Research Article

PHOTOBIOMODULATION VS PHOTODYNAMIC THERAPY AS ADJUVANT TREATMENTS IN PATIENTS WITH MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ): A PILOT STUDY.

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Medication-related osteonecrosis of the jaw (MRONJ) is a well-known potential side effect of antiresorptive treatment. A growing body of literature indicates photobiomodulation (PBM) and photodynamic therapy (PDT) as adjuvant therapies against MRONJ. Aim of this pilot study was to assess and compare effectiveness of PBM and PDT. From September 2019 to January 2020, 18 patients with clinic-radiographic MRONJ were enrolled and assigned to 2 groups of 9 patients each. Group 1: 7 F, 2 M; mean age: 71.3 ± 12.76 years; 7 cancer patients and 2 osteoporotic patients; Group 2: 8 F, 1 M; age range: 53-87 years; mean age: 71.4 ± 11.52 years; 6 cancer patients and 3 osteoporotic patients. Group 1 was exposed to a two-week protocol of 4 PBM sessions (GaAIAs 810 nm laser; output power: 50 mW; energy: 3750 J, duration: 300 s). Group 2 was treated with a two-week protocol of 4 PDT session (GaAIAs 810 nm laser combined with blue-purple methylene photosensitizer output power: 600 mW; energy: 24 J, duration: 40s/cm^2). Four parameters were investigated before (T0) and after (T1) end of protocol: NRS for subjective pain, Masse Healing scale, probing depth, and size of lesion. Statistical evaluation showed a quasi-significant reduction of Masse healing scale in Group 1 ($p = 0.06$), and a significant reduction in Group 2 ($p = 0.01$) after PBM and PDT treatment, respectively. Comparison between Group 1 and Group revealed a significant difference in probing depth at T0, and no significant differences for any of the 4 parameters in T1 ($p > 0.05$). Despite the limited number of patients enrolled, PBM and PDT displayed an overlapping

therapeutic outcome, since both provided an objective improvement of MRONJ lesion appearance, without a significant pain relief. Further studies with larger samples, in a randomized controlled setting, are warranted for further evaluations.

