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FAKTORI RIZIKA ZA POJAVU OSTONEKROZE VILICA POVEZANA SA UPOTREBOM MEDIKAMENATA

RISK FACTORS FOR THE OCCURRENCE OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW

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Sažetak

Uvod: *Osteonekroza vilica povezana sa upotrebom lekova (medikamenata) ili poznata kao „Medicine related osteonecrosis of jaw“ MRONJ - predstavlja novi patološki entitet, koji se pojavio kao neželjeno dejstvo lekova koji se koriste kod različitih oboljenja a narušavaju normalnu homeostazu koštanog tkiva. Ova vrsta osteonekroze nastaje kod primene antiresorptivnih lekova prvenstveno iz grupe bisfosfonata, ali i drugih lekova koji imaju različiti mehanizam delovanja na koštano tkivo, ali sa posledičnim razvojem osteonekroze.*
Cilj *rada bio je ukazati na faktore koji utiču na razvoj MRONJ-a.*
Rezultati: *Sistemski faktori pored upotebe lekova su brojni, a pre svega endokrini i hormonalni poremećaji kao i imunodefiijencija organizma. Faktori rizika za razvoj MRONJ su vađenje zuba u najvećem broju slučajeva, zatim intervencije koje uključuju zahvatanje koštanog tkiva vilica, implantološke procedure, kiretaža parodontalnog džepa, periapikalne operacije, itd. Preventiva MRONJ-a sprovodi se multidisciplinarnim pristupom koji podrazumeva saradnju reumatologa, onkologa i stomatologa. Usaglašeni multidisciplinarni premedikacijski tertman smanjuje incidencu pojave MRONJ-a za 77,3%. U zavisnosti od stadijuma razvoja MRONJ, postoje konzervativne i hirurške metode lečenja, koje se moraju izvoditi blagovremeno, jer neprepoznavanje i napredovanje lezije dovodi do značajnih posledica po zdravlje i život pacijenta.*
Zaključak: *Osteonekroza vilica povezana sa upotrebom lekova može biti asimptomatska, neodređena lezija koja se veome teško dijagnostikuje, ali se bez blagovreene dijagnostike i terapije može razviti i preći u teži oblik, komplikovan za lečenje, sa patološkom frakturom vilice, mukokutanim fistulama i velikim ožiljcima i unakaženjem Preventiva i multidisciplinarni pretretman i tretman su od ključnog značaja za redukciju pojave i napredovanja ove lezije.*

Ključne reči: *osteonekroza,lekovi, prevencija, terapija*

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Abstract

Introduction *Medication-related osteonecrosis of the jaw (MRONJ) represents a new pathological entity that appears as a side effect of medications used in various diseases disrupting the normal homeostasis of bone tissue. This type of osteonecrosis occurs as consequence of antiresorptive drugs, primarily from the bisphosphonate group, but also other drugs that have a different mechanism of action on bone tissue.*
Aim was *to point out the factors leading to the development of MRONJ.*
Rezults: *There are many systemic factors, primarily endocrine and hormonal disorders, as well as the body's immunodeficiency. Risk factors for the development of MRONJ are interventions that involve the bone tissue of the jaws, primarily tooth extraction, implant procedures, curettage of the periodontal pocket, periapical operations, etc. Prevention from MRONJ is carried out with a multidisciplinary approach that involves the cooperation of rheumatologists, oncologists and dentists. Coordinately applied multidisciplinary premedication treatment reduces the incidence of MRONJ by 77.3%. Depending on the stage of development of MRONJ, there are conservative and surgical methods of treatment, which must be performed in a timely manner, because the progression of the lesion leads to significant consequences for the patient's health and life.*
Conclusion: *Osteonecrosis of the jaw associated with the use of medicaments can be an asymptomatic, indeterminate lesion that is very difficult to diagnose, but without proper diagnosis and therapy it can develop and turn into a more severe form, complicated for treatment, with a pathological fracture of the jaw, mucocutaneous fistulas and large scars and mutilation. Prevention and multidisciplinary pretreatment and treatment are of key importance for reducing the occurrence and progression of this lesion.*

Key words: *osteonecrosis,medications, prevention, therapy*

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Introduction

Medication-related osteonecrosis of the jaw presents the new pathological entity that appeared in the medical public less than two decades ago. MRONJ is actually a side effect of some medicaments used for treating different illnesses, endangering normal homeostasis of the bone tissue. MRONJ happens during or after using antiresorptive therapy such as bisphosphonates, non-bisphosphonates, antiangiogenic, oncological or immunomodulating therapy. The typical clinical presentation is a necrotic bone that is partially exposed necrotic jawbone in the mouth cavity. The prevalence of MRONJ is different, according to the literature, it amounts to 2.3–3.4%[1,2] depending on the type and the length of the therapy[3,4]. Most of the MRONJ cases are related to tooth extraction[5]. There is data about the deaths caused by complications of MRONJ[6].

