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CASE REPORT
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UČINAK TERAPIJE OZONOM U LEČENJU BISFOSFONATNE OSTONEKROZE VILICA

THE EFFECT OF OZONE THERAPY IN THE TREATMENT OF BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAWS

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Sažetak

Uvod: *Bisffosfonatna steonekroza vilica, ili BRONJ (Bisphosphonate related osteonecrosis of the jaws), definiše se kao izložena kost vilice (deo vilične kosti) u usnoj duplji sa ekspozicijom duže od osam nedelja , koja ne reaguje na terapiju, kod pacijenata koji nnisu na radioterapiji i nemaju metatstske promene u viličnim kostima.. Uticaj ozona (ozonirano ulje i ozon gas) zbog antibakterijskog, antivirusnog i antifungalnog dejstva, dovodi do poboljšanja oksigenacije tkiva, kao i njegovog uticaja na epitelizaciju rane, stimulaciju lokalnog imuniteta.*
Cilj *ovog istraživanja bio je da se utvrdi efekat ozona u lečenju bisfosfonatne osteonekroze vilica nakon njegove primene u obliku gasa i ozonskog ulja u osteonekrotičnom području.*
Prikaz slučaja: *Kroz prikaz dva slična slučaja, prikazujemo uticaj ozona, u obliku gasa ozona i ozonskog ulja, na zarastanje rana kod BRONJ kod dva pacijenta starija od 60 godina. Oba pacijenta su primala bisfosfonatnu terapiju više od 2 godine i imaju eksponiranu kost koja je nastala nakon vađenja zuba. Pacijentima je urađena hirurška intervencija (sekvestrotomija) u kombinaciji sa konzervativnim lečenjem antibioticima i ozonom terapijom.*
Zaključak: *Upotreba gasa ozona i ozonskog ulja u lečenju osteonekroze vilice izazvane bisfosfonatima ima pozitivan efekat na zarastanje rana u predelu osteonekrotičnog tkiva, kod pacijenata koji su primali ili su još uvek na terapiji bisfosfonatima.*

Ključne reči: BRONJ, bisfosfonatna terapija, ozon, osteonekroza

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Abstract

Introduction: *The osteonecrosis of the jaws, or bisphosphonate-related osteonecrosis of the jaws (BRONJ), is defined as the exposed jawbone (part of the jawbone) in the oral cavity that persists for more than eight weeks despite a given therapy in the patient with no history of undergoing radiotherapy, and there is no evidence of bone metastases. The influence of ozone (as ozone gas and ozone oil) is due to its antibacterial, antiviral and antifungal effect, improving the oxygenation of tissues, as well as its impact on wound epithelialization, and the stimulation of local immunity.*
Aim: *This study aimed to determine the effect of ozone in the treatment of bisphosphonate-related osteonecrosis of the jaws after its application in the form of gas and ozone oil in the osteonecrotic area.*
Case report: *Through the presentation of two similar cases, we presented the influence of ozone, in the form of ozone gas and ozone oil, on wounds healing in two BRONJ patients over 60. Both patients have been receiving bisphosphonate therapy for more than 2 years and experienced exposed bone following tooth extraction. The patients underwent surgical intervention (sequestrotomy) in combination with conservative treatment with antibiotics and ozone therapy, after which tissue epithelization was stimulated.*
Conclusion: *The use of ozone gas and ozone oil in the treatment of bisphosphonate-related osteonecrosis of the jaws has a positive effect on wound healing in the area of the osteonecrotic tissue.*

Key words: *bisphosphonate-related osteonecrosis of the jaws, bisphosphonate therapy, osteonecrosis*

