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# PREVENCIJA NASTANKA BISFOSFONATNE OSTEONEKROZE VILICA UPOTREBOM AUTOLOGNOG TROMBOCITNOG **KONCENTARATA**

# PREVENTION OF BISPHOSPHONATE RELATED **OSTEONECROSES OF THE JAW USING AUTOLOGOUS** PLATELET CONCENTRATE

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#### Sažetak

Uvod: Fibrin bogat trombocitima (PRF) se sada široko koristi u

različitim oblastima medicine, uključujući regeneraciju tkiva. **Cilj rada** je bio da se analizira efekat PRF-a na poboljšanje postoperativnog zarastanja rana kod pacijenata sa rizikom od razvoja bisfosfonatne osteonekroze vilice.

Prikaz slučaja: Žena, stara 71 godinu, koja je na bisfosfonatnoj terapiji, zbog generaliznove osteoporoze, javila se na kliniku sa indikacijom za hiruršku ekstrakciju impaktiranog gornjeg levog očnjaka. Oralno hirurško lečenje je sprovedeno nakon tromesečnog prekida terapije. Tokom hirurške ekstrakcije impaktiranih zuba, postavljen je fibrinski bogat trombocitima i prekriven membranom bogatom trombocitima. Zarastanje rane bilo je uspešno.

Zaključak: Primena PRF-a za oralne hirurške intervencije kod pacijenata koji uzimaju BP izgleda kao obećavajuće rešenje i odličan alternativni tretman za zarastanje oralnih tkiva.

Ključne reči: bisfosfonati, osteonekroza, osteonekroza vilice povezana sa bisfosfonatima, fibrin bogat trombocitima, oralne hirurške intervencije.

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#### Abstract

Introduction: Platelet-rich fibrin (PRF) is now widely used in various fields of medicine, including tissue regeneration.

The aim of the work was to analyze the effect of PRF on improving postoperative wound healing in a patient with a risk of developing bisphosphonate osteonecrosis of the jaws. Case report: Case report: A 71-year-old woman, who is on

bisphosphonate therapy due to generalized osteoporosis, came to the clinic with an indication for surgical extraction of an impacted upper left canine. Oral surgical treatment was performed after a three-month interruption of therapy. During the surgical extraction of impacted teeth, a platelet-rich fibrin is placed and covered with a

Conclusion: The use of PRF for oral surgical interventions in patients taking BPs appears to be a promising solution and an excellent alternative treatment for the healing of oral tissues. Key words: bisphosphonates, osteonecrosis, BRONJ, platelet-rich fibrin, oral surgical interventions.

Key words: bisphosphonates, osteonecrosis, bisphosphonate-related osteonecrosis of the jaw, platelet-rich fibrin, oral surgical interventions.

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# Introduction

Bisphosphonates are used for the prevention and treatment of numerous bone diseases in which there is an impairment of bone metabolism. These medications are indicated in multiple myeloma, bone metastases that develop as a result of breast and prostate cancer, as well as in Paget's disease. They are also used in patients with primary or secondary osteoporosis to prevent pathological fractures<sup>1,2</sup>. The bone action of these medications focuses on reducing bone resorption through the inhibition of osteoclast activity, as these cells play a central role in both physiological and pathological bone resorption<sup>3,10</sup>. Bisphosphonates are generally classified into two groups based on the presence or absence of an amino group:

• Bisphosphonates without an amino group (non-nitrogen-containing bisphosphonates);

• Bisphosphonates with an amino group (nitrogen-containing bisphosphonates).

Bisphosphonates that contain an amino group (alendronate, risedronate, ibandronate, zoledronate) are stronger inhibitors of osteoclast activity, meaning their potency is greater. It is particularly emphasized that amino group-containing bisphosphonates have a higher risk of causing bisphosphonate osteonecrosis<sup>4</sup>. It has been observed that bisphosphonate osteonecrosis can develop spontaneously or be associated with certain dental procedures, such as tooth extractions or the use of dentures<sup>7,8</sup>.

