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Treatment of BRONJ with ozone/oxygen therapy and debridement with piezoelectric surgery

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Abstract. – OBJECTIVE: Bisphosphonate related osteonecrosis of the jaw (BRONJ) is progressive bone destruction in the maxillofacial region of patients under current or previous treatment with Bisphosphonates. The present case series study aimed to evaluate if ozone/oxygen therapy and debridement with piezoelectric surgery may improve the treatment of BRONJ.

PATIENTS AND METHODS: The treatment modality of the patients included ozone/oxygen mixture from medical oxygen. The protocol for ozone/oxygen mixture therapy appointments was set as twice a week for 10 weeks, for a total of 20 applications for each patient. The evaluation of the lesions was based on the clinical and radiologic parameters. The primary outcome was the necrotic lesion reduction during ozone/oxygen therapy sessions and up to the end of follow up periods. The healing of the lesion was taken as a positive result. The level of significance was taken as $p < 0.05$.

RESULTS: A total of 14 patients affected by osteonecrosis were included. The mean follow-up of the patients was 14.3 months. The overall success rate after treatment was 64.2%.

CONCLUSIONS: According to the results, ozone/oxygen therapy and debridement with Piezoelectric surgery for BRONJ treatment is a safe procedure with successful outcomes.

Key Words:
BRONJ, Bisphosphonates, BRONJ treatment, Ozone therapy, Piezoelectric surgery, Oxygen therapy.

Introduction

The bisphosphonates (BPs), referred to as bisphosphonates or diphosphonates, are analogues of inorganic pyrophosphate[1-3]. BP therapy medications can be administered either orally or parenterally, and in the body BPs are adsorbed onto hydroxyapatite crystals in bone mineral. Their structure provides them resistant to enzyme degradation, and they act principally by blocking the action of osteoclasts[2-4]. BPs represent a reference therapy for prevention and treatment of various metabolic and oncological pathologies involving the skeletal system, such as, various forms of osteoporosis (postmenopausal, male and corticosteroid osteoporosis), Paget's disease of bone, bone metastasis (with or without hypercalcemia), multiple myeloma, fibrous dysplasia, primary hyperparathyroidism, osteogenesis imperfecta, and other conditions that exhibit bone fragility[4-7].

Bisphosphonate related osteonecrosis of the jaw (BRONJ) has been recognized as a potential side effect in patients on long-term bisphosphonate therapy[7,8]. Osteonecrosis (ON) is the death of bone cells due to decreased blood flow[9]. BRONJ is defined as a "diffuse bone disease characterized by the presence of bone exposed to oral cavity that does not heal within 8 weeks of observation and conventional treatment, in patients under or have taken bisphosphonate therapy, with no history of radiation therapy in the head and neck region"[3,10]. More recently, the definition was updated as medication-related osteonecrosis of the jaw (MRONJ). MRONJ was defined as a "rare and severe adverse drug side effect that may occur in cancer and osteoporosis patients being treated with antiresorptive and/or antiangiogenics"[11]. BRONJ/MRONJ is a progressive bone destruction in the maxillofacial region which can be accompanied by pain, paresthesia, discomfort, exposed bone, difficulty eating, mucosal swelling, soft tissue ulceration, suppuration, intra-/extra oral sinus tracts, long term unhealed extraction/implant sites, tooth mobility, and fractures[11].

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The most important predisposing factor for BRONJ is the type and total dosage of BP or other medications. Overall, the risk for BRONJ increases by high dosage, therapy duration more than 3 years, and intravascular administration instead of oral intake[2,4,11]. Other elements that can influence BRONJ can be listed as follows; the type of molecule, adjunctive therapies (chemotherapy, corticosteroids, antiangiogenic drugs), concomitant diseases (diabetes, renal insufficiency, obesity, vascular diseases, blood coagulation disorders), consumption of alcohol/tobacco, and advanced age[2,4,11]. The main triggering factor for BRONJ is considered as the dentoalveolar surgery procedures in the maxillo-facial region[11]. Anatomical alterations (both mandibular and palatal exostoses), pressure sores of the dental prosthesis and inflammatory diseases of the oral cavity are also reported literature as risks[6,11,12].