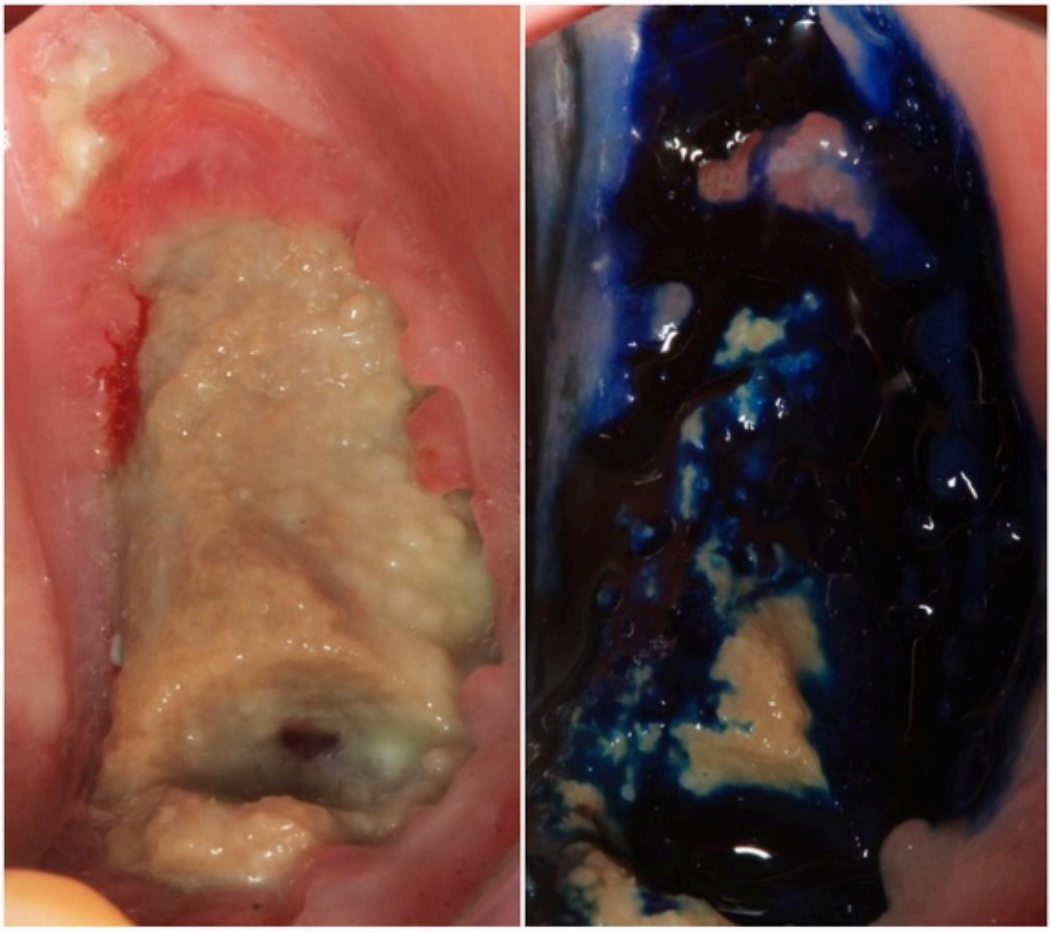
Masse et al. Healing scale

Introduction: Medication-related osteonecrosis of the Jaw (MRONJ) is a worrisome potential side effect of assumption of bisphosphonates or antiresorptive/biologic agents administered against bone metastatic cancer (i.e., breast cancer, prostate cancer), multiple myeloma, and/or bone metabolic disorders (osteoporosis, rheumatoid arthritis, Paget disease etc) and requires careful management by a multidisciplinary team[1] . Surgical and/or pharmacological management of MRONJ has been associated with photobiomodulation (PBM), aiming to stimulate cell metabolism, improve wound healing, reduce the inflammatory cascade, and provide pain relief[2]. Similarly, promising evidence emerged on the role of photodynamic therapy (PDT), where light is indirectly deployed to trigger the production of bactericidal molecules (i.e., singlet oxygen) from photosensitive dyes, thus playing a potential role against bacterial infection over the MRONJ site [3] ,[4]. Aim of the present study was to

assess efficacy of PBM and PDT as adjuvant therapies against MRONJ, and to compare the effectiveness of the two treatments.

Material and Methods: A two-arms pilot study was carried out with 2 groups of patients enrolled from the Oral Surgery Department. Inclusion criteria were the following: patients undergoing treatment with either bisphosphonates or denosumab for metastatic bone cancer or bone metabolic disorders, with clinic-radiographic signs of MRONJ, according to the Italian SIPMO-SICMF recommendations[5]. Exclusion criteria were the following: age < 18 years; history of previous head-and-neck radiotherapy, history of allergy to the chemical components of the photosensitizer (i.e., 3,7-bis dimethylamino-phenothiazin chloride).

Group 1 was exposed to 4 photobiomodulation (PBM) sessions for 2 weeks with a GaAIAs diode laser (Oralia, medical GmbH, Konstanz, Germany), with the following parameters: wavelength: 810 nm, Output power: 50 mW; energy: 3750 J, duration: 300 s - 150 s on the vestibular side of the lesion, 150 s on the lingual/palatal surface - with the laser probe kept 1 cm above the lesion. Group 2 was treated with 4 PDT sessions for 2 weeks with the same diode laser deployed in Group 1, but with the following parameters: wavelength: 810 nm, Output power: 600 mW; energy: 24 J, duration: 40s/cm^2; laser probe kept 1 cm above the lesion. The photosensitizer was a specific sensitizer on the basis of Phenothiazin (Photolase, Photolase Europe Ltd, Hamburg, Germany).



Four parameters were investigated: NRS unidimensional scale for pain assessment; Masse Healing scale[6] (1-3 numeric scale inclusive of 4 parameters: colour, texture, suppuration, bleeding) for appearance of MRONJ lesion; probing depth, as a mean of probing measurements in 8 different sites around the lesion; size of lesion, in mm^2, estimated with the same periodontal probe through timing of longitudinal and transversal diameters of MRONJ lesions' surface. These parameters were acquired before (T0) and after the end (T1) of PBM/PDT protocol. Statistical evaluation (T1 vs T0) within Group 1 and Group 2 was pursued with Wilcoxon signed-rank test, whereas Mann-Whitney test was used for comparisons between the Group 1 and Group 2, both at T0 and T1. Statistical significance was set at $p < 0.05$.

Results: Between September 2019 and January 2020, 18 patients were enrolled. Group 1 consisted of 9 patients (7 F, 2 M; mean age: 71.3 ± 12.76 years) of whom 7 as cancer patients (4 with metastatic breast cancer, 1 with metastatic prostate cancer, 2 with multiple myeloma) and 2 had bone metabolic

disorder (osteoporosis). Antiresorptive treatments were administered as zoledronate (5), denosumab (3), and risedronate (1). Five sites of MRONJ were mandibular, 4 were maxillary. Group 2 consisted of 9 patients (8 F, 1 M; age range: 53-87 years; mean age: 71.4 ± 11.52 years). Of these, 6 were cancer patients (4 with metastatic breast cancer, 1 with metastatic prostate cancer, 1 with multiple myeloma) and 3 had bone metabolic disorder (osteoporosis). Antiresorptive treatments were administered as zoledronate (4), denosumab (5). Six sites of MRONJ were mandibular, 3 were maxillary.

In Group 1, PBM did not lead to a significant improvement, with Wilcoxon test revealing no statistical differences between T1 and T0 concerning NRS, probing depth, and size of lesion ($p > 0.05$), whereas Mass-healing scale experienced a quasi-significant improvement ($p = 0.06$). In Group 2, PDT did not lead to significant clinical improvement concerning NRS, probing depth and size of lesion ($p > 0.05$), whereas Masse Healing scale was significantly reduced ($p = 0.01$).

Concerning Group 1 vs Group 2 comparison, Mann-Whitney showed no significant differences at T0 concerning NRS, Mass Healing scale and size of lesion ($p > 0.05$). Conversely, probing depth was significantly different between the two groups ($p < 0.05$). At T1, Mann-Whitney showed no significant difference concerning NRS, Mass healing scale, probing depth and size of lesion ($p > 0.05$).

Conclusions: Both PBM and PDT displayed some encouraging properties in improving the overall severity of the clinical pattern of MRONJ lesions, with no higher effectiveness of one of the two treatments. None of them seemed to provide a significant pain relief, instead. The main limitations of the present work rely in the smallness of samples, and in the absence of a control group. Further studies are needed, ideally in a randomized setting and with larger samples, to better assess the validity of these preliminary results.

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Declarations

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