1. Main causes for the occurrence of MRONJ

1.1 Bisphosphonates (BP) are medicaments used in pathological conditions of the body's bones, such as osteoporosis, osteomalacia, osteogenesis imperfecta, multiple myeloma, and bone metastases of the breast, prostate and other cancers. Bisphosphonates are divided into two groups: nitrogen-containing BP, which include zoledronate and alendronate and non-nitrogen-containing BP, which include etidronate and clodronate. The presence of two amino groups is a significant factor differentiating their affinity for bone hydroxyapatite[7], where BP fulfil their main role. There are three potential mechanisms of BP acting that give them unique effects. The first one is the inhibition of calcium carbonate precipitation while molecules of bisphosphonates incorporate into hydroxyapatite matrix. BP make a hard connection with osteoclasts, and after osteoclast apoptosis, BP stay in the extracellular matrix where they incorporate into surrounding bone, and show cumulative effects[8]. This way of acting enables BP to be in the bone for more than 11 years[9]. Microstructure of bone tissue changes preventing pathological fracture of the bones. The second manner is the inhibition of osteoclast differentiation and osteoclast apoptosis, resulting in decreased bone resorption. The third manner is reduction of bone metabolic activity. Osteoblast bone repairing activity depends on increasing osteoclasts bone resorption activity in normal homeostasis process. This results in fewer cellular elements left into bone tissue, poorer blood and bone remodeling process.

The first time the side effects of BP became known was in 2003 after some reports about osteonecrosis in oncological patients[10,11]. The first known medications that caused osteonecrosis of the jaw were BP, so this condition was named bisphosphonate related osteonecrosis of the jaw (BRONJ). Still, after getting knowledge that other medications are also able to cause similar symptoms, the name was changed into medication-related osteonecrosis of the jaw (MRONJ[12]). The main reason for occurrence of this lesion in the jaw rather than in some other bones is that jaws have much faster “turn over” than the other tubular bones, especially pronounced in the lower jaw[13]. The physiological process of tissue damage and tissue repair is constantly present in the bones by virtuing normal homeostasis. Bisphosphonates disturb normal homeostasis process and physiological remodelation of jaws. BP also reduce proli-feration and transport of oral keratinocytes, and intoxicate oral mucosa[14] causing fragility to trauma and lack of resistance to small damage. This enables ingress of infections and the creation of fistulas. BP also reduce circulation and normal blood flow through the bones, independently of osteoblastic osteoclastic activity[15]. The lower jaw has a stronger cortex, fewer nutritional channels and reduced circulation, i.e. blood supply, especially in the elderly, so this may be why the presence of MRONJ is higher in the mandible (73%) than in the maxilla (22.5%)[7].

1.2. The non-bisphosphonate antiresorptive drug—denosumab (Prolia) is an antiresorptive agent that exists as a humanized RANK monoclonal antibody that inhibits the RANK ligand, which is necessary for the maturation of osteoclasts from precursor cells in the bone marrow, as well as for the stimulation of osteoclasts to resorb bone. It has been in circulation since 2009. Unlike bisphosphonates, denosumab has a half-life of 30 days, does not have a cumulative effect[5,16] and has a more transient effect on the inhibition of bone resorption. The effect on bone remodeling generally diminishes within 6 months of stopping therapy. Surprisingly, the studies show a high incidence of MRONJ with the use of denosumab[17].

1.3. Antiangiogenic drugs are used in the suppression of malignant tumors, and their official use began in 2004[18]. Antiangiogenic drugs are divided into vascular endothelial growth factor inhibitors VEGF: bevacizumab (Avastin), aflibercept (Eylea); tyrosine kinase inhibitors sunitinib (Sutent), sorafenib (Nexavar), cabozantinib (Cabometyx); and anti-mTor drugs—everolimus. This kind of

medications reduce angiogenesis in malignant but also in normal tissue[10]. VEGF plays a very important role in the regulation of osteoclast differentiation and function[13,14] while the decrease in angiogenesis affects the ability of the bone to regenerate, remodelate and heal, and increases the possibilities of super-infections. A combination of antiresorptive and antiangiogenic drugs increases the risk of developing MRONJ by about 16%[19].

