Global Journal of Anesthesiology

Peertechz

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Dates: Received: 22 September, 2016; **Accepted:** 15 October, 2016; **Published:** 17 October, 2016

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www.peertechz.com

ISSN: 2455-3476

Keywords: Bisphosphonate; Jaw osteonecrosis; Ozone therapy

Case Report

Oxygen-Ozone Treatment in Bisphosphonate Related Osteonecrosis of the Jaw: A Case Report

Introduction

The bisphosphonate related osteonecrosis of the jaws (BRONJ) is defined as a drug-adverse reaction that involves the maxillary bones.

It develops during or after a long-term bisphosphonate therapy in absence of radiotherapy [1].

The clinical pattern was described for the first time by Marx RE in 2003, who observed the development of jaws osteonecrosis in patients underwent to Multiple Myeloma and Mammary Cancer therapy [2]. Bisphosphonates (BF) pharmacokinetics consist in the osteoclast function interruption, angiogenesis inhibition, as well as blocking any cancer cell line activity together with the interruption of signal transduction [3]. In this way the bone regeneration is interrupted and osteonecrosis is more probable.

Although BF are administered to prevent secondary diseases linked to tumors and to manage osteoporosis and metabolic diseases of the bone [4], several reports connect BF administration with intraoral lesions [2,5-15].

A review shows that the incidence of BRONJ is between 1% and 15% in oncological population, between 0,001% and 0,01% in osteoporosis population and <0,001 in the general population [16].

Patients treated with BF therapy have more chances to develop BRONJ, depending on the doses, the bioavailability of the drug and the comorbidity [17].

The pathogenesis of BRONJ is caused by the BF selectivity for tissues with elevated turn-over [7], in particular for the alveolar bone which is in constant regeneration [2].

Osteonecrosis is, in many cases, subsequent to a dental extraction [7,18] or to other conditions which implicate bone remodeling. Only in few cases, it is a spontaneous process [19]. Particular attention is recommended in dental management of these patients [20].

BRONJ is characterizes by a wide range bone exposure with a great deal of variables. The lesions are often anticipated by inflammation of the mucosa together with reddening and/or pain. The bone exposure is often associated with bacterial infection and abscess. The most common complications are: nerves involvement, abscesses in the nasal cavity or in paranasal sinuses and pathological bones fractures.

Considering the pathogenesis and the clinical outcome, the therapeutic strategy is oriented to face the infective complications (antibiotic, antiseptic, antifungal) and to remove the necrotic bone (minimally-invasive surgery). Bio-stimulation of involved tissue is also recommended.

Background

At the present state two different methods are proposed for biostimulation: Low Level Laser Therapy, the efficacy of which is shown by many works [21-24], and Oxygen/Ozone therapy.

The use of Oxygen/Ozone in BRONJ therapy was introduced by Agrillo et al. in 2007 [25]. Some of its therapeutic properties are: bactericide and virustatic effects, anti-oxidant power and bio-stimulation [26,27]. The efficacy on wound healing, blood circulation, immunological response, and microbicide power make this molecule an interesting therapeutic aid for many diseases, including BRONJ [28].

Studies lead by several authors [3,19,25,29-31] showed how Ozone could induce bone sequestrum and revascularization; in some cases, the removal of bone sequestrum lead to the complete healing without the necessity of any other treatment (including surgery).

Aim

To evaluate the efficacy of local Oxygen/Ozone applications in the treatment of BRONJ.

Case Presentation

L.M., a 69 female patient, arrived to Oral Surgical Ward of Policlinico Umberto I, Sapienza, University of Rome, Rome, Italy in November 2014.

Anamnesis referred breast cancer with bone metastasis diagnosed in 2013 treated by bilateral mastectomy and adjuvant chemotherapy. Because of occurring osteoporosis, the patient underwent to bisphosphonates administration. All the needed treatments were

carried out by her dentist before the administration of intravenous Zolendronic Acid (Zometa Novartis).

