

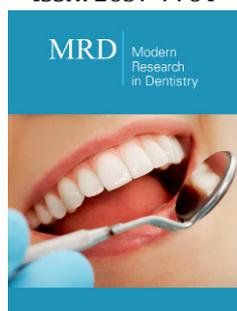
Prevention of Drug Osteonekrosis of Jaws: Current State of the Problem

Elena M Spevak^{1*} and Dmitry Y Christoforando²

¹Oral and Maxillofacial Surgeon, Stavropol City Clinical Emergency Hospital, Russia

²Doctor of Science, Stavropol State Medical University of the Ministry of Health of Russia, Russia

ISSN: 2637-7764



***Corresponding author:** Spevak EM, Oral and Maxillofacial Surgeon, Stavropol City Clinical Emergency Hospital, 355040, Stavropol region, Stavropol, Tukhachevsky St., 17, Russia

Submission: 📅 September 20, 2021

Published: 📅 November 29, 2021

Volume 7 - Issue 1

How to cite this article: Elena M Spevak, Dmitry Y Christoforando. Prevention of Drug Osteonekrosis of Jaws: Current State of the Problem. Mod Res Dent. 7(1). MRD. 000651. 2021. DOI: [10.31031/MRD.2021.07.000651](https://doi.org/10.31031/MRD.2021.07.000651)

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Abstract

The problem of prevention of medicinal osteonecrosis of the jaws is one of the lively discussions of the last decade in dentistry. Osteomodifying drugs (bisphosphonates, denosumab) most often cause medicinal osteonecrosis of the jaws. They are used to suppress resorption in osteoporosis, metastatic lesions of the bones of the skeleton, aseptic necrosis of the femoral and humerus heads, various genetic diseases accompanied by osteogenesis imperfecta and osteopenic syndrome. Due to the high prevalence of osteoporosis and malignant neoplasms in the population, the prescription of osteomodifying drugs has become a routine practice. Medicinal osteonecrosis of the jaws is an iatrogenic disease that is difficult to treat and leads to serious consequences in the form of a pathological fracture of the jaw, a chronic purulent-inflammatory process, and extensive defects in the jaw bone tissue. It is known that the most common drug osteonecrosis of the jaws occurs after tooth extraction surgery in patients taking osteomodifying drugs. To date, no method has been developed with proven efficacy that can completely prevent the disease, therefore, much attention is paid to measures that reduce the risks of complications. Providing surgical dental care to this category of patients is a difficult task. All of the above determined the task of researching and generalizing the basic principles of prevention of drug-induced osteonecrosis of the jaws in patients with a history of osteomodifying therapy, which are presented in this review.

Keywords: Bisphosphonates; Denosumab; Osteonecrosis; Tooth extraction

Introduction

As shown by static studies, indicators of dental health, oral hygiene and general somatic status of dental patients leave much to be desired from year to year, which is associated with a large number of factors - environmental, nutritional, stressful, economic [1]. The need to provide quality dental care remains at a high level [2]. A dental surgeon today must be fluent in not only his skills, but also be aware of the latest pharmaceutical developments and their possible iatrogenic consequences [3].

One of the most lively discussions of the last decade is the problem of the occurrence of osteonecrosis of the jaws in patients taking antiresorptive drugs [4]. From isolated events, this complication has firmly taken its place in the structure of maxillofacial pathology [5,6]. It is known that osteonecrosis of the jaws is difficult to treat and leads to serious consequences in the form of a pathological fracture of the jaw, chronic pyoinflammatory process, extended defects in the bone tissue of the jaws [7,8]. The most likely risk of developing osteonecrosis due to tooth extraction, in second place - trauma to the mucous membrane of an irrationally manufactured removable prosthesis [9]. There have been reports of cases when dental surgeons refused to allow their patients to have their patients routinely extracted on the basis of the possibility of developing such a complication in them [10]. The main reason that interferes with the effective performance of their duties, of course, is the lack of a clear

understanding of the mechanism of development of osteonecrosis of the jaws, as well as the methods of its effective prevention. All of the above determined the task of researching and generalizing the basic principles of prevention of drug-induced osteonecrosis of the jaws in patients with a history of osteomodifying therapy, which are presented in this review. To achieve this goal, the latest literary sources on this topic have been analyzed, including positional documents on osteonecrosis of the jaws [5-9], adopted by the world communities of maxillofacial surgeons and dental surgeons in the USA, Italy, Japan, South Korea, Austria.

Osteomodifying agents-indications for use, principle of action

Osteomodifying drugs have been widely used in medical practice for the last two decades [11]. Today osteomodifying agents are indicated for patients with osteoporosis, with metastatic lesions of the bones of the skeleton, with aseptic necrosis of the femoral and humerus heads, with osteogenesis imperfecta and osteopenic syndrome [12,13]. Osteomodifying agents that cause medicinal osteonecrosis of the jaws include bisphosphonates and denosumab [5-9].

