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## Aquacell® Ag i ozonska terapija u liječenju bisfosfonatima inducirane osteonekroze čeljusti (BIONJ): prikaz slučaja

### Aquacel® Ag and Ozone in Bisphosphonate Induced Osteonecrosis of the Jaws (BIONJ) Therapy: a Case Report

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#### Sažetak

**Svrha istraživanja:** Bisfosfonatima inducirana osteonekroza čeljusti (BIONJ), nakon elektivnih dentalnih zahvata, sve je češća kod onkoloških bolesnika s koštanim metastazama koji se intravenski liječe bisfosfonatima. **Klinički slučaj:** Opisan je slučaj BIONJ-a u području drugoga desnog gornjeg premolara nakon vađenja zuba. Pacijentica je anamnestički bolovala od karcinoma dojke s koštanim metastazama, a kao terapija određeni su joj bili bisfosfonati intravenski i antimitotička kemoterapija. U prvom i drugom stadiju BIONJ-a liječena je konzervativno antiseptičkim otopinama za ispiranje usta, antibioticima i dodatno oblogama za rane *Aquacell Ag* te ozonskom terapijom. Nakon što šest mjeseci nije bila na bisfosfonatima, odlučili smo se za kirurški zahvat (resekcija bolesnog dijela kosti), a poslije je dobila djelomičnu gornju protezu. **Zaključak:** Konzervativna terapija, zajedno s *Aquacellom Ag* i heal ozonom reducirala je bol i gnojnu infekciju u razdoblju dok je pacijentica bila bez bisfosfonata, iako rana nije u cijelosti zacijeljela. Nakon šest mjeseci obavljen je uspješan kirurški zahvat. Prevencija je najbolji izbor u liječenju BIONJ-a.

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#### Ključne riječi

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#### Uvod

Bisfosfonati su lijekovi koji smanjuju resorpciju kostiju inducirajući apoptozu osteoklasta te smanjujući njihovu aktivnost tako da se kost slabo resorbira (1). Propisuju se u slučaju prevencije i liječenja bolesti koje utječu na lomljivost kostiju, kao što su osteoporozna, metastaze u kostima, višestruki mijelom, osteitis deformans i osteogenesis imperfecta. Bisfosfonatima inducirana osteonekroza čeljusti (BIONJ) najčešća je komplikacija među pacijentima na intravenskoj terapiji s incidencijom od 0,8 do 12 posto, za razliku od onih na oralnoj terapiji s incidencijom od 0,01 do 0,04 posto (2). Što terapija dulje traje, rizik je veći. Osteonekroza je češća u mandibuli negoli u maksili (odnos 2:1)(3). Ovdje želimo predstaviti dodatne metode konzervativnog liječenja prvog i drugog stadija BIONJ-a prema AAOMS-u koje su pomogle našoj pacijentici dok smo čekali najbolji trenutak za kirurško liječenje (tablica 1.)(3). Dodatne metode uključuju terapiju ozonom (Biozonix) koja je dokumentirana u literaturi i *Aquacell Ag* (Na carboxymethylcellulose, ConvaTec Ltd, Middlesex, Ujedinjeno Kraljevstvo). Naime, ozon potiče regeneraciju tkiva, a *Aquacell Ag* ima jak lokalni antimikrobni učinak (4 – 6).

#### Introduction

Bisphosphonates are drugs which decrease bone resorption by inducing osteoclast apoptosis and decreasing their activity so that the bone resorbs poorly (1). They are used in prevention and treatment of conditions which affect bone fragility such as osteoporosis, bone metastasis, multiple myeloma, osteitis deformans, osteogenesis imperfecta. Bisphosphonate induced osteonecrosis of the jaw (BIONJ) is a complication that most frequently occurs in patients on intravenous therapy with incidence from 0.8-12%, unlike oral therapy with incidence of 0.01-0.04% (2). The longer the duration of therapy, the greater the risk becomes. Osteonecrosis is more common in the mandible than in the maxilla (2:1 ratio) (3). We want to show additional methods in conservative treatment of stages 1 and 2 BIONJ according to AAOMS, which helped our patient in the waiting period for surgical treatment (Table 1) (3). Additional methods include ozone therapy which is well documented in literature and Aquacel Ag (sodium carboxymethylcellulose, ConvaTec Ltd, Middlesex, United Kingdom) in addition to HealOzone. Ozone helps in tissue regeneration and Aquacel Ag has a strong local antimicrobial effect (4-6).