The therapy was interrupted in August 2014 when jaw bone exposure was diagnosed.

Objective examination showed three different injuries: a lesion of 5 cm on the right side of the superior arch and two lesions of 1 and 0,5 cm in the left side of the superior arch (Table 1, Figure 1)

The bone tissues appeared as yellowish, with signs of bacterial infection, soft in some areas and of vitreous consistence in others; the surrounding mucous membrane appeared reddened, edematous and purulent. The panoramic radiograph showed a bone densification in the interested areas. Moreover TC Dental-scan was prescribed.

In partnership with the "Pain Therapy Center" of Policlinico Umberto I, Sapienza, University of Rome, Rome, Italy, a double approach was planned: surgical and Oxygen/Ozone treatments. Each oxygen-ozone treatment consisted of:

- A rinse with bi-distilled ozonized water [37 mcg/ml O_3] for 30 seconds.
- Oxygen /Ozone gas administration: [20mcg/ml], 10 minutes.
- A rinse with bi-distilled ozonized water [37 mcg/ml O_3] for 30 seconds.

An insufflation camera was built basing on the silicone arch prints (Optosil/Xantopren Heraeus Kulzer GmbH). The camera presented two valves (an inlet and outlet) for insufflation and aspiration of oxygen-ozone.

The administration of oxygen-ozone was simultaneously delivered and removed by a continuous gas flow and aspiration, in order to enhance a continuous replacement of the gas and a better efficacy of its therapeutic effect (Figure 2).

Each oxygen-ozone cycle lasted for 8 treatments.

A Medica-srl ozone generator, model E100, was used to generate medical ozone (Ozone line International, Medica S.r.l. Via SanteVincenzi, 48 - 40138 Bologna Italy) from pure oxygen and electricity. The ozone generator converts medical oxygen into a mixture of O_3 and O_2 through an electrochemical process. The Medica-srl Generator is equipped with a photometer, calibrated according to the classic iodometric titration of ozone, and a voltage system which regulates the concentration within a range from 5 to 100 µg/ml.

- First treatment consisted in a debridement with a piezoelectric surgical hand piece, executed in association with local antiseptics to reduce the bacterial load and enhance the reactivity of zone exposition. Before and after the treatment the patient underwent azithromycin 500 mg once a day for 5 days. A week later, the patient underwent to 8 treatments of Oxygen/Ozone therapy, three times a week.

A panoramic radiograph and a clinical evaluation were scheduled and assessed after the treatments: fester and inflammation signs appeared to be reduced and epithelialization was increased.

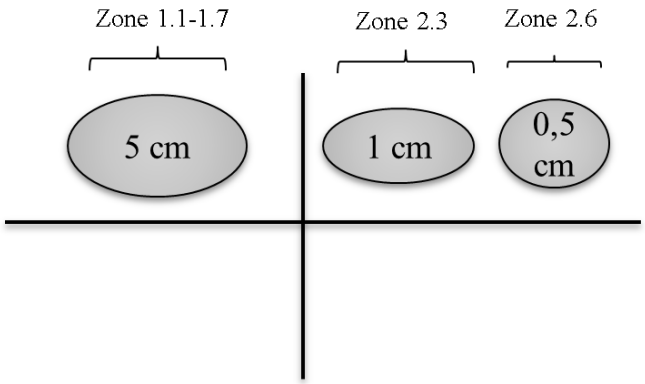
- Second treatment consisted in a sequestrectomy, executed with piezoelectric surgical hand piece; azithromycin 500 mg once a day for 5 days was administrated before and after the treatment. Anatomopathological analysis of the excised necrotic tissues showed necrotic bone associated with microbial flora and inflammatory infiltrate (plasma cells and neutrophils). The patient underwent to a second cycle of 8 administrations of oxygen-ozone.
- Third treatment consisted in a second debridement with piezoelectric surgical hand piece; azithromycin 500 mg once a day for 5 days was administrated before and after the treatment. After the surgery, 8 treatments of Oxygen/Ozone therapy were made and a faster epithelialization occurred again.