Bisphosphonates - stable analogs of inorganic pyrophosphates, accumulate in osteoclasts and block their action both by direct cytotoxic effect ("simple" BP) and by acting on intracellular enzyme systems necessary for the normal functioning of osteoclasts (nitrogen-containing bisphosphonates). Thus, the osteoclast first loses its ability to lysis, and then its apoptosis occurs [13]. Due to the fact that bisphosphonates have a high chemical affinity for bone tissue and accumulate in it, this antiresorptive effect is very pronounced and persists for a long time even after the drug is discontinued [14].

Due to genetic engineering and high demand for this segment of drugs, in 2010. a qualitatively new group of drugs with an antiresorptive effect has appeared on the pharmaceutical market - a monoclonal antibody to the ligand of the receptor-activator of nuclear factor kappa-beta (RANKL)-denosumab [15]. Unlike bisphosphonates, which inhibit the activity and death of mature osteoclasts, denosumab acts extracellularly, acting as an analogue of osteoprotegerin (OPG), an endogenous inhibitor of RANKL in the RANK / RANKL / OPG regulatory receptor ligand system [16]. Denosumab interacts with RANKL, which is expressed by the stromal precursors of osteoblasts, which prevents its interaction with the receptor-activator of nuclear factor kappa-beta (RANK), which is secreted by preosteoclasts from myeloid cells. As a result, the differentiation and survival of osteoclasts is impaired, the rate of bone resorption is significantly reduced. Thus, denosumab affects the maturation of "young" osteoclasts and does not affect the function of mature cells, therefore it is believed that the effect

of denosumab is reversible. Inhibition of the resorption process leads to an increase in bone strength due to the mineral component, which largely prevents low-energy bone fractures and reduces pain by eliminating hypercalcemia [17].

Pathogenesis of medicinal osteonecrosis of the jaws

Normally, bone tissue repair is impossible both without the synthetic function of osteoblasts and without the resorptive action of osteoclasts; therefore, the regenerative potential of bone tissue decreases against the background of the action of antiresorptive drugs [18]. For the jaw bones, this is especially critical, since they are covered with a thin mucous membrane, actively colonized by microflora, communicate with the external environment through periodontal fissures and experience constant stress [7]. Operation of tooth extraction, trauma to the oral mucosa with sharp edges of crowns and prostheses trigger the wound process, which in the presence of oral microflora is often accompanied by inflammation [2]. Normally, with timely treatment, such interventions end with complete restoration of the defect and epithelialization. But, unfortunately, it has been proven that in a certain part of patients taking antiresorptive therapy (from 1.5 to 15% according to various sources), an osteonecrosis focus appears at the site of injury, which is no longer capable of self-healing [19]. According to the definition given by the AAOMS (American Association of Dental and Maxillofacial Surgeons), osteonecrosis of the jaw is a complication of osteomodifying drug therapy and is characterized by necrosis and exposure of a bone site that persists for more than 8 weeks, with subsequent progression of the process, provided that there is no history of radiation therapy to the head area [5]. To date, it has been proven that both bisphosphonates and denosumab are equally capable of causing such a complication [6].

Methods for the prevention of medicinal osteonecrosis of the jaws

To date, unfortunately, no method has been developed with proven efficacy that can completely prevent the disease. Therefore, much attention is paid to those measures that can, to some extent, reduce the risks of drug-induced osteonecrosis of the jaws. The most significant specialists include dental screening and oral cavity sanitation in patients planning to start taking antiresorptive drugs [5-9]. In practice, unfortunately, even those patients who are warned about osteonecrosis do not always visit the dentist before starting treatment. It is no wonder why the prevalence of osteonecrosis of the jaws is increasing from year to year.

Most researchers put the issue of oral hygiene at the forefront when assessing the risk of osteonecrosis of the jaws. A dental surgeon should be aware that, according to many studies, professional cleaning of the oral cavity before elective interventions reduces the risk of osteonecrosis by several times [19].

Since the most important provoking factor in the development of osteonecrosis of the jaws is the previous bone injury, interventions in the oral cavity should be divided into conditionally safe and potentially risky in terms of the development of osteonecrosis. Most researchers consider all minor operations on the skin of the face and oral mucosa as conditionally safe, including excision of neoplasms, retention cysts, and soft tissue biopsy. Such interventions can be performed without special training of the patient, since they do not carry the risk of developing the osteonecrotic process, but with caution so as not to damage the periosteum of the jaws and the periodontium of the teeth [4,5].