**Tablica 1.** Klinička klasifikacija BIONJ-a – Ruggiero (2006.) i modifikacije AAOMS-a iz 2009.  
**Table 1** Clinical classification of BIONJ by Ruggiero (2006) and successive modifications by AAOMS 2009.

BIONJ stadij • BIONJ stage	Opis • Description	Strategija terapije • Treatment strategies
Ugroženi • At risk category	svi pacijenti koji su liječeni bilo oralno ili i.v. bisfosfonatima bez vidljive nekrotične kosti • No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	nije potrebna terapija, edukacija pacijenata • No treatment Patients education
Stadij 0 • Stage 0	nije moguće klinički dokazati nekrotične kosti, ali prisutni su nespecifični znakovi • No clinical evidence of necrotic bone, but non specific clinical findings and symptoms	sistemska terapija analgeticima i antibioticima • Systemic therapies including pain medications and antibiotics
Stadij I. • Stage I	asimptomatska lezija s ekspanzijom kosti, bez znakova infekcije • No-symptomatic lesions with bone exposure in absence of infection's signs	topikalna antiseptička terapija, kontrole • Topical antiseptic therapy Follow-up
Stadij II. • Stage II	ekspanzirana kost s bolovima, infekcijom i oteklinom u području lezije • Bone exposure with pain, infection and swelling in the lesion's area	antibiotici per os, analgetici, površinski debridment (čišćenje) radi smanjivanja iritacije mekih tkiva • Oral antibiotics - antibacterial mouth rinse - pain control Superficial debridement to relieve soft tissues irritation
Stadij III. • Stage III	ekspanzirana kost, bol, upala, zahvaćenost maksilarnog sinusa, kutana fistula i patološka fraktura • Bone exposure, pain, inflammation, maxillary sinus involvement, cutaneous fistulas and pathological fractures	antiseptičke otopine za ispiranje, antibiotici i analgetici, kirurški debridment i resekcija radi redukcije infekcije i boli • Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement and resection for longer term palliation of infection and pain