In most clinical trials, a strong correlation has been established between the use of these drugs and the occurrence of osteonecrosis of the jaws<sup>5,6</sup>. **Bisphosphonate-Related** Osteonecrosis of the Jaws (BRONJ), is a rare but serious complication of the jawbones that can occur following therapy with antiresorptive or antiangiogenic drugs. According to the Association American of Oral and Maxillofacial Surgeons (AAOMS)<sup>9</sup>, BRONJ presents as an area of exposed bone in the maxillofacial region (jaws) that does not heal within eight weeks. It occurs in patients who are receiving or have received bisphosphonates or other antiresorptive drugs and who have no history of radiation therapy or metastatic disease in the jaws.

While there is considerable agreement among reports regarding the clinical presentation and risk factors associated with BRONJ, the exact etiology and pathogenesis remain unclear. Therefore, there is an ongoing effort in the literature to provide a suitable explanation for this adverse effect of bisphosphonate therapy<sup>11</sup>. Suggested

hypotheses relate to bone turnover suppression, angiogenesis suppression, soft tissue toxicity, infection, changes in local pH values, immune system deficiency, and genetic predisposition<sup>11</sup>.

There are numerous hypotheses for the causes of BRONJ, but the most common cause or trigger is tooth extraction<sup>7,8</sup>. The most widely accepted hypotheses for the occurrence of osteonecrosis are the inhibitory effect of bisphosphonates on osteoclastic activity in bone cells, as well as their toxic effect on soft tissues and their antiangiogenic effects<sup>12,13</sup>. The influence of bisphosphonates on the oral microflora and the formation of biofilm (microbiota) at the site of osteonecrosis is one of the possible causes of its occurrence<sup>14,15</sup>.

Biofilm consists of numerous bacterial colonies interconnected by fibronectin fibers <sup>17</sup>. These colonies coat the necrotic tissue and are the most common cause of frequent and recurrent infections in these patients<sup>15</sup>.

In a study by Hristamyan Meri A. et al.<sup>16</sup>, among 112 cancer patients diagnosed with BRONJ, the highest proportion of patients were smokers/ex-smokers and consumed alcoholic beverages occasionally, linking them to these potential risk factors.

## Aim

The use of platelet-rich fibrin (PRF) is a novel approach to tissue regeneration and is gradually becoming a valuable tool in promoting tissue healing in a wide range of oral surgical interventions. The aim of this clinical study was to confirm the influence of platelet-rich fibrin on bone and soft tissue defects during oral surgical intervention in a patient undergoing bisphosphonate therapy.

# Case Report

A 71-year-old female patient was referred to the Clinic for Oral Surgery and Implantology of the University Dental Clinical Centre "St. Pantelejmon" in Skopje with a diagnosis of a fissure in the alveolar ridge mucosa. Two months before presenting to the Clinic for Oral Surgery, she had been treated by her dentist and prosthodontist for pain localized on the palatal side in the frontal region of the maxillary alveolar ridge. Her dentist treated the condition as if it were an exostosis, prescribing a gingival gel and frequent rinsing of the wound with herbal teas. According to the medical history obtained upon admission to the Clinic of Oral Surgery, it was determined that the patient was still experiencing the same subjective symptoms, i.e., persistent pain and discomfort in the frontal maxillary region.

Objectively, the presence of an area of hyperemia in the oral mucosa of the maxillary alveolar ridge was noted (Figure 1). Additionally, the patient was receiving regular bisphosphonate therapy due to osteoporosis resulting from her primary diagnosis of Following osteoporosis. the clinical examination, the patient was instructed to obtain a retro-alveolar X-ray, which revealed the presence of impacted maxillary canines on the left and right sides (Figure 2). The patient was scheduled for an oral surgical intervention and premedication was in one week, prescribed: an antibiotic (Amoxiclav); Chlorhexil EXTRA, a wound rinsing solution; and Chlorhexil Gingival Gel, an antiseptic gel. Additionally, the patient was instructed to

provide a report from a rheumatologist because of her ongoing therapy and the upcoming oral surgical intervention.

After one week, the patient was fully prepared for the intervention. The rheumatology report recommended discontinuation of bisphosphonate therapy for the next three months. The patient had discontinued the therapy for three months, and a noninvasive oral surgical intervention was then proceeded with.

Before the procedure was carried out, written informed consent was obtained from the patient. The clinical case was conducted by the ethical standards set by the World Medical Association's Declaration of Helsinki.



