

Review Article

Combined Phototherapies (aPDT and PBM Therapy) Protocol for Medication-Related Osteonecrosis of the Jaw (MRONJ) in a Cancer Patient: Scope Literature Review and A Case Report

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Abstract

Purpose: Medication-Related Osteonecrosis of the Jaw (MRONJ) is an oral complication in patients on ongoing or previous treatment with antiresorptive or antiangiogenic drugs. Many treatments have been proposed, but the management of MRONJ lesions is still challenging. The objective of this article is to present a literature review on aPDT and PBM in the management of MRONJ. Accompanying the review, a protocol and its outcome, for treating MRONJ in a cancer patient, where the association of photobiomodulation (PBM) therapy and antimicrobial photodynamic therapy (aPDT) was applied is presented.

Methods: This is the clinical case report of a 58-year-old male patient, with prostate cancer presenting a bone metastasis that was treated with chemotherapy and intravenous antiresorptive Zometa®. On intraoral clinical examination, in the region of the lower alveolar ridge, a lesion with necrotic bone exposed was observed. After clinical and radiographic evaluation of the lesion, it was diagnosed as MRONJ. The association of PBM and aPDT was applied at pre, trans and post-surgery. The pre-surgical phase lasted about two months. The post-surgical protocol was implemented 48 hours after surgery and lasted two months.

Results: The search included articles in the databases MEDLINE/Pubmed and Scopus. Nine studies were included 6 of combined aPDT and PBM and 3 studies investigated isolated aPDT published in English from 2016 to 2023. The proposed protocol resulted in the complete closure of the lesion. The patient was undergoing clinical follow-up for 3 years without recurrences.

Conclusion: Based on the positive outcome of the proposed phototherapy protocol, one can infer that the combination of PBM and aPDT in the pre, trans and post-surgery showed to be efficient in the treatment of MRONJ lesion.

Keywords: Medication-Related Osteonecrosis of the Jaw; MRONJ; Phototherapy; Photobiomodulation Therapy; Antimicrobial Photodynamic Therapy

Introduction

Medication-Related Osteonecrosis of the Jaw (MRONJ) is an oral complication in patients on ongoing or previous treatment with antiresorptive or antiangiogenic drugs. It is characterized by the presence of exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region, which persisted for more than 8 weeks in patients with no history of radiation therapy or obvious metastatic disease in the jaws [1,2]. Thus, MRONJ can be an adverse reaction of cancer therapies

being the oral cavity an important target organ [3].

The exact mechanism of MRONJ generation is not yet fully understood. It is believed to be a multifactorial disease with immunological and genetic elements. The alteration in bone metabolism, the hypovascularization of the region due to the inhibition of angiogenesis caused using the antiresorptive and/or antiangiogenic drug, associated with a local trauma in need of bone repair, with or without infection, are factors that can lead to MRONJ lesion [4]. In addition, some risk factors have already been identified, such as: older age; comorbidities such as diabetes mellitus and thrombosis; the cumulative dose of the antiresorptive drugs intake for a period greater than 3 years; the route of medication administration (the intravenous route being associated with a greater risk); the use of systemic corticosteroids; history of oral inflammatory disease; poor oral hygiene; trauma and tooth extraction, which can contribute to the development of the disease [5-7]. Most antiresorptive and/or antiangiogenic drugs may also cause soft tissue and cell toxicity at the site in which osteonecrosis develops [8]. These drugs, upon manipulation (or trauma) of the diseased bone can be released affecting the overlying soft tissue cells, such as epithelial cells, fibroblasts and macrophages in its dendritic cell differentiation and maturation which could cause loss of local immunity, culminating in healing inhibition [9-11].

Diagnosis and treatment of MRONJ can be challenging and require a comprehensive evaluation and complete treatment plan [12]. Many treatments for MRONJ have been proposed, but a gold standard treatment has not yet been available. Nowadays, the most used treatment categories are conservative interventions, with the use of mouthwashes and antibiotics; surgical treatment with lesion debridement and, non-surgical supporting treatments, such as hyperbaric oxygen chamber, platelet-rich plasma and laser, which are normally used in combination with other techniques [5]. Weber, et al., conducted a systematic review of the literature that showed that treatment modalities that included association with laser had a better outcome of the lesions than conventional surgical treatments or just antibiotic therapy. The authors concluded in this study that treatments that combine the use of antibiotics, minimally invasive surgery and low-power laser in the early stages of the disease, should be considered the standard treatment for the management of MRONJ lesions [13].