According to an updated classification for BRONJ based on clinical parameters, it is divided into four stages (Table I)[11]. There is no ideal consensus for the treatment of BRONJ. The two main therapeutic approaches for the treatment are antibiotic therapy and surgical approach[4,13-18]. Antibiotic therapy does not lead to the complete resolution of the pathology and has limited effectiveness over time. The surgical approach involves the removal of the necrotic bone and is usually recommended for more advanced stages[6,11,12].

The surgery represents the risk of relapse with extension of the areas of bone exposure and aggravation of the symptoms[19,20]. Several alternatives and adjunctive therapies (low level laser, hyperbaric oxygen, ozone therapy) and different biological agents (autologous platelet concentrates, recombinant growth and differentiation factors, parathyroid hormone) were proposed in the literature with beneficial results[3,5,6,21-24].

Ozone (O3) is normally present as a gas made of three atoms of oxygen with a cyclic structure and is a natural component of the atmosphere[25-29]. In ozone/oxygen therapy, a mixture of oxygen and ozone is transferred to the body with different amounts/techniques depending on the pathologies to be treated[25,27-30]. Ozone has an indisputable and effective antiseptic activity. Ozone therapy has been used for a variety of indications such as infectious diseases, immune dysfunctions, articular pathologies, ischemic pathologies, neurodegenerative pathologies, and degenerative vascular diseases in ophthalmology[27,29,31].

Ozone therapy for patients suffering from BRONJ was introduced by Agrillo et al[21], because of its positive effect on avascular necrosis-related pathologies. Ozone acts with stimulation and/or preservation of the endogen antioxidant system, by activating blood circulation, increasing red blood cells/hemoglobin concentration, stimulating biologic reactions, and by its bactericidal action[21,22].

Piezoelectric surgery is an innovative technique of bone surgery, which uses particular devices that produce ultrasonic pulses, with microscopic horizontal and vertical oscillations. Piezoelectric surgery instruments are capable of generating a micrometric cut by vibrations between the 24 and 37 kHz with amplitude from 60 to 200 μm and a power of 50 watts[32-35]. Ultrasounds produce not only a mechanical but also a thermal and cavitation effect on the tissues. The small gas bubbles generated by the ultrasonic pulses increase the cutting of the instrument. Piezoelectric surgery provides a bloodless field with excellent

Table I. Clinical staging of MRONJ*.

At risk	No apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates
Stage 0	No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms
Stage 1	Exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone or fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and ≥ 1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor

*Staging from the 2014 update of American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw.

intraoperative visibility with a low temperature increase, which is favorable for the bone tissue healing[32-37]. Another peculiarity of the piezoelectric technique is the selectivity of its cut, which is generated by micro-vibrations of the ultrasonic pulses. Piezoelectric surgery instruments have the ability to cut the mineralized tissues, but they are little or not at all effective on the soft tissues. Consequently, they cause no damage to nerves or other noble anatomical structures, in cases of accidental contact[32-37].

The present case series study aimed to evaluate if ozone/oxygen therapy and debridement with piezoelectric surgery may improve the treatment of BRONJ lesions. The authors proposed that ozone/oxygen therapy bio-stimulants might be beneficial for the treatment of BRONJ without any side effects.

Patients and Methods

The study population of this study included 14 patients, which referred to the Clinic of Dental Medicine at Luigi Sacco Hospital (Milan, Italy), between 14/06/2015 and 14/06/2019. The study protocol was approved by the Ethics Committee of Milano Area A on date 12/02/2015 by no 0004902. The study was in compliance with the principles laid down in the Declaration of Helsinki on medical protocol. A signed an informed consent agreement form was obtained from all the patients. In the present study American Association for Oral and Maxillofacial Surgeons classification 2014 was used to indicate the stage of MRONJ for the patients [11]. Inclusion criteria were set as 1st and 2nd stage patients with bisphosphonate-related osteonecrosis of the jaws and necrotic lesion equal or smaller than 5 mm. Exclusion criteria were patients with no BRONJ and BRONJ 3rd stage patients.

The treatment modality of the patients included ozone/oxygen mixture from a medical device. The protocol for ozone/oxygen mixture therapy appointments was set as twice a week for 10 weeks, for a total of 20 applications for each patient. The evaluation of the lesions was based on the clinical and radiologic parameters. The primary objective was necrotic lesion reduction during ozone/oxygen therapy and up to the end of follow-up periods. Healing of the necrotic tissue was taken as a positive result. The presence of side effects and complications were additionally evaluated.