*Figure 1.* Situation in the mouth before oral surgical intervention (redness of the oral mucosa and apex of the impacted right maxillary canine)



Figure 2. X-Rays show impacted left and right maxillary canines

# Surgical Procedure

Under infiltrative plexus anesthesia, a horizontal incision was made along the ridge with distal relaxing incision. a The mucoperiosteal flap was created from both the palatal and vestibular sides. After the flap was gentle osteotomy raised. а was performed—circularly around the neck of the tooth—and with upper premolar forceps, the tooth was extracted. A noninvasive approach was prioritized because, in patients on bisphosphonate therapy, particular care is necessary, with minimal removal of bone tissue and constant cooling, to avoid heating the bone and reducing the additional risk of bone necrosis (Figure 3 a, b, c). Furthermore, a PRF plug was applied in the extraction wound, covered with an A-PRF membrane.

The oral surgical intervention was completed by closing the wound and stabilizing the flap with a non-resorbable silk suture to ensure primary wound healing. In these patients, the suture remains in place for a longer period, approximately 10 days, before being removed.

# Blood Collection Procedure for PRF and Preparation of PRF Plug and Membrane

blood was collected Venous via venipuncture in 10 mL tubes (two tubes for balance in the PRF centrifuge) without the addition of an anticoagulant and was immediately centrifuged at 1300 rpm for 14 minutes. In this way, a fibrin clot formed in the middle of the test tube, between the red blood cells which settled at the bottom and the acellular plasma on the surface. The formed fibrin clot was removed from the tubes and separated from the red cell base at the bottom of the tube using closed scissors.

The PRF membrane and plug were prepared in the PRF Box developed by Dr. J.

Choukroun. The PRF clot from the first tube was placed in the Teflon cylinder and then pressed using the piston from the PRF box, forming the PRF plug. The PRF clot from the second tube was placed on the perforated tray in the PRF box and left for a few minutes, covered. The resulting PRF membrane was then used for the oral surgical intervention (Figure 4 a, b).

Our choice to use PRF plugs was based on the inherent benefits of PRF: its anti-inflammatory, anti-edematous, and regenerative effects.

# **Results**

When the patient returned for follow-up, one week after the surgical intervention, it was possible to observe the presence of fibrin deposits on the suture, which indicates the formation of new keratinized gingiva without signs of infection or inflammation (Figure 5 a).

After 10 days, the suture was completely removed, and healthy, pinkish soft tissues were observed. According to the Landry, Turnbull, and Howley healing index, the healing was rated as excellent with a score of 5, indicating no exposure of connective tissue and complete closure of the gingival margins. There was no granulation tissue and no pain or bleeding upon palpation.

One month after the surgical intervention, the patient returned for another follow-up. She was in good health, with an excellent condition of the supporting soft tissue apparatus (Figure 5 b).

As a result of the treatment, the wound showed complete epithelialization without infection. Four months after the intervention, an oral examination and control X-ray revealed the formation of new bone tissue and keratinized gingiva. The prosthodontist created new full dentures that fit the alveolar ridge without causing irritation or trauma to the soft and bone tissues.



*Figure 3* a, b, c. Noninvasive approach: horizontal incision and gentle osteotomy was performed—circularly around the neck of the tooth



*Figure 4* a, b. a) Venous blood taken in 10 mL tubes and preparation of PRF plugs and PRF membranes; b) PRF plugs applied in the extraction wound, and covered with PRF membranes



*Figure 5* a, b. a) Presence of fibrin deposits around the sutures; b) Removed suture after 10 days with presence of healthy, pinkish soft tissues.

# Discussion

Since it has been observed in dental practice that the number of patients receiving bisphosphonate therapy constantly is increasing<sup>5,6</sup>, certain preventive measures are strongly recommended for these patients before starting bisphosphonate therapy. The preventive approach focuses on eliminating all dental infections, which helps to avoid the need for further tooth extraction after starting this therapy<sup>3</sup>.

According to the generally accepted protocol for patients on bisphosphonate therapy, specialists in oral and maxillofacial surgery primarily recommend avoiding invasive oral surgical procedures<sup>18</sup>. However, if such procedures are necessary, it is recommended to perform a minimally invasive, atraumatic intervention. The standard surgical procedure for these patients includes the preparation of a mucoperiosteal flap to allow primary intraoperative closure and promote wound healing, thereby avoiding infection of the exposed bone<sup>19</sup>.