Based on the above, the management of MRONJ lesions remains challenging for dentists, especially in cases of tooth extraction need in patients under antiresorptive and/or antiangiogenic drugs due to either cancer or osteoporosis treatment. In these cases, protocols able to prevent MRONJ lesions are of relevance. Tartarotti, et al., in 2020 presented a prospective study that showed a protocol based on the association of phototherapies [Photobiomodulation (PBM) therapy and antimicrobial Photodynamic Therapy (aPDT)] that showed to be effective as adjuvant approach not only for preventing MRONJ development due to tooth extraction but also for treating MRONJ lesions at early stages [14].

Preclinical studies demonstrate that treatment with aPDT results in a decrease in pro-inflammatory cytokines and reduces the microbial load, which improves the bone tissue repair process and prevents the occurrence of osteonecrosis [15,16]. Photobiomodulation also presents beneficial therapeutic outcomes, such as pain and inflammation control, wound healing and tissue regeneration, inducing vascular formation and cell proliferation and migration [17-23]. Both therapies are effective, non-invasive and low-cost [24] and the association between them has potential in the management of MRONJ, since it combines the antimicrobial effect of aPDT with the regenerative effects of PBM. In fact, management of patients with MRONJ lesions with the combination of these two phototherapies (PBM and aPDT) has been also successful for treating cancer patient under dental care [25]. Thus, phototherapies (PBM and aPDT) can be applied, isolated or in association, at different time points during the MRONJ lesions management.

The literature on aPDT applied solo or combined with PBM for treatment and prevention of MRONJ is scarce [14,25-33]. Based on it, the objective of this article is to present a literature review on aPDT and PBM in the management of MRONJ. The review is accompanied by a protocol and its outcome for treating MRONJ in a cancer patient, where the association of PBM and aPDT was successfully applied in a protocol of combined phototherapies applied at pre, trans and post-surgery.

Results

Literature Review

An electronic search with a systematic approach was performed on December 01, 2024. The search included articles in the databases MEDLINE/Pubmed and Scopus. Key words were used for searching and Boolean operators (OR, AND) were used to

combine searches. The following keywords were used: “photodynamic therapy” OR “antimicrobial photodynamic therapy” OR “photobiomodulation” AND “medication-related osteonecrosis of the jaw” OR “bisphosphonate-associated osteonecrosis of the jaw”. All duplicates were deleted and titles and abstracts of studies found were assessed by two reviewers (M.E.M and M.S.M.), based on the following inclusion criteria: (1) studies evaluating aPDT and PBM for treatment of osteonecrosis; (2) patients in the use of antiresorptives, antiangiogenic or other drugs with potential for cause MRONJ. The reviewers assessed the full text, considering the following exclusion criterion: (1) patients submitted to head and neck radiotherapy. Information extracted from the articles included: author and year, number of patients, study design, sex/age of the patients, drug associated with MRONJ, dose and finality, stage of MRONJ and classification, proposed treatment and main results. The parameters of aPDT and PBM were also collected.

Of the initial 106 potentially relevant articles, 64 duplicates were excluded and 42 were considered eligible. Of these, 33 were excluded based on the inclusion and exclusion criteria. Finally, 9 studies were included [14,26-33]. Six studies investigated combined aPDT and PBM (4 case reports, 1 case series and 1 prospective study) and 3 studies investigated isolated aPDT (2 case reports and 1 case series) published in English from 2016 to 2023 were evaluated [14,26-33]. A total of 54 patients with 46-85 years were diagnosed with benign and malignant bone diseases in treatment with bisphosphonates and denosumab [14,26-33].