The time interval (T) of measurements and the variations that were examined are listed in detail on Table II. On the first screening visit (T0) the following data was obtained from each patient: • *Anamnestic data* • *Medical history* • *Reason for BP therapy (e.g., Osteopenia/Osteoporosis, Neoplasia, Multiple myeloma, and other).*

Table II. Flow chart for patient appointments.

Treatment weeks	T0 1 w	T1 2 w	3 w	4 w	T2 5 w	6 w	T3 7 w	8 w	9 w	T4 10 w	T5 12 w	T6 24 w	T7 48 w	T8 96 w
Anamnesis	x													
Osteonecrotic lesion dimension	x	x			x		x			x	x	x	x	x
Edema	x	x			x		x			x	x	x	x	x
Purulent material	x	x			x		x			x	x	x	x	x
Ortopantomography (OPT)	x				x						x		x	x
Computerized axial	x				x						x		x	x
Tomography														
Control	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ozone	2x	2x	2x	2x	2x	2x	2x	2x	2x	2x				
Surgical debridment			x											

Screening during treatment: T0: The first appointment, T1: follow-up appointment at 2nd week, T2: follow-up appointment at 5th week, T3: follow-up appointment at 7th week, T4: follow-up appointment at 10th week. Follow-up after treatment: T5: follow-up appointment at 12th week, T6: follow-up appointment at 24th week, T7: follow-up appointment at 48th week, T8: follow-up appointment at 96th week. w: week, x= single application, 2x= 2 times a-week application.

Analysis of the presence of the main radiographic signs as indicators of osteonecrosis:

Orthopantomography (OPT): (1) Thickening of alveolar crest and hard lamina, (2) Persistence of the post-extractive alveolar site, (3) Sequestrum of bone, (4) Periodontal space enlargement, (5) Diffuse osteosclerosis, (6) Thickening of the alveolar nerve canal, (7) Periosteal reactions.

Computerized axial tomography (TAC): (1) Cortical erosion, (2) Thickening of the alveolar crest and lamina dura, (3) Trabecular thickening, (4) Focal medullary osteosclerosis, (5) Persistence of the post-extraction alveolar site, (6) Periodontal space enlargement, (7) Diffuse osteosclerosis 8. Periosteal reactions, (9) Thickening of the alveolar nerve canal.

Ozone/Oxygen Mixture Applications

14 patients affected by BRONJ corresponded to the inclusion criteria of the study.

Patients were treated with a Multiossigen MEDICAL 99 IR (Multiossigen S.P.A., Gorle, Bergamo, Lombardy, Italy) generator producing ozone/oxygen mixture from medical oxygen. All the surgical procedures were done by a single surgeon (D.G.). The treatment appointments were twice a week for 10 weeks, for a total of 20 applications with the ozone/oxygen mixture. The appointments include a rest interval of three to four days.

The ozone/oxygen mixture was applied with local submucosal infiltrations around the necrotic area and in fistulous tracts. Infiltrations were performed with a 10cc syringe, with 30 gauges needle, 0.30 × 13. The injections were 2/3 cc for inoculation up to a maximum of 15 cc. The ozone/oxygen mixture was at a concentration of 10 micrograms/ml by using an individual ozone tray. The ozone/oxygen mixture was applied at a total concentration of 30 micrograms/ml for 2 minutes. The ozone tray, custom-built by the dental laboratory, included an entrance and exit hole. The entrance was directly connected to the ozone generator while the exit was connected to the unit's aspirator. To ensure complete suction of the gas, a high-speed suction was placed at the bottom of the oral cavity.

After 10 applications, at the end of the 5th week (after the T2 time), the patients underwent surgical debridement of the necrotic tissue which might compromise wound healing under local anesthesia using sterile surgical instruments such as scissors, forceps, scalpel and piezoelectric scalpel.

All the patients were evaluated for any changes or complications and any adverse was added to the flow chart for each patient. Figures 1 to 4 show intraoral views of a patient with ONJ lesion during treatment with ozone/oxygen therapy.

Primary endpoint: Clinical detection for variation of necrotic lesion at times T1, T2, T3, T4, T5, T6, T7, T8 relative to the evaluation at time T0.