Potentially risky in terms of the development of osteonecrosis of the jaws are all manipulations in which the bone tissue of the jaws is traumatized, as well as the periosteum and periodontium of the teeth. These manipulations include tooth extraction, periostotomy and pericoronarotomy, periodontal surgery, dental implantation, operations for jaw cysts [6-9]. Leading associations of specialists in the pathology of the oral cavity and maxillofacial surgery in the USA, Italy, Japan, South Korea, Austria agree that the risk of drug-induced osteonecrosis of the jaws cannot be assessed in the long term, and we are talking about a more or less high risk of occurrence complications that the specialist should try to reduce as much as possible in his favor together with the patient. And in this case, the only correct tactic on the part of the dentist will be to fully inform the patient about the presence of any dental pathology and about the likelihood of osteonecrosis of the jaws during manipulations in the oral cavity. With a planned intervention, you first need to assess the risk / benefit ratio for a particular patient and his dental diagnosis. Much attention should be paid to taking anamnesis and talking with the patient. When examining the oral cavity, it is necessary to make sure that there are no clinical signs of osteonecrosis (pain without an odontogenic or stomatogenic cause, the presence of a bare area of the jawbone or fistulous passages without an odontogenic cause). Orthopantomography is mandatory in this case. This measure will greatly simplify the follow-up of the patient and will serve as a control tool in the event of controversial and conflict situations [5-9]. The patient should be informed that, unfortunately, even with all possible recommendations available today, the development of osteonecrosis of the jaws for him is likely in about 1.5-7.7% of cases for cancer patients and about 0.3-1.5% for patients with osteoporosis. You should also inform the patient that if he does not follow the rules of oral hygiene, the presence of numerous foci of odontogenic infection, as well as with prolonged (more than 12 months) use and increased doses of drugs for antiresorptive therapy, the risk of osteonecrosis of the jaws for him significantly increases and is about 10-15% [20]. The latter is relevant both for patients with malignant neoplasms (high doses of drugs) and for patients with osteoporosis (long-term therapy,

frequent combinations of bisphosphonates with denosumab). In this case, the patient should receive comprehensive information about such a complication and be able to participate in the decision to carry out any surgical procedures in the oral cavity. The principle of informed voluntary consent in this case works primarily in favor of the doctor, since it protects him from negative legal consequences.

If there is no need for emergency care, it will be correct to refer the patient to the attending oncologist (endocrinologist, traumatologist) who has prescribed antiresorptive therapy in order to obtain a conclusion about the underlying disease at the moment and the possibility of discontinuing drugs for the period necessary for preoperative preparation and postoperative wound healing. ... Discussion of the need for a "drug holiday" is one of the most controversial aspects of the prevention of osteonecrosis of the jaws [21,22]. To date, researchers do not have an unambiguous answer to the question of whether the withdrawal of antiresorptive therapy for a certain period of time before invasive dental treatment is an effective way to prevent drug-induced osteonecrosis. American researchers and AAOMS specialists in their position paper from 2014. recommend the abolition of antiresorptive therapy for a period of at least 2 months for bisphosphonates and 6 months for denosumab before the intervention and up to 3 months after, until the surgical wound (hole) is completely healed, if the patient's condition allows the drug to be canceled. For denosumab, the withdrawal period corresponds to the frequency of administration of the drug (1 time in 6 months), since it is believed that its effect is reversible [5]. For bisphosphonates, this approach is based on the physiology of bones and the pharmacokinetics of antiresorptive drugs: since 50% of the drug dissolved in the serum is excreted by the kidneys, the main reservoir of bisphosphonates is the osteoclast, which lasts 2 weeks. Thus, most serum free drug will be extremely low 2 months after the last dose, and a 2-month drug-free period should be sufficient prior to invasive dental procedure [21]. According to AAOMS, a prerequisite for a "drug holiday" is the decision of the attending physician, who takes into account the possibility of adverse consequences that can be caused by the cancellation of therapy during this period (pathological fracture, increased pain syndrome, etc.), or the decision of the patient himself. This circumstance is emphasized in the document, since the legal consequences are of great importance in the event of an unfavorable outcome.

The Italian Society of Oral Pathology and Medicine (SIPMO) recommends that bisphosphonates be discontinued at least 1 week before the intervention and resumed 4-6 weeks afterwards to ensure an adequate healing period. When taking denosumab, SIPMO specialists consider it advisable to perform invasive procedures in the oral cavity 4 weeks after the last injection and no later than 6 weeks before the next injection [6].

