Research Article

Oxygen/Ozone Therapy: a promising approach for the treatment of biphosphonate-related osteonecrosis of the jaw

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Biphosphonate-related osteonecrosis of the jaw (BRONJ), a side effect following biphosphonate treatment, consists of a progressive bone destruction in the maxillofacial region and it is traditionally treated with antibiotic therapy and surgical removal of the necrotic bone. Among the studied alternative therapies, oxygen/ozone therapy has shown positive results.

In the present study, we evaluated how the ozone/oxygen therapy (O_2/O_3 mixture from medical oxygen) and the debridement with piezoelectric surgery may improve the treatment of BRONJ reaching a complete healing of the lesion. The experimental protocol consisted of the application of an O_2/O_3 mixture twice a week for 10 weeks before the debridement surgery and afterwards. Clinical and radiological parameters were used to evaluate the lesions.

Following up on the preliminary data recently published by Goker et al. (2020)[1], here we present the updated case reports. Until now, sixteen patients with BRONJ at stage 1 and 2 (classified according to the SICMF-SIPMO – Sistema di stadiazione clinica e radiologica) have been included in the treatment. After the O_2/O_3 therapy, 12 patients recovered from osteonecrosis and, in seven among these, the spontaneous expulsion of the bone fragment was observed. Relapses were recorded in two patients with extended lesions and in one with reduced oral hygiene and reduced adherence to the protocol schedule.

To conclude, the O_2/O_3 therapy with and without the debridement with piezoelectric surgery represents a promising approach to improve the treatment of BRONJ and therefore the life quality of the patients. Further studies should be conducted with the inclusion of a larger number of patients.

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Introduction

Biphosphonate-related osteonecrosis of the jaw (BRONJ), recently re-named as medication-related osteonecrosis of the jaw (MRONJ), is the progressive death of bone cells caused by a reduced blood flow (osteonecrosis, ON) in the maxillofacial region of patients during and after biphosphonate therapy (long-term or high doses)[2] [3] [4]. Dentoalveolar invasive surgery procedures such as implant insertions, periodontal surgery, surgical endodontics and tooth extractions are considered the main triggers for BRONJ. Anatomical alterations, dental prosthesis, inflammatory diseases of the oral cavity, smoking and other comorbidities (e.g. anemia, obesity) can also contribute to the development of this severe side effect of the bisphosphonate therapy [4] [5].

Among the investigated alternatives to the mainstream therapeutic approaches (antibiotic therapy and surgical removal) which have limited efficacy, oxygen/ozone (O_2/O_3) therapy (a mixture of O_2 and O_3 is transferred to the body) has shown positive results [6] [7]. Indeed, O_3 acts as a bactericidal agent and activates blood circulation by increasing the erythrocytes number and the hemoglobin concentration [6] [8]. At the Dentistry Department of the ASST Fatebenefratelli Sacco Hospital (Milan, Italy), an experimental protocol (approved by the Ethics Committee of Milano Area A) for the treatment of BRONJ with the O_2/O_3 therapy and the debridement with piezoelectric surgery has been followed since 2015. Preliminary data were recently published [1]. Here we report the updated case reports.

Materials and methods

Sixteen patients with BRONJ at stage 1 and 2 (classified according to the SICMF-SIPMO – Sistema di stadiazione clinica e radiologica) were included in the experimental protocol. The treatment was performed as described by Goker et al. (2020)[1]. Before and following the debridement with piezoelectric surgery, the O_2/O_3 mixture was administered locally twice a week for 10 weeks with a 3-4 day interval between applications according to the SIOOT (Società Italiana di Ossigeno-ozono terapia) guidelines (**Figure 1**). Clinical (e.g. pain, edema, presence of inflammation and bacterial infection, photographs) and radiological (Orthopantomography (OPT) and Computerized axial tomography (TAC)) parameters were used to evaluate the lesions.