Secondary endpoints: Clinically detected variations of the following parameters with respect to the baseline visit: inflammatory and infectious parameters (edema, purulent material); radiological changes detected in orthopantomography (OPT) or CBCT; incidence of complications or adverse events.

Statistical Analysis

Descriptive statistics were done using mean values and standard deviation (SD) for quantitative variables normally distributed. Normality of distributions was assessed using the d'Agostino and Pearson omnibus test. The effect of the different variables (age, gender, location (maxilla *vs.* mandible), disease type) on complete healing was evaluated by using the Fisher's exact test. Statistical analysis was performed using GraphPad Prism 5.03 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance for all analyses was $p < 0.05$.

Figure 1. The intra-oral view of the patient showing BRONJ lesion before ozone/oxygen treatment.

Figure 2. Intra-oral view of the patient showing replacement of ozone tray.

Results

A total of 14 patients (11 female, 3 male) with 15 necrotic lesions were included in the study with a mean age of 71.5 years (range 43-87 years). The mean follow-up of the patients was 14.3 months (max 53.8 months- min 6 months, SD 18.2). The overall success rate after treatment was 64.2% on patient number basis. The overall success rate after treatment was 66.6% on site number basis.

During treatment period there were no dropouts. Six patients died after the ozone/oxygen treatment was completed, during follow-up period, due to fatal progression of the condition. These six deceased patients included 3 healed and 3 unhealed defects (at a follow-up of 3 months) at the point when the treatment protocol was concluded. The results did not change after. Due to that reason, these patients were not considered as dropouts. No adverse event or complications were seen in any of the patients.

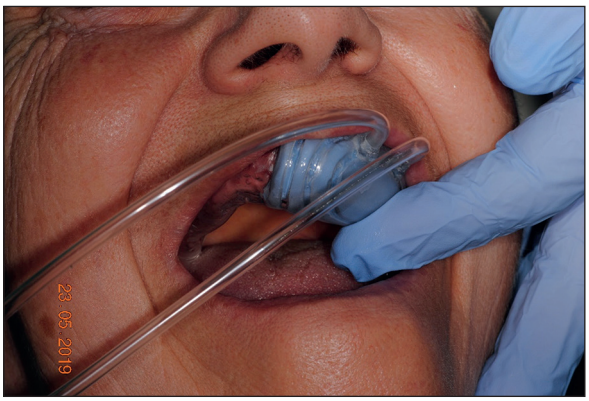

Figure 3. Intra-oral view of the patient during ozone/oxygen application.

Figure 4. Intra-oral view of the patient showing BRONJ lesion at 8 month follow up appointment.

Detailed data of each patient concerning treatment modality and outcomes at appointments is listed in Table III. The results concerning gender, age, necrotic lesion arch location and reason for bisphosphonate treatment are listed in Table VI.

According to the results, ozone/oxygen therapy success was not influenced by any factor such as; gender, age, necrotic lesion arch location, and reason for bisphosphonate treatment. No specific characteristic was found to be beneficial in terms of osteonecrotic lesion healing.

Discussion

BRONJ was described by Marx[7], as a rare but serious adverse event of the bisphosphonate therapy[7]. BRONJ mainly affects oncological patients; however, it can also occur in patients with other bone diseases. The lesions of BRONJ significantly impair the quality of life of the patients. In some rare cases, BRONJ can be a life-threatening condition[13].

BRONJ manifests itself with untreatable pain, difficulty in feeding, sinusitis, onset of fistulas and abscesses in soft tissues[38]. Several treatment modalities and adjunctive therapies for BRONJ, such as antibiotic use, surgical debridement, necrotic bone resection, were proposed in the literature to enhance bone and soft tissue healing[4,5,8,13,14]. Antibiotic therapy is considered as a conservative approach. Antibiotics are usually used either for Stage I and II patients or as an adjunctive therapy to surgical interventions for patients with more advanced Stages. Stage II lesions that do not respond to antibiotic therapy can be treated with superficial surgical debridment[11,12]. However, the treatment modality should

Table III. Detailed data on treatment modality and outcomes at appointments for each patient.