Combined aPDT and PBM were utilized for the treatment of MRONJ in stages 1-3 in 3 studies [27,31,32]. Two reports studied these therapies for the prevention of MRONJ after oral surgeries [28,33] and 1 study evaluated the protocol for prevention and treatment [14]. All studies associated aPDT and PBM with antibiotic therapy (Amoxicillin, Clindamycin, Ampicillin and Doxycycline) [14,27,28,31-33]. Rinse with chlorhexidine was also associated [14,27,28,32,33]. APDT and PBM therapies were performed in the trans-surgical of bone debridement in most studies (Table 3) [14,27,28,31,33]. The resolution of the diseases was observed in 6-36 months, with mucosa closure, absence of signs of infection, fistulae or exposed necrotic bone [14,27,28,31,32]. Prevention of MRONJ with combination therapies was observed in 3 studies, with absence of signs and symptoms of MRONJ up to 29 months [14,28,33].

Isolated aPDT was investigated for the treatment of MRONJ in stages 2-3 [26,29,30]. All studies associated aPDT therapy with antibiotics (Amoxicillin, Clindamycin and Metronidazole) [26,29,30]. Furthermore, PENTO protocol (Pentoxifilina and Tocopherol) was associated in 1 study [30] and rinse with chlorhexidine in 2 studies [29,30]. Resolution of the diseases was observed in two studies, with mucosa closure, bone neoformation and absence of signs and symptoms of MRONJ [26,29]. Additionally, a study demonstrated incomplete healing of MRONJ due to severity of the disease and control of the condition with therapies in 12 months of follow-up [30] (Table 4).

Table 5 presents the parameters utilized in all protocols. In general, most studies utilized methylene blue in different concentrations (0.005%-0.5%) as photosensitizer, 37.5 mg/L toluidine blue was used in 1 study [26]. Furthermore, the total energy of irradiation varied from 10.8 J to 32 J [14,26-33].

Clinical Case

This is the case of a 58-year-old male patient, Caucasian, smoker, diabetic and with prostate cancer diagnosed and treated with radiotherapy and chemotherapy in 2013. In 2016, a bone metastasis was treated with chemotherapy and intravenous antiresorptive Zometa®. Three years later, with the complaint of “a wound that did not heal” in the right jaw (region of 47), the patient was referred for care at the Sorrir Para Vida Institute, a clinic dedicated to treat patients with cancer treatment oral sequelae. On intraoral clinical examination, in the region of the lower alveolar ridge, under a poorly adapted prosthesis, a lesion with necrotic bone exposed was observed. After clinical and radiographic evaluation of the lesion, it was diagnosed as MRONJ (Fig. 1).

In agreement with the medical team, it was decided to not suspend the anti-resorptive medication (Zometa) and to implement the pre-surgical protocol with phototherapies.

Association of PBM and aPDT

The irradiation parameters for both phototherapies are presented in the Table 1 and the protocols in Table 2. The PBMT was applied using a diode laser (Laser DMC Therapy XT, DMC, SP, Brazil) in two wavelengths (660 nm or 808 nm). For the aPDT,

the lesion was fulfilled with 0.01% methylene blue aqueous solution during 5 min. Next, the excess solution was wiped off and the irradiations were done using the same parameters as those for PBMT for red laser (660 nm). The laser was applied in contact, punctually around the lesions taking care for maintaining approximately 1 cm distance between each point.

Pre-Surgical Treatment

The pre-surgical treatment was applied following the parameters presented in of Table 1 and the protocol of Table 2. It was carried out on five working days of the week, as follows: daily sessions of PBM with red and infrared laser with 2J per point applied around the lesion (total of 6 points) followed by the application of the aPDT protocol, which occurred only on 3 interspersed days (Monday, Wednesday and Friday) - with application of 0.01% methylene blue photosensitizer for 5 minutes, 6 J of red laser per point (5 points) distributed every 1 cm around the lesion, totaling an energy of 30 J. The pre-surgical phase lasted about two months, when the radiographic (Fig. 1) and tomographic examinations showed images suggestive of bone sequestration and then, the surgery was scheduled.

Trans-Surgical Treatment

Antibiotic therapy was prescribed with Amoxicillin 1g, 1 hour before the procedure, followed by a dosage of 500 mg of Amoxicillin for 6 days in the postoperative period. The surgery was performed in a minimally invasive manner, with only the bone sequestration removal (Fig. 1), which led to bone defect (Fig. 1), where aPDT was applied (Fig. 1) as described above. Then, the mucosa was sutured (Fig. 1).