2. Criteria for defining MRONJ

MRONJ is becoming increasingly prevalent overtime due to the cumulative effects of the drugs. Prevalence of MRONJ rises rapidly after two or more years from medication. The following criteria must be met so that a lesion can be declared as MRONJ[3]:

- Patient uses medication belonging to a group of medications that can cause MRONJ
- Presence of intraoral or extraoral fistula which lasts longer than 8 weeks
- Patient did not undergo radiation therapy of the head and neck, and there is no metastatic cancer in area of lesion

3. Predisposing factors for the occurrence of MRONJ

The main factor causing MRONJ is the damage of jawbones associated with some kind of local or systemic factors. A bone can be damaged by extraction of the tooth or many other minor dental interventions such as implantations, curettage of periodontal pockets, drainage of abscesses etc.

Table 1: Predisposing factors for MRONJ

Predisposing factors	Patient-dependent factors	Intervention depending factors
Local	Poor oral hygiene Periodontitis Periapical pathology Non-vital teeth Periodontal abscesses and other infections of the orofacial region Periimplantitis Bony exostoses and toruses Bad habits, biting hard objects	Tooth extraction Poorly adapted prostheses Presence of implants Implantation procedures Curettage of periodontal pockets Oral-surgical and maxillofacial interventions Poor dental fillings
Systemic	Age over 65 years Smoking Hyperthyroidism Diabetes mellitus Autoimmune diseases Anemia Chronic renal insufficiency Hypocalcemia Hypovitaminosis	Simultaneous use of antiresorptive therapy with: Antiangiogenic Oncology therapy: radiation chemotherapy Immunosuppressive therapy Hormonal therapy

Some cases of MRONJ can happen even when none of obvious dental factors are present.

4. Stages of MRONJ

Stage 0 is generally without clear symptoms that would raise suspicion of MRONJ.

The jaw bone is not exposed at this stage, and there are no specific clinical symptoms. Sometimes, odontalgia without clear dental causes, unspecified neuralgiform pain in the jaws or the maxillary sinus, and rarely in the temporomandibular joint could be present. Radiological diagnostics show resorption or sclerosis of the alveolar bone, thickening of the laminae dura, expansion of the periodontal ligament, or discrete thinning of the bone trabeculas that can be observed even in completely healthy patients.

Stage 1. There is minimal or minor exposition of the necrotic bone or a fistula. The bone can be probed through the fistula. Most patients at this stage have no symptoms, and there are no signs of inflammation or infection. A tooth can be luxated without the presence of periodontal disease, periapical fistula also can be present but without pulp necrosis. Radiological diagnosis may resemble the first stage. An alveolus that does not heal is often present. The most often common findings are osteolysis or osteosclerosis of bone. Characteristic radiography shows that all radiological changes are observed within the alveolar ridge of the jaw bone.

Stage 2. There is an intraoral fistula that makes necrotic bone exposed and clearly visible in the oral cavity. Large exposition of

the necrotic bone is accompanied by pain and infection. Oral functions such as swallowing or speech cause discomfort or pain to the patient. Symptoms of inflammation and infection of the surrounding soft tissue region are always present often accompanied by suppuration. Radiological diagnostics can resemble the first or second stage. Sometimes there is diffuse sclerosis of the bone marrow, with or without cortical erosion, thickening of the alveolar ridge, thickening of the mandibular canal, sequestration, periosteal reaction and cloudy appearance of the maxillary sinus. All radiological changes are observed within the alveolar ridge of the jawbones.

Stage 3. This stage is followed by great local morbidity, exposed and necrotic bone, intraoral or extraoral fistulas, with infection, suppuration, and bone necrosis extending beyond the alveolar ridge region. Huge sequesters extend to the base of the mandible, or the maxillary sinus or zygomatic process of the maxilla. Extraoral fistula, oroantral or oronasal communication is mostly present. Spontaneously, smaller fragments breaking off of the necrotic bone may occur. Radiological findings indicate osteolysis extending to the base of the mandible, sinuses, and nose, with pathological fractures, and osteosclerosis of adjacent bones (zygomatic bone and hard palate).

Clinical signs and symptoms that may arouse suspicion of MRONJ are: abscess, exposed bone, intraoral or extraoral fistula, purulent discharge from the nose, oral mucosa, halitosis, jaw pain of unknown origin, deformity or fracture of the mandible, alveolus that does not heal after extraction, paresthesia, i.e. numbness of the lower lip, intraoral soft tissue swelling, spontaneous appearance of bone fragments, appearance of mobility of teeth and implants, and odontalgia without a clear cause. Differential diagnosis should exclude other conditions. Similar symptoms such as alveolitis, sinusitis, periodontitis, periapical processes, atypical neuralgia, fibroses lesions, sarcoma, osteomyelitis, temporomandibular joint disorders may appear[16].