Patient number and reason for BP	T0	T1 2 w	T2 5 w	T3 7 w	T4 10 w	T5 12 w	T6 24 w	T7 48 w	T8 96 w	Heal
1 (P)	OZ	OZ	OZ + SD	OZ	OZ	Healed	C	C	C	Yes
2 (O)	OZ	OZ	Spontaneous expulsion (2 weeks) No surgery	OZ	OZ	Healed	C	Deceased at 28 weeks	x	Yes
3 (O)	OZ	OZ	OZ + SD	3 months break	OZ 15 additional ozone applications	No remission and new formation of lesion with additional surgical debridement-better margins after 7 weeks	Not healed	C	Deceased at 4th year	No
4 (O)	OZ	OZ	OZ + SD	OZ	Suspended ozone	Deceased without remission	-	-	-	No
5 (O)	OZ	OZ	OZ + SD	OZ	Suspended ozone	Deceased without remission	-	-	-	No
6 (O)	OZ	OZ	Spontaneous expulsion (3 weeks) No surgery	OZ	OZ	Healed	Deceased at 16 weeks	-	-	Yes
6 (O)	OZ	OZ	Spontaneous expulsion (5 weeks) No surgery	OZ	OZ	Healed	Deceased at 16 weeks	-	-	Yes
7 (P)	OZ	OZ	OZ + SD	OZ	OZ	Healed	C	C	C	Yes
8 (O)	OZ	OZ	OZ + SD	OZ	OZ	No remission	C	C	New lesion	No
9 (O)	OZ	OZ	Spontaneous expulsion (5 weeks) No surgery	OZ	OZ	Healed	C	C	C	Yes
10 (P)	OZ	OZ	Spontaneous expulsion (5 weeks) No surgery	OZ	OZ	Healed	C	C	C	Yes
11 (P)	OZ	OZ	Patient absent for 4 weeks Abscess formation-antibio treatment with break	Absent	OZ	OZ continues for 5 weeks as scheduled with no remission	No remission	C	C	No
12 (A)	OZ	OZ	Spontaneous expulsion (in 5 weeks) No surgery	OZ	OZ	Healed	C	C	C	Yes
13 (A)	OZ	OZ	OZ + SD	OZ	OZ	Healed	C	C	C	Yes
14 (O)	OZ	OZ	Spontaneous expulsion No surgery	OZ	OZ	Healed	C	C	C	Yes

P= Osteoporosis, O= Oncology, A= Arthritis/Arthrosis OZ= Ozone application, S.OZ.= Suspended Ozone application, SD= Surgical Debridement, C= Follow up control appointment.

Table IV. Comparison of patient characteristics.

Patient	Characteristics	Healed/Total no of sites	Success %	*p*-value
Gender	Male	2/3	66.6	0.49
	Female	8/12	66.6	
Arch	Maxilla	2/5	40.0	0.15
	Mandible	8/10	80.0	
Reason for BP therapy	Oncology	5/9	55.5	1.00
	Osteoporosis	4/4	100	
	Rheumatoid Arthritis	1/2	50.0	
Age	< 70	3/6	50.0	0.24
	≥ 70	7/9	77.7	
Total patients	9/14	64.2		
Total sites	10/15	66.6		

always be conservative. The surgical resection of osteonecrotic tissues should be considered just in advanced cases, for avoiding additional areas of exposed necrotic bone[11,39].

Ozone therapy is being used as a treatment for a variety of indications in medicine, due to its positive effect on soft and hard tissues through the stimulation of endogenous antioxidants[27,29,31]. Ozone increases the concentration of red blood cells and hemoglobin, stimulates leukocyte diapedesis (diapedesis: passage of leukocytes from blood to tissues through the endothelial cells) and phagocytosis of the histiocytic reticulum system[25,27,28].

Intra-oral applications of ozone also attracted the attention of the researchers. Pre-clinical studies were performed in animals testing effects of ozone on periodontal disease.

As a result, the animals that were treated with *in situ* ozone infusion, showed a reduction in infection and inflammation[29,40].

Agrillo et al[20] tested ozone therapy as a tissue regenerative factor as a treatment for BRONJ. According to this study, 90% of the cases confirmed the effectiveness of the ozone treatment, and as a result, this procedure was suggested as beneficial for improving the quality of life of the patients[20].