Introduction

The osteonecrosis of the jaws, or bisphosphonate-related osteonecrosis of the jaws (BRONJ), is characterized by the exposed jawbone (part of the jawbone) in the oral cavity that persists for more than eight weeks despite a given therapy in the patient who had no history of undergoing radiotherapy, and there is no evidence of bone metastases[1]. This is a serious complication in patients receiving bisphosphonate therapy, especially in patients who receive the therapy intravenously[2]. Bisphosphonates as a therapeutic procedure are used as potent inhibitors of bone resorption in various diseases and conditions of the bones; such as malignancies, osteoporosis, and bone metastases[3,4,5,6,7,8,9]. Marx first described osteonecrosis of the jaws (ONJ) in 2003 as a result of receiving bisphosphonate therapy, therefore it is called bisphosphonate-related osteonecrosis of the jaws (BRONJ)[10]. Later, in the period from 2008 to 2011 with the increasing use of other antiresorptive drugs in therapy for malignant diseases, American Association of Oral and Maxillofacial Surgeons renamed it as antiresorptive drugs-related osteonecrosis of the jaws (ARONJ). The special committee in the position paper of AAOMS from 2014 suggests the term medication-related osteonecrosis of the jaws (MRONJ), due to the increase in cases of osteonecrosis of the upper and lower jaw following the application of other antiresorptive drugs (denosumab) and antiangiogenic drugs, besides bisphosphonates[11]. There are numerous hypotheses about the causes of BRONJ occurrence, but the most common "trigger" is tooth extraction[12]. The most commonly accepted hypotheses of osteonecrosis are the inhibitory effect of bisphosphonates on the osteoclastic activity of bone tissue cells, their toxic effects on soft tissue and their anti-angiogenic effect. The influence of bisphosphonates on the oral microflora, as well as the creation of biofilm (microbiota) at the site of osteonecrosis, is one of the possible reasons for its occurrence. Biofilm is a set of bacterial colonies that are interconnected with fibronectin. They cover the necrotic tissue, which is the commonest cause of frequent and recurrent infections in these patients[13]. In the paper by Hristamyan et al., smoking is mentioned as a risk factor in increasing the incidence of BRONJ14. According to the American Association of Oral and Maxillofacial Surgeons (AAOMS, 2009) there are several clinical stages (Staging) of BRONJ: patients at risk, clinical stage 0, clinical stage I, clinical stage II, and clinical stage III. Numerous studies are related to the impact of medical ozone on wound healing in bisphosphonate osteonecrosis[14]. In the last update of AAOMS, it has been decided to maintain the current classification system with no modifications[15]. Several authors have shown the effect of ozone therapy on wound healing in the osteonecrosis area in patients who are receiving or have received bisphosphonate therapy. The influence of ozone is due to its antibacterial, antiviral and antifungal effect, improving the oxygenation of tissues, its impact on wound epithelialization, and the stimulation of local immunity. Basic forms of ozone application in the oral cavity are: ozone gas, ozone oil and ozone water[16].

This study aimed to determine the effect of ozone in treating bisphosphonate-related osteonecrosis of the jaws at a different stage of the disease after its application in the form of gas and ozone oil in the osteonecrotic area.

Case report 1

A 60-year-old patient came to the Clinic of Oral Surgery because he had pain in the area of the lower jaw on the left side. Clinical examination revealed partial edentulism, and exposed bone visible in the area of the lower third molar (Figure 1). The patient's anamnestic data revealed that he had undergone surgery for prostate cancer two years ago, followed by two years of bisphosphonate therapy (Zometa). After conducting a thorough anamnesis and clinical examination, the decision was made for surgical intervention which was carried out after conservative treatment of the patient.

The patient was administered antibiotic therapy and ozone therapy was performed until the local inflammation around the exposed bone subsided. Then surgery was performed under the local anesthesia with Scandonest 3%. The necrotic bone was removed (Figure 2) and curettage of the wound was performed (Figure 3).

Ozone therapy (Ozone DTA, Apoza device) was applied in the wound with a gingival and bone probe discharger (Figure 4). A suture was placed to reduce the wound (Picture 5).

The patient continued with antibiotic therapy and rinsed the wound with antiseptic solutions in the next days until the sutures were removed, which was followed by ozone retreatment. The postoperative period had an orderly course without pain or any other complications. Regular checkups were made after 2 weeks, 1 month and three months after surgery. There was complete epithelization of gingival tissue (Figure 6).

Figure 1. Exposed bone

Figure 2. Necrotic bone

Figure 3. Wound after sequestrotomy

Figure 4. Application of ozone gas

Figure 5. Suturing

Figure 6. Wound after 2 weeks of healing

Case report 2

A 66-year-old patient attended the Clinic of Oral Surgery for pain in the area of the upper jaw on the left side. Clinical examination revealed partial edentulism. Exposed bone was visible in the area of the upper left first premolar (Figure 7).

The patient's anamnestic data indicated that he had undergone surgery for kidney cancer three years ago, followed by three years of bisphosphonate therapy (Zometa). The X-ray showed a small bone sequestration in the region of the first maxillary premolar (Figure 8).

We prepared the patient with antibiotic therapy determined according to a previously made antibiogram. The patient was under antibiotic therapy until the local inflammation around the exposed bone subsided and then surgery was performed under local anesthesia with Lidocain 2%. The bone sequester was removed with forceps (Figure 9), which was followed by curettage of the wound (Figures 10 and 11).

The ready-made (fabricated) ozone oil was applied to the wound and a suture was placed to reduce the wound (Figure 12).