5. Multidisciplinary approach to MRONJ

Beforehand considering the treatment of patients with medicaments that can cause MRONJ, a consultation with a rheumatologist, oncologist, and dentist should be done. Multidisciplinary pretreatment should be coordinated and provided timely, reducing the incidence of MRONJ by 77.3%[17]. Pretreatment significantly contributes to the improvement of oral health and raising the awareness of patients about the importance of maintaining hygiene and regular checkups at the dentists.

Table 2. Specialists and specific interventions involved in the prevention of MRONJ

Specialist	Intervention
ONCOLOGIST	Diagnosing the presence of malignancy Biochemical lab. (Ca, P, etc.) Counseling on timely dental treatment Assessment of the urgency of including therapy due to the presence of a malignant disease Considering monotherapy or combining dual or more therapies that may lead to MRONJ **REFER THE PATIENT TO THE DOCTOR OF DENTAL MEDICINE** **WARN THE PATIENT ABOUT THE POSSIBILITY OF MRONJ DEVELOPMENT**
RHEUMATOLOGIST	Diagnosing the presence and the stage of osteoporosis Assessment of bone tissue condition Densitometry of bone tissue Biochemical lab. (Ca, P) Hormonal status Diagnosing the presence of comorbidities, autoimmune or systemic diseases **REFER THE PATIENT TO THE DOCTOR OF DENTAL MEDICINE** **WARN THE PATIENT ABOUT THE POSSIBILITY OF MRONJ DEVELOPMENT**
DENTIST	Premedication and regular appointments with the dentist Mouth rinsing with 0.12% chlorhexidine twice a day Removal of soft and hard deposits Teeth with a good prognosis should be taken care of with conservative treatment Teeth with a poor prognosis should be extracted with minimal trauma Adjustment of prostheses without pressure on the bone tissue Advising the patient not to use prostheses during treatment with antiresorptive drugs Treatment of initial periodontal disease Treatment of initial peri-implantitis Appoint regular checkups every 3–6 months **WARN THE PATIENT ABOUT THE POSSIBILITY OF MRONJ DEVELOPMENT**

6. *Minor oral surgical interventions with risk of MRONJ*

6.1. Tooth extraction

Acute or chronic infection is the main predisposing factor related to the appearance of MRONJ in risk patients. The tooth that cannot be restored conservatively poses a threat to infection and extraction should be performed correctly and in a timely manner.

Patients treated with low doses of oral BP for a period of less than two years, due to osteoporosis and without other comorbidities, can undergo routine tooth extraction with primary wound closure[1,18.] Patients at high risk, treated with high doses of antiresorptive drugs, or intravenous therapy due to oncological diseases, or those who have combined antiresorptive and antiangiogenic therapy, pose other comorbidities, should be treated using specific surgical protocols that include raising the mucoperiosteal flap, tooth extraction, careful treatment of bone edges, bone polishing and complete closure of the flap without tension[1,19]. It is not wrong to consider every tooth extraction as a high risk intervention, whereby the wound should be completely sutured.

Perioperative application of antibiotic therapy, drugs from the group of penicillins or beta-lactam penicillins, usually with the addition of metronidazole is mandatory. Antibiotics therapy should start at least one day from a minimum of 1 day preoperatively to 7–10 days after the intervention[20]. There is no uniform opinion about drug holiday. There are some opposite opinions due to the effectiveness of drug holiday related to bisphosphonate therapy, due to the multi-year cumulative effects. Denosumab therapy can be excluded 1–2 months before the intervention, in consultation with ordinarius treating osteoporosis or malignancy, and continued 4–6 weeks after the surgical intervention, i.e. until the wound is completely healed[5].

6.2. Dental implants and the risk of MRONJ

Implant procedures are generally contraindicated in patients treated with high doses of BP. Patients treated with low doses of BP may be candidates for implantation, but it is necessary to inform the patient about the potential even higher risk of MRONJ lesions. It is proposed to have written consent, because of the increased risk of MRONJ1 and decreased implantation success. Before any type of intervention that includes damage to the bone, bisphosphonate treatment duration should be taken into account, because the risk increases overtime[3,5,12].

7.Assessment of the degree of risk for the occurrence of MRONJ

Experience of the doctors and data suggest that some of the predisposing factors, which can be found by detailed anamnesis and clinical examination, could help reduce the development of MRONJ. Evaluation of the patients is shown in Table 3.