In addition to a strictly defined and controlled surgical procedure, prophylactic

antibiotic therapy is prescribed. Several antibiotic protocols have been suggested for this high-risk patient group. Broad-spectrum antibiotics, such as amoxicillin (1 g, three times a day) with or without clavulanic acid, in combination with metronidazole (500 mg, twice a day), are standard. In cases of penicillin allergy, erythromycin (600 mg, three times a day) or clindamycin (600 mg, three times a day) is administered. The therapeutic protocol proposed by Lodi et al. is based on combined antibiotic and antiseptic therapy<sup>20</sup>. This therapy starts three days before the oral surgical intervention and continues for at least one week postoperatively, though it may be extended depending on the wound healing progress<sup>19</sup>.

In addition to antibiotic prophylaxis, ozone gas insufflation can be applied preventively several days before the oral surgical intervention and also after suture removal, to help prevent bisphosphonate-related osteonecrosis of the jaws<sup>20</sup>.

Furthermore, several studies suggest a protocol for oral surgical interventions with the use of platelet-rich fibrin (PRF) in patients undergoing bisphosphonate therapy<sup>21,22</sup>. These

guidelines are based on the following steps: anesthesia; preparation of a mucoperiosteal flap; excision of the osteonecrotic lesion; hemostasis; application of platelet-rich fibrin (PRF); and primary closure (suturing) of the surgical wound.

After completing the minimally invasive oral surgical intervention, the application of autologous biomaterials is essential for faster and safer healing of the surgical wound, without the risk of complications.

Specifically, the growth factors present in platelets are significant for directing regenerative cells to the healing site<sup>23,26</sup>. These platelet growth factors include: PDGF (Platelet-Derived Growth Factor) - promotes cell growth, angiogenesis, and collagen synthesis; EGF (Epidermal Growth Factor) stimulates the growth of epithelial cells, promotes angiogenesis, and accelerates wound healing; VEGF (Vascular Endothelial Growth - supports angiogenesis; TGF-β Factor) (Transforming Growth Factor Beta) stimulates the growth of epithelial a endothelial cells and accelerates woo and wound healing; IGF (Insulin-Like Growth Factor) stimulates the differentiation and proliferation of mesenchymal cells; FGF (Fibroblast Growth Factor) - accelerates wound healing and collagen synthesis.

The application of platelet-rich fibrin (PRF), an autologous biomaterial rich in these growth factors, promotes faster and safer healing of the surgical wound in patients on bisphosphonate therapy by stimulating angiogenesis, cell proliferation, and tissue regeneration while reducing inflammation and edema.

Platelet degranulation leads to the release of cytokines, which stimulate the migration and proliferation of cells within the fibrin matrix, initiating the early phases of healing<sup>24,25</sup>. The platelet half-life is 8 to 14 days, which supports the idea of using platelets as a therapeutic tool to enhance tissue regeneration<sup>26</sup>.

Since PRF supplements the natural wound healing process, it has the following effects when used in oral surgical interventions: The fibrin clot acts as a scaffold, providing mechanical support, protecting graft materials, and serving as a biological connector between bone particles. The fibrin network supports cell migration, especially of endothelial cells necessary for neoangiogenesis, vascularization, and graft survival.

3.The healing process is further enhanced by the sustained release of various growth factors (PDGF, TGF- $\beta$ , IGF-1).

4. The presence of leukocytes and various cytokines enables self-regulation of infectious and inflammatory processes.

5.PRF has a platelet concentration 10 times higher than normal blood, making this biomaterial a true physiological concentrate with excellent immunogenic and regenerative properties<sup>27</sup>.

# Conclusion

The encouraging results obtained suggest that the use of PRF in oral surgical interventions for patients taking BPs is a promising solution and an excellent alternative treatment for the healing of oral tissues. We recommend that PRF be applied as a preventive measure for BRONJ after tooth extraction, especially in high-risk patients. Introducing a unified protocol for oral surgical treatment in patients receiving bisphosphonate therapy is necessary.

## Conflicts of Interest

The authors declare that they have no conflict of interest.

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