Post-Surgical Treatment

The post-surgical protocol was implemented 48 hours after surgery with the application of PBM and aPDT on the same day, with PBM performed before aPDT. The phototherapy treatments were applied 3 times a week, for two months, when the complete closure of the lesion was observed (Fig. 1). The patient received a new removable prosthesis with adequate adaptation 5 months after the complete closure of the lesion and is undergoing clinical follow-up for 1 year without recurrences.

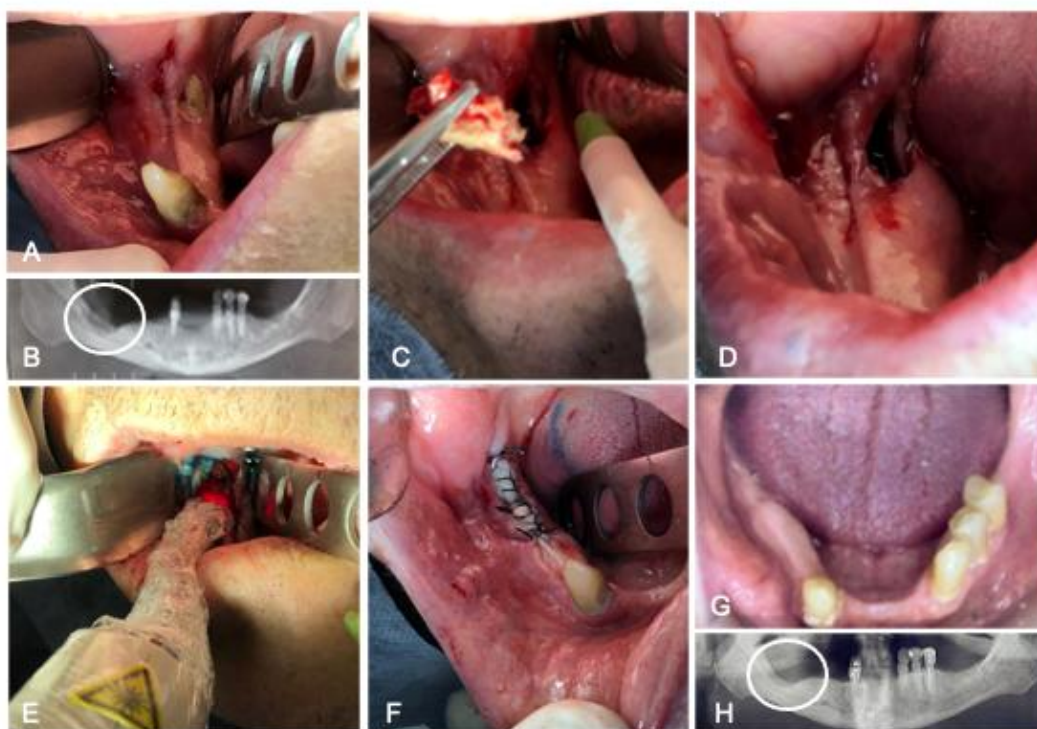


Figure 1: Illustrative images of the clinical case. (A) Initial photograph of the oral lesion; (B) Panoramic radiography showing a diffuse radiolucency at the region of 47 (inside the circle); (C) bone sequestration removal; (D) bone defect before aPDT; (E) aPDT: after fulfilling the bone defect with 0.01% methylene blue it is being irradiated with red laser; (F) suture; (G) the lesion is covered by mucosa and (H) panoramic radiograph shows a shallow radiolucency with more defined edges (circle).

Parameters	Wavelength (nm)	Power (mW)	Spot area (cm ²)	Power Density (W/cm ²)	Time (s)	Energy density (J/cm ²)	Energy / point (J)	Photosensitizer 0.01% Methylene blue
aPDT	660	100	0.028	3.57	60	214.28	6	Yes (5 min prior irradiation)
PBM red	660	100	0.028	3.57	20	71.42	2	No
PBM infrared	808	100	0.028	3.57	20	71.42	2	No

PBM: Photobiomodulation; aPDT: antimicrobial Photodynamic Therapy