The patient continued with antibiotic therapy and rinsed the wound with antiseptic solutions until the sutures were removed. The treatment with ozone oil was repeated in the first seven days after sequestrectomy. Ozone oil was applied for the next 7 days, after removing the suture, for complete epithelization of the wound. The postoperative period had an orderly course without pain or any other complications. Partial epithelization of the wound was visible after 10 days (Figure 13). We are still following the patient until complete epithelization of the wound.

Figure 7. Exposed bone ***Figure 8.*** Rtg panoramix

Figure 9. Necrotic bone ***Figures 10 and 11***. Wound after sequestretomy

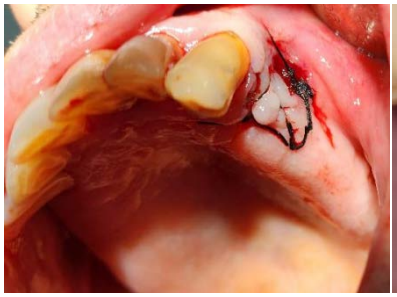

Figure 12. Suture ***Figure 13.*** 10th day after surgery

Discussion

BRONJ is a serious complication that occurs in patients receiving bisphosphonate therapy and in whom dental intervention was performed. This complication dramatically affects the quality of life of these patients and requires a serious approach to solving it. Further, patients with BRONJs suffer from various symptoms such as exposed and necrotic bone, ulceration and inflammation of the surrounding mucosa, pain, infection, as well as further loss of adjacent teeth. According to Kishimoto et al.[17], the nonsurgical management of BRONJ is aimed at improving the stage of the disease and avoiding its progression. Nonsurgical options include the use of antimicrobial mouth rinses, local disinfection/cleaning of exposed bone and fistulae, pain control, and the administration of antibiotics and nutritional support when required. In the presence of exposed bone, superficial debridement may be useful for reducing sharp edges and relieving soft tissue irritation. Even for cases in which surgery is indicated, nonsurgical management before and after surgery (i.e., during the perioperative period) is critical. As surgery is not indicated for all patients with BRONJ, further research is required to identify the most appropriate methods of nonsurgical management[17].

In both of the cases presented, we made a conservative therapy in combination with surgery.

In the treatment of BRONJ, ozone therapy can be used as an adjunctive therapy. Numerous studies are related to the influence of medical ozone on wound healing in bisphosphonate osteonecrosis. Several authors have proof of the impact of ozone therapy on wound healing in the region of osteonecrosis in patients who have received or are receiving bisphosphonate therapy. The impact of ozone is due to its antibacterial[18,19] antiviral[20,21] and antifungal action[22], improvement of oxygenation of the tissues, its influence in wound epithelization[23], what is in line with our case reports, as well as the stimulation of local immunity. In these case reports of patients having exposed bones associated with infection, the epithelialization of the wounds was evident. In the first patient, epithelization was complete after two weeks and in the second one, partial epithelization occurred over 10 days. Basic application forms of ozone in the oral cavity are ozone gas which we used in the first reported case, ozone oil used in the second reported case and ozone water. Bocci et al.[24] investigated the impact of medical ozone on the stimulation or suppression of the immune system and the use of ozone in small concentrations with its oxidative influence.

Agrillo et al.[25] applied ozone therapy as gas insufflations in five-year research as a conservative treatment or as an additional therapy in minimal sequestrotomy in patients with bisphosphonate osteonecrosis of the jaws, as same as our case report. They also describe the reduction of the pain, as well as the reduction of the secretion from the osteonecrotic lesion.

In our cases we used ozone therapy in two different forms, ozon gas and ozone oil, as an adjuvant therapy in combination with surgery and antibiotic therapy.

Nogales[26] in his review describes the impact of ozone oil in the treatment of alveolitis sicca compared with antibiotic therapy.

According to the results of Goker et al., ozone/oxygen therapy and debridement with Piezoelectric surgery for BRONJ treatment is a safe procedure with successful outcomes[27].

Di Fede et al. are using the OZOPROMAF protocol with intra-tissue injections of a 15 mL OxigenOzone (O2O3) mixture with a 26Gx 1⁄2–0.45 × 13 mm needle into the mucosal margin, surrounding the bone exposure or around the site, which had previously been highlighted by a CBCT scan[28].

Conclusion

The use of ozone gas and ozone oil in the treatment of bisphosphonate-related osteonecrosis of the jaws has a positive effect on wound healing in the area of the osteonecrotic tissue, in patients who have received or have been still receiving bisphosphonate therapy.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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