJ. The literature shows that using systemic antibiotics has become part of the protocol (7,9). However, it is difficult to compare individual protocols and their success rates. These cases differ both by the level of MRONJ that was treated, as well as by the success rate of the therapy (3). The success rate reports for antibiotic use range between 22–100% (10). There is also no single opinion on whether the duration of receiving a systemic antibiotic impacts the success of the therapy (7). The literature shows that systemic antibiotics do not significantly reduce the bacterial load; however, the profile of the bacteria present does change (11,12). An animal model showed a statistically significant lower incidence of MRONJ with the use of systemic antibiotics after a dental extraction (13). Experts agree that preventive measures, such as preventive dental procedures before beginning ARD therapy, and dental extraction of the teeth with no hope of recovery, are key in preventing the onset of MRONJ. If a situation develops after the start of the ARD therapy, when a tooth must be extracted, adherence to the basic principles that are common for most protocols or guidelines is required. Dental extraction should be as atraumatic as possible, with a good alveolar excoriation, and a smoothing or alveoloplasty of sharp bone edges. This is followed by tight, plastic closure of the edges of mucosa. Using prosthetics is not advised until soft tissues heal properly (14). The use of systemic antibiotics remains an open question that requires additional systemic studies. According to the guidelines that were developed for Slovenia by Dr. Kocjan and Dr. Sapundžiev, antibiotic therapy after dental extraction with ARD patients is suitable only with a general indication for the use of systemic antibiotic therapy with dental and oral surgery procedures (15).

5 Conclusion

Additional systemic studies are needed to finally confirm the pathogenesis of the development of MRONJ and the significance of the bacterial infection in this scope. This would also confirm or refute the sensibility of using systemic antibiotics with oral surgery procedures, especially with extractions with patients who are receiving ARD therapy.

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