### Klinički slučaj

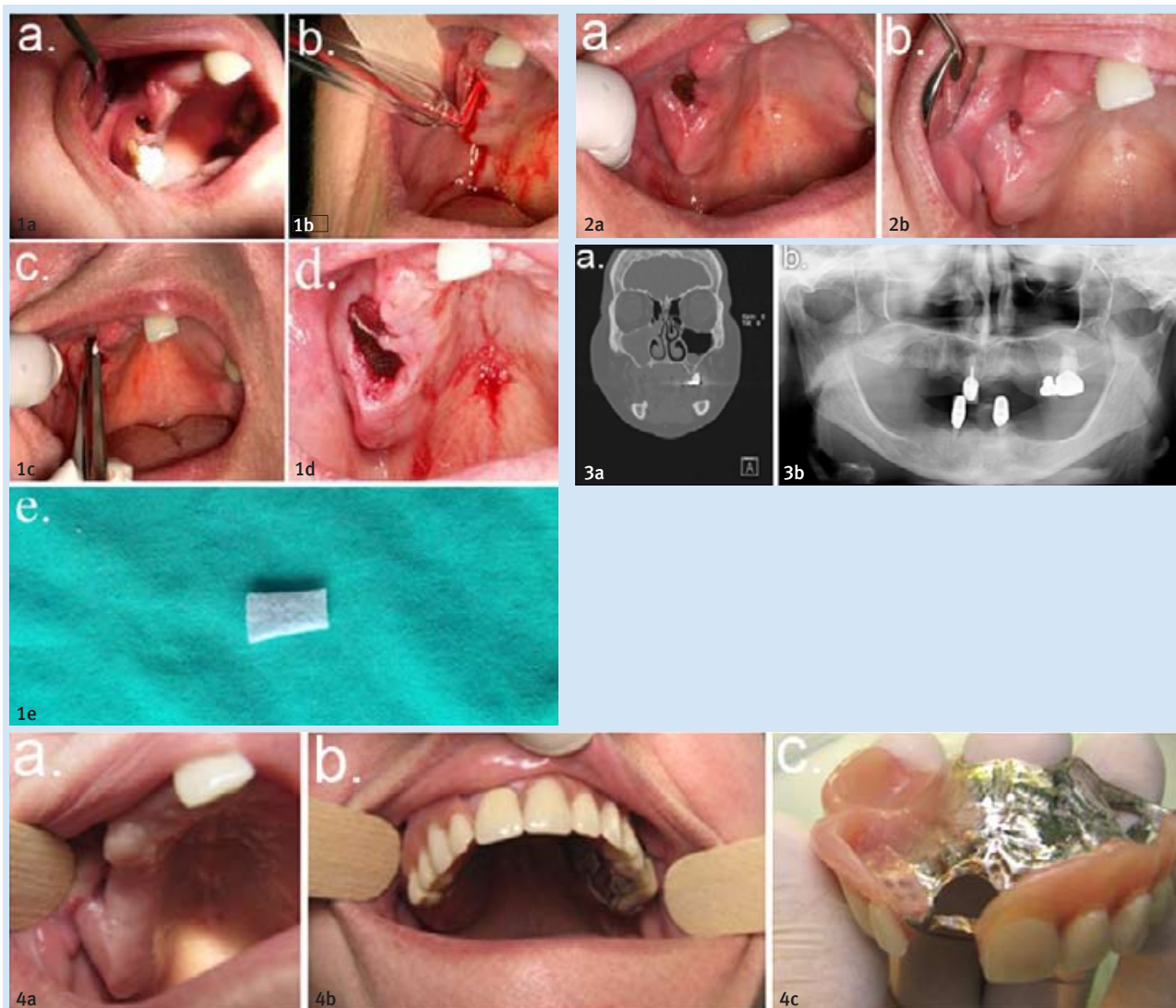
Bjelkinja u dobi od 68 godina s rakom dojke (od 2004.) i metastazama u plućima i kostima (od 2005.) uzimala je tri i pol godine intravenski pamidronate disodium (Aredia, Novartis Pharma Stein AG, Stein, Švicarska) i antimikotičku kemoterapiju (Taxotere, docetaxel, Aventis Pharma Dagenham, Essex, Velika Britanija). U srpnju 2007. godine u ordinaciji opće stomatologije izvađena su joj četiri frontalna zuba mandibule i drugi desni gornji premolar (zub 15). Pacijentica je u srpnju 2008. došla oralnom kirurgu radi vađenja prvoga gornjeg desnog molara (zub 16) i tada joj je dijagnosticiran prvi stadij BIONJ-a u regiji zuba 15. Obaviještena je o svojem stanju, ali se zbog primarne bolesti zadržalo liječenje bisfosfonatima i kemoterapija. Pacijentici je bio preporučeno tri puta na dan lokalno chlorhexetidin te endodontsko liječenje kanala zuba 16 kod specijalista dentalne patologije. U veljači 2009. ponovno je došla oralnom kirurgu zbog bolova na desnoj strani maksile gdje je klinički i dalje bio prisutan BIONJ u regiji zuba 15, te neuspjelo liječenje zuba 16. Kako je dulje patila od jakih bolova (sedam mjeseci), preporučeno je prekid terapije bisfosfonatima, ako to dopusti onkolog zbog njezina medicinskog stanja. S antibiotskom terapijom (Klavocin bid 1g, 2 x 1, amoxicillin clavulanate, Pliva, Zagreb, Hrvatska) počelo se tri dana prije ekstrakcije, kada je onkolog prekinuo terapiju bisfosfonatima i kemoterapiju. Prije i poslije ekstrakcije korišten je heal ozon (40 sekundi) te je nakon vađenja zuba 16 obavljena kiretaža i kontrola hemostaze. Očišćena je i rana te obavljena terapija ozonom u regiji 15. Dva tjedna poslije rana je uredno cijelila i nije bilo bolova. No nakon mjesec dana ponovno su počeli, a pojavio se i gnoj u regiji 15 (drugi stupanj). Ordinirani su antibiotici (Klavocin bid 1 g, 2 x 1, amoxicillin clavulanate, Pliva, Zagreb, Hrvatska), terapija ozonom (heal ozon) 40 sekundi svaki drugi dan, *Neocone* (benzocaine i neomycin sulfat, Septodont, Špa-

### Clinical course

A 68-year-old white female patient with breast cancer (since 2004) and metastasis in lungs and bones (since 2005) used pamidronate disodium (Aredia, Novartis Pharma Stein AG, Stein, Switzerland) intravenously for 3 and a half years and anti-mitotic chemotherapy medication (Taxotere, Docetaxel, Aventis Pharma Dagenham, Essex, Great Britain). In July 2007, four teeth (anterior region) in the mandible and upper right second premolar (tooth 15) were extracted by a general dental practitioner. The patient visited the oral surgeon in July 2008 to extract the upper right first molar (tooth 16) when BIONJ, stage 1 in the second upper right premolar region was diagnosed. The patient was informed about her condition, but because of her primary illness it was decided not to interrupt bisphosphonate and chemotherapy. The patient was advised to use local chlorhexetidine three times per day and sent to dental pathologist for root canal therapy for upper right first molar. In February 2009, the patient came to our institution because of pain in the right maxilla. After seeing medical documentation, clinical status showed: still present BIONJ in area of upper right second premolar (region 15) and failed endodontic treatment of tooth 16. Since the patient suffered from severe pain for a longer time (7 months) and clinically evident acute inflammation of tooth 16, we suggested the cessation of bisphosphonate therapy if the patient's medical condition allowed it (oncologist consulted). Antibiotic therapy started (Klavocin bid 1g, 2 x 1, amoxicillin clavulanate, Pliva, Zagreb, Croatia) three days before extraction, the oncologist stopped Aredia and Taxotere therapy. Before and after the extraction we used HealOzone (40 seconds), and after the extraction of tooth 16, curettage and haemostatic control were performed. Also, wound debridement and HealOzone therapy were performed in the region of tooth 15 (7). Two weeks later, we observed locally normal post-operative healing