A remarkable improvement of the clinical presentation was diagnosed at the end of the treatment (Figure 3).

Discussion

The management of BRONJ patients consist of topic and systemic approaches listed by different authors, but at the moment there aren't common guide lines [7]. In this case report we focused on the possible role of Oxygen-Ozone therapy in the treatment of this disease. The properties of ozone are known since many years in medicine: in particular the antimicrobial power, the immunity modulation effect, the role on metabolism and on blood circulation [28]. Some authors, for these reasons, proposed its use in the treatment of BRONJ [1-19,25-29-31).

Table 1: Injuries size and localizations.



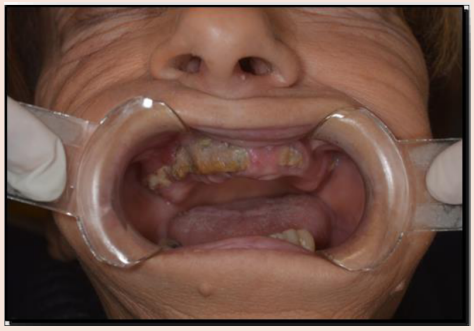


Figure 1: Superior arch before the treatment.

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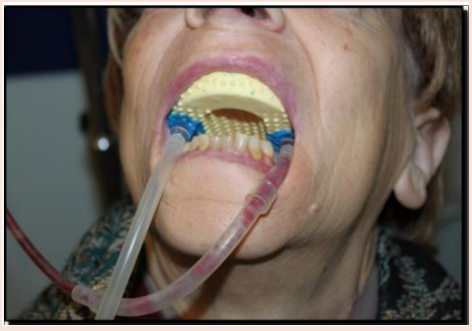

Figure 2: Oxygen/Ozone treatment.

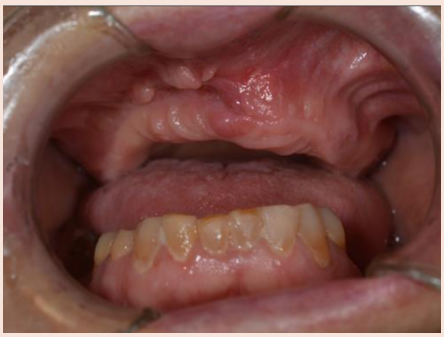

Figure 3: Superior arch after the treatment.

The clinical case presented gave way to verify the therapeutic role of O_2/O_3 local therapy. The local administration of oxygen-ozone mixture lead to a remarkable reduction of infection and inflammation signs. Moreover it provided also a better and faster healing of tissues in the post- operative period.

The dental tray was specifically customized in order to achieve a perfect adherence avoiding the Oxygen/Ozone loss completely. In this way we increased the therapeutic effects of Oxygen/Ozone mixture and, at the same time, we guaranteed the procedure safety. Oxygen/Ozone is toxic for alveolar cells and causes the following side effects: airway irritation, cough, dyspnea and pulmonary lungs fibrosis. For these reasons, we suggest the use of a personal and specifically customized dental tray.

Some authors reported cases of spontaneous recovery after the O_2/O_3 administration without the need for any surgical procedure [3-19]. Unfortunately our patient also needed for surgical intervention. Maybe treatment efficacy could depend on the lesion size and patient conditions.

Moreover should be also considered that this is a time consuming procedure. In order to have therapeutic effects patients need to undergo three times a week in the hospital.

Another point is ozone concentration: in our case we decided to administrate O_3 20 mcg, it would be interesting to develop further studies with a different concentration of this gas.

Conclusions

Local application of oxygen-ozone could be a valuable therapeutic tool in the treatment of BRONJ and also in any lesions of the oral cavity thanks to the regenerative effects that this gas mixture has. However, in the particular case of BRONJ more studies are needed in order to encode a standardized protocol based on the severity of the lesions and the clinical stage.

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