In turn, the Japanese Union Committee on Osteonecrosis of the Jaws, according to the position document of 2017, is skeptical about the abolition of bisphosphonate therapy in order to prevent drug osteonecrosis. The authors rely on the physicochemical properties of bisphosphonates, which are deposited and retained in the bone for a long period of time, so it seems unlikely that short-term discontinuation of the drug will prevent osteonecrosis. With regard to denosumab, their position coincides with American researchers, but in general, they do not recommend discontinuing drugs for patients with osteoporosis due to the fact that their risk of developing osteonecrosis medication is much less than that of a low-energy fracture. Much more important for reducing the risk of osteonecrosis, in their opinion, is the prophylactic administration of antibacterial drugs [7].

According to the researchers, the appointment of antibiotic therapy before surgical interventions in the oral cavity is an important part of the prevention of osteonecrosis of the jaws in connection with the alleged role of the oral microflora in the pathogenesis of the disease. Most researchers advise to start taking medications 2-3 days before the proposed operation in case of planned interventions and immediately before intervention in emergency cases. Preference is given to amoxicillin with clavulanic acid in combination with metronidazole. In patients allergic to penicillin, erythromycin, clindamycin, clarithromycin, or ciprofloxacin are recommended orally for at least 7-10 days until the surgical site heals [7-9].

The provision of surgical dental care is often required urgently in the presence of an acute inflammatory process in the oral cavity. The most common reason for treatment is the exacerbation of chronic periodontitis and the need for tooth extraction [2]. In the latter case, the dentist has fewer opportunities to prepare the patient as described above. It should be said right away that postponing tooth extraction in this case is the wrong tactic, especially in elderly weakened patients, since in this case the risk of pyoinflammatory complications significantly exceeds the likelihood of osteonecrosis [23]. Careful collection of anamnesis, warning of a possible complication and informed voluntary consent of the patient in this case are of particular importance. Orthopantomography is an important condition for the success of the patient's further treatment. Antibiotic therapy for such patients is recommended to be prescribed on the day of treatment and until the wound heals (up to 14 days).

Researchers pay special attention to the technique of tooth extraction surgery as the most common manipulation in dental surgical practice. It is recommended to perform removal with the minimum possible level of trauma, using periostomes and luxators, smoothing the sharp edges of the bone and suturing the wound tightly [5]. Wound care is carried out until the mucous

membrane is completely healed. Control examination is carried out in 6-8 weeks. The patient is recommended to rinse with antiseptic solutions (0.12% aqueous solution of chlorhexidine) for the entire specified period. Positional documents describe the effectiveness of introducing a clot centrifuged from the patient's plasma into the socket of an extracted tooth, a course of local ozone therapy or laser therapy in the area of the sockets [5-9].

Separately, it should be said about the dental implantation procedure. The attitude of researchers to this procedure in patients receiving antiresorptive therapy is rather negative. Most experts on this issue are categorical: the installation of dental implants should be avoided in patients receiving intravenous antiresorptive therapy. In some cases, it is stipulated that for patients taking oral bisphosphonates for osteoporosis, it is possible to carry out the implantation procedure with the informed consent of the patient [5-9].

Conclusion

Summarizing the above, we believe that the outpatient stage of the provision of surgical dental care is important for patients receiving therapy with osteomodifying agents, since the competence of a specialist, in this case, depends not only on the correct attitude of the patient and reasonable treatment tactics, but the ability of the dental surgeon to make the right decision in the event of a complication. According to experts, many patients with jaw necrosis are sent to the departments of maxillofacial surgery from dental clinics after tooth extraction and subsequent repeated unsuccessful attempts to treat the complication that has arisen, including curettage and revision of the holes, tooth extraction near the emerging focus of exposed bone tissue, necrectomy, the imposition of secondary sutures, the laying of various osteotropic drugs. All these manipulations led to the expansion of the necrosis zone, and with an insignificant positive effect in the long term, there was a divergence of the sutures, the appearance of fistulous passages and an exacerbation of the process with the addition of a secondary infection. All of the above manipulations refer to irrational tactics and lead to a deterioration in the patient's condition. If, upon examination by a specialist, there is a suspicion of an existing osteonecrosis of the jaws, the correct tactics will be to provide the patient with the necessary emergency assistance (opening and drainage of abscesses, removal of movable teeth, immobilization in case of a pathological fracture of the jaw), adequately anesthetize, prescribe antibiotic therapy and refer the patient to the consultation of the jaw - a facial surgeon.

The realities of today's medicine are such that the number of patients who are prescribed osteomodifying agents is very large and will grow steadily from year to year. Therefore, unfortunately, medicinal osteonecrosis of the jaws is a complication that every

actively practicing dentist will have to face. Accessible information and a qualified interdisciplinary approach in the provision of surgical dental care to such a category of patients is the key to a successful treatment outcome.

Conflict of Interest

The authors declare no conflicts of interest.

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