Various authors have used ozone therapy through local infusions in avascular necrosis of the jaw with success. The rationale for ozone applications is based on the antibacterial, antalgic properties and stimulating effects of ozone[20-22,29,41]. Ozone therapy in combination with antibiotic therapy can be administered before and after the dental intervention, and the risk of developing a BRONJ can be reduced[20-22,41].

Ripamonti et al[30] proposed local applications of ozonated oil (with custom-made siliconized medical device) associated with antibiotic therapy with very encouraging results[30]. Ozone therapy through the stimulation of cell proliferation promotes the formation of bone sequestration and soft tissue healing[20]. The elimination of bone sequestration (superficial debridement) is a subsequent step in the healing process and takes place with a surgical procedure which consists in removing dead, damaged or infected tissues, which could otherwise compromise the healing of the lesion[21,22,31].

In this study, ozone/oxygen therapy was selected as an adjunctive treatment to surgical debridement because of the several advantages as explained previously. As a result, there was an increase in most of the patients' quality of life. In 6 out of 14 patients surgical debridement appointments were cancelled due to spontaneous expulsion of the necrotic tissues. In those cases, the appointments were continued with ozone/oxygen therapy applications as planned. 9 out of 14 patients and 10 out of 15 sites healed. There was no statistically significant difference between age, gender and between disease type. No statistical difference was found between maxilla and mandible. These results are in accordance with the reports in the literature on promising results of ozone applications[20-22,29].

In this present study, the surgical debridement was done by piezoelectric instruments. Piezoelectric surgery has advantages for the bone tissue in terms of healing when compared to conventional bone surgery. Traditional bone surgery is performed with surgical drills mounted on rotary instruments and despite being at low speed (15,000-40,000 rpm) there is a risk of overheating the bone margin, which can compromise healing process[33-35]. The advantages of piezoelectric surgery can be listed as follows; better healing, less pain for the patient, clear and well-defined lines of osteotomy, minimum risk of damaging

anatomical critical structures, absence of vibrations on the handpiece and a bloodless field with excellent intraoperative visibility with a low temperature increase[36,37].

The most important aims in BRONJ patients are to minimize progression of the lesion, to promote tissue healing and to control infection[42]. Several adjunctive treatment modalities were presented in the literature with successful outcomes in the management of BRONJ lesions. Biological agents, such as autologous platelet concentrates, recombinant growth factors, and parathyroid hormone, can be used during surgical interventions in order to enhance the positive results[42]. However, one of the main advantages of this present study on ozone/oxygen therapy was the spontaneous expulsion of the necrotic tissue in six patients. These patients did not need any other intervention and the surgical intervention that was planned was cancelled. This result seems very promising in terms of eliminating new surgical sites that may become additional areas of exposed necrotic bone in BRONJ patients.

Currently, there are no reports on comparison of low levels of laser, hyperbaric oxygen and ozone therapy in BRONJ management and it can be interesting to test the results.

The present case series study aimed at evaluating if ozone/oxygen therapy and debridement with piezoelectric surgery may improve the treatment of BRONJ. The authors proposed that ozone/oxygen therapy might be beneficial for the treatment of BRONJ. The complete healing of the necrotic tissues was achieved in 64.2% of the patients (9 out of 14). No adverse events or complications were seen in any of the patients. This result also indicated that ozone/oxygen therapy and debridement with Piezoelectric surgery can be a safe alternative to other treatment modalities.

The results of this present study show that ozone/oxygen therapy applications can be applied even in patients with severe compromised health, such as oncological conditions. As a consequence, the quality of life of these patients can benefit from this adjunctive therapy.

Conclusions

According to the results of this study, ozone/oxygen therapy and debridement with Piezoelectric surgery for the management of BRONJ lesions can be considered as a promising and safe treatment modality for BRONJ patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

F.G., D.G., Fr.G., and M.D.F. conceived and designed the analysis. Databases were searched and data was collected by F.G., D.G., Fr.G., and M.D.F. Ozone/oxygen applications and surgical interventions were performed by D.G. All the authors contributed on analysis and interpretation of data for the work. F.G. drafted the work and wrote the manuscript with input from all authors. F.G., D.G., Fr.G., S.A., G.M., R.V., C.A.R. and M.D.F. revised the work critically for intellectual content. Integrity of the work was appropriately investigated and resolved by all authors. All authors contributed and approved equally to the final version of the manuscript. .

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