Table 3. Evaluation of patient's condition for MRONJ development

General anamnesis	Data on the use of: Bisphosphonates Other antiresorptive agents Drugs with antiangiogenic activity Drugs for reduced circulation Antidiabetics Radiopharmaceutical preparations (radium-223) Estrogen inhibitors (raloxifene) Immunomodulators (methotrexate and corticosteroids)
Dental anamnesis	Data on: Occurrence of any change in sensitivity Condition of teeth, soft tissues and periodontium Occurrence of lesions (time, cause) Presence of pain Presence of post dental intervention (postextraction) non-healing wound
Clinical examination	Vitality test Probing Percussive sensitivity Poor dental fillings Initial periodontitis Initial peri-implantitis Inflammation and infection of soft tissues
Radiological examination	Orthopantomography Three-dimensional orthopantomography Come Beam Dental Scanner Computed tomography Magnetic resonance
Biopsy	Only in case of suspected metastatic changes in the jawbones

8. ***Therapy of MRONJ***[3,5,12,21]

The first rule is not to begin with the treatment of MRONJ without appropriate radiography. If some radiological methods, for example, retroalveolar or orthopanthomographic records make some indecisivnesses, do the second, technologically more advanced.

The treatment of MRONJ can be conservative or surgical, depending on the stage of developing lesions and other symptoms. There are some opposite opinions in view of surgery considering changes in the structure and functions of jawbones. Surgical treatment implies sequestrectomy that extends to the limit of healthy bones, but considering that the whole bone structure is similar, surgery should be done very sparingly and carefully. This is the reason why most protocols advocate primarily curative—conservative therapy.

Conservative therapy is desirable in any stage of MRONJ. Especially in case where the surgical treatment can be complicated with the presence of comorbidities. The curative preventive methods enable remission or complete healing, depending on the stage of lesions, and other local and systemic factors.

In the zero stage of MRONJ preventive hygienic dietary measures (vitamin A, D, C) and maintenance of oral hygiene with soft brushes, usage of oral antiseptic solutions (0.12% chlorhexidine twice a day) are recommended. This way of acting enables removing of biofilm from teeth and mucosa, reducing the number of microorganisms.

In the first stage of MRONJ, suggested treatment is strict oral hygiene, rinsing mouth with oral suspensions of chlorhexidine 0.12%, twice per day. Biofilm from the necrotic exposed bone can be removed by a cotton swab dipped in chorchexidine. If the pain is present, some analgesics should be prescribed.

In the second stage of MRONJ, treatment is the combination of preventive hygienic dietary measures and surgery. Application of antibiotics, primarily penicillin with clavulonic acid in combination with metronidazole is mandatory. The duration of antibiotic therapy lasts from 7 to 14 days. In case of penicillin allergy, it can be changed with erythromycin, clindamycin or ciprofloxacin. If the bone sequester is formed, operative removal could be postponed by curettage and polishing of the surface layer of the bone. That means a gentle sequestrectomy only of the exposed bone in patients who are not favorable candidates for surgical therapy (oncology patients, patients with major comorbidities). If this treatment provides no improvement, surgical treatment should be performed. The exposed necrotic bone is a continuous source of irritation and infection, so sequestrectomy is the solution. In case of surgical removal of the sequester, antibiotic therapy lasts 21–28 days[10,12].

In the third stage of MRONJ, standard non-surgical treatment must be combined with surgical treatment, including removal of necrotic sequestrated and surrounding damaged bone, until the surrounding jawbone does bleed. Marginal mandibulectomy or maxillectomy is suggested considering the size of the necrotic lesion and bone sequester. In more severe cases, segmental or en bloc resection followed by osteoplasty of the defect is indicated. Bone removal should always be done from macroscopically visible altered bone tissue to vital vascularized bone tissue, allowing the healing. Antibiotic and analgesic therapy are mandatory, but show less effectiveness over time[3,5,10,12,21].

Surgical therapy is not reserved exclusively for the third stage but can be carried out in the first and second stages as well if there is no improvement in symptoms or disease progression occurs.

Conclusion

Medication-related osteonecrosis of the jaw negatively affects quality of life and leads to significant morbidity. Changes in the jawbones, more common in the mandibula than maxilla, can vary from asymptomatic, through discrete undefined pain, to very severe lesions. Pathological fracture of the jawbones, infection, cutaneous fistulas and large scars and disfigurement can develop in case of non-timely diagnosis and prevention Neglecting prevention, late diagnosis and delaying treatment of MRONJ can lead the patient to mutilation, dysfunction and poor life quality.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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