njolska) svakih 4 do 5 dana te *Aquacell Ag* dva tjedna svakih 4 do 5 dana za debridment i antibakterijsko djelovanje (slika 1.). Nakon toga rana je zarasla bez bolova i gnojnog sadržaja. Nakon mjesec dana rana je još bila prisutna, ali manja (1,5 mm u promjeru) (slika 2.). U kolovozu 2009. Multislice CT (MSCT) zabilježio je sjenu u desnom maksilarnom sinusu (slika 3.). Kako pacijentica šest mjeseci nije bila na bisfosfonatima i kemoterapiji, odlučeno je da se obavi radikalna kirurška terapija desnoga maksilarnog sinusa i zahvaćenog dijela alveolarnog grebena, nakon čega je ostala komunikacija između sinusa i oralne šupljine. Histopatološki nalaz poka-

without pain. After 1 month the patient returned with pain and purulent discharge in the region of tooth 15 (stage 2). We administered antibiotics (Klavocin bid), and HealOzone for 40 seconds every second day, Neocones every 4 to 5 days (benzocaine and neomycin sulphate, Septodont, Spain) and Aquacel Ag hydrofiber every 4 to 5 days for debridement and antibacterial treatment (Figure 1). Two weeks later the wound was healing, without pain and purulent discharge. After one month of therapy, the wound was still persistent but smaller (1.5 mm in diameter) (Figure 2). In August 2009, the multislice computed tomography (MSCT) shows a shadow in the



**Slika 1.** a) stanje prije ekstrakcije prvoga gornjeg desnog molara i eksponirana nekrotična kost u području drugoga gornjeg desnog premolara; b) aplikacija heal ozona nakon ekstrakcije; c) aplikacija analgetika i antiseptika; d) postekstrakcijska rana, e) obloga Aquacella Ag  
**Figure 1** a) situation before extraction of upper right primary molar and exposed necrotic bone at upper right premolar region; b) application of HealOzone probe after tooth extraction; c) application of analgesic and antiseptic cushion; d) wounds after extraction; e) Aquacel Ag dressing  
**Slika 2.** a) cijeljenje nakon dva tjedna, b) cijeljenje nakon mjesec dana  
**Figure 2** a) wound two weeks after treatment; b) wound 1 month after treatment  
**Slika 3.** a) Multislice CT (MSCT) – vidljiva sjena u desnom maksilarnom sinusu (kolovoz 2009.); b) ortopantomogram – upala vidljiva na alveolarnom grebenu, ne vidi se upala u maksilarnom sinusu (svibanj 2009.)  
**Figure 3** a) Multislice CT scan shows shadow in right maxillary sinus (August 2009); b) ortopantomograph shows an ongoing bone process in right alveolar ridge and no maxillary sinus involvement (May 2009)  
**Slika 4.** a) malena oroantralna komunikacija; b) djelomična proteza u ustima, c) djelomična proteza s obturatorom  
**Figure 4** a) barely visible oroantral communication; b) prosthodontics in place; c) removable prosthodontics with obturator



zao je nespecifično nekrotično tkivo. Kad je rana zacijelila, na Odjelu za protetiku izrađena je gornja djelomična proteza s obturatorom za maksilarni sinus (slika 4.) Pacijentica je nakon toga bila bez bolova i infekcije te nije imala problema s konzumacijom hrane i govorom. Nažalost, umrla je od osnovne bolesti u svibnju 2010.