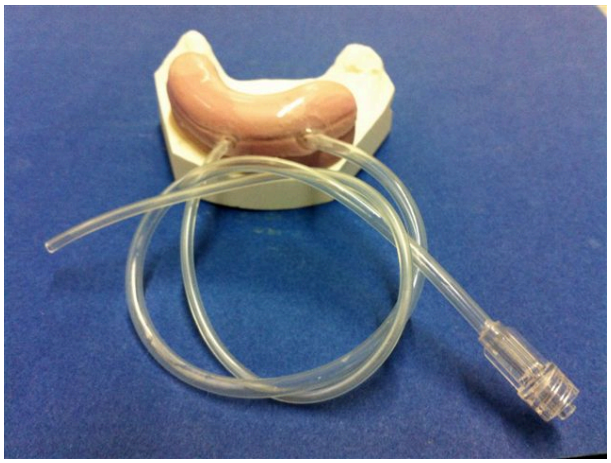

Figure 1. Application device.

Results

After the O_2/O_3 therapy, 12 of the 16 patients recovered from osteonecrosis and, in seven cases, the spontaneous expulsion of the bone fragment was observed (**Table 1** and **Figure 2**). Thus, surgery procedures (debridement with piezoelectric surgery) were not necessary for six patients (two surgery procedures were planned for one of them). The lesions of one patient healed after two sessions: following relapses after the first O_2/O_3 session, the protocol was repeated with the recovery of the patient. In another case, the patient who had previously undergone the mainstream surgery procedures without any positive outcome was completely recovered after one O_2/O_3 session. Relapses were observed in two patients with extended lesions (the initial stage of the lesions was probably underestimated) and in one with reduced oral hygiene and reduced adherence to the protocol schedule (the patient would often postpone the appointments).

Table 1. Overview of the results obtained and of the characteristics of the 16 patients included in the treatment.		Healed patients	NOT healed patients
TOTAL		12	4
of which spontaneous expulsion		7	-
Characteristics of patients			
Age	40-60	2	1
	>60	10	3
Gender	F	10	3
	M	2	1
Pathology	Neoplasia	6	4
	Others	6	0
MRONJ area	Maxilla	5	1
	Mandible	7	3

A

B

C

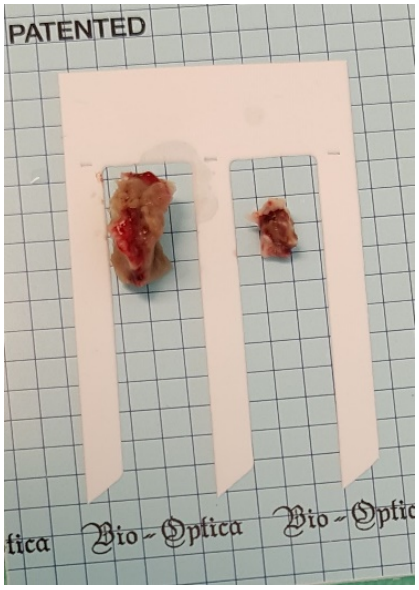

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Figure 2. Case report. A, B) Initial status of BRONJ in one of the included patients (Maj 2019); **C)** Ozone/oxygen application; **D)** Spontaneous bone expulsion one month after the end of the O_2/O_3 therapy (September 2019); **E)** Complete healing of the lesion observed one year later (September 2020).

Conclusions

The O_2/O_3 therapy with and without the debridement with piezoelectric surgery represents a promising approach to improve the treatment of BRONJ and therefore the life quality of the patients. With the current experimental protocol, no side effects/adverse reactions to the O_2/O_3 mixture were recorded. The therapy was well tolerated in patients with compromised health conditions. Furthermore, the O_2/O_3 therapy has a low biological and economic impact thus representing a valuable therapeutic approach that could be considered/implemented as the mainstream therapy for the treatment of BRONJ. Further studies should be conducted with the inclusion of a larger number of patients.

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Declarations

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