## Rasprava

Pacijentica je liječena prema protokolu Američkoga društva oralne i maksilofacijalne kirurgije, uz terapije ozonom i *Aquacelom Ag*. Tijekom konzervativne terapije neprestance je osjećala tupu bol, a povremeno je imala i gnojni iscjedak. Bila je u terminalnoj fazi karcinoma dojke, ali je bol na desnoj strani maksile bila akutni problem zbog čega je u dogovoru s onkologom prekinuta terapija bisfosfonatima i zamijenjena konzervativnim pristupom. Terapija ozonom korištena je prije i poslije ekstrakcije kako bi potaknula cijeljenje tkiva (8). *Aquacell* je odabran iz više razloga – poslužio je kao mehanička zapreka skupljanju ostataka hrane, sline i mikroorganizama u defektu alveolarnog grebena (konkavnog oblika), a srebro je dokazano aktivna komponenta korisna u suzbijanju oralnih patogena (9). Nisu nađene kontraindikacije za intraoralno korištenje *Aquacella* (10), a rabi se za vlažne rane na koži (11). Također može pomoći u staničnom procesu regeneracije kostiju (12). Odlučili smo se za ozon i *Aquacell Ag* kako bismo pomogli pacijentici u razdoblju bez bisfosfonata (šest mjeseci, a to je razdoblje bilo nužno kako bi se moglo obaviti kirurško liječenje) čime je konstantna tupa bol svedena na minimum.

## Zaključak

Terapija ozonom i *Aquacell Ag* uklonili su bol i gnojni sadržaj u razdoblju čekanja (šest mjeseci bez bisfosfonata prije kirurške terapije). U kasnijem stadiju bila je indicirana radikalna kirurška terapija.

## Sukob interesa

Autori potvrđuju da nisu u sukobu interesa.

right maxillary sinus (Figure 3). Since the patient did not receive bisphosphonate and chemotherapy for 6 months, a radical surgery of the right maxillary sinus and affected alveolar ridge bone was indicated. Radical sinus surgery was performed and sinus cavity was widely connected with the oral cavity. The histopathological test showed unspecific necrotic tissue.

After the wound healed, prosthodontics department supplied the upper jaw with a removable prosthesis with obturator for maxillary sinus (Figure 4). Patient was free of pain, infection and had no trouble with eating and communicating after treatment. Unfortunately, the patient died in May 2010.

## Discussion

Our patient was treated in accordance with the American Association of Oral and Maxillofacial Surgeons protocol; in addition we started HealOzone therapy and Aquacel Ag. During the conservative treatment, patient experienced constant dull pain and occasional purulent discharge. Since the patient was in the terminal phase of breast cancer and pain in the right maxilla was an acute problem, we decided (in consent with oncologist) to stop bisphosphonate therapy and to use additional treatments before surgical treatment. Ozone therapy was used in the periextraction period and later, as it helps with tissue regeneration (8). We used Aquacel Ag for more reasons. It is a mechanical barrier and it prevents accumulation of food rests, saliva and microorganisms in alveolar ridge defect (concave shaped). Silver as active component is proved to be efficient against oral pathogens (9). We found no contraindication for the use of Aquacel Ag intraorally (10). Aquacel Ag is well known for use in moist wounds on skin (11). Carboxymethylcellulose might help in the cellular process of bone regeneration (12). We decided to use ozone and Aquacel Ag to help patient during drug absence period (6 months). During this additional treatment, the patient's constant dull pain was reduced to minimum.

## Conclusion

HealOzone and Aquacel Ag helped in eliminating pain and purulent discharge in the waiting period (six months without bisphosphonate therapy before surgery). In the later stage radical surgery was indicated.

## Conflict of interest

Authors have no conflict of interest to declare.

### Abstract

**Objective:** Bisphosphonate induced osteonecrosis of the jaw (BIONJ) is often seen in oncologic patients with bone metastasis, who are treated with intravenous bisphosphonates as a result of elective dental treatment. **Clinical course:** We present a case report of a 68-year-old patient with BIONJ in the right maxillary premolar region after a tooth extraction. The patient had breast cancer, bone metastasis, and received intravenous bisphosphonate therapy and anti-mitotic chemotherapy. Conservative therapy for stages 1 and 2 of BIONJ was indicated with mouth washes, antibiotics and, in addition, local Aquacel Ag wound dressing and HealOzone therapy. After 6 months of drug absence (bisphosphonates), the surgical procedure was performed and the patient obtained a removable prosthetic appliance. **Discussion and conclusion:** Conservative treatment in addition with Aquacel Ag and HealOzone reduced pain and infection in the waiting period, but the wound did not heal. The surgical procedure after the drug treatment was an efficient solution. Prevention is the best treatment of BIONJ.

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### Key words

Biphosphonates; Carboxymethylcellulose Sodium; Ozone; Osteonecrosis; Jaw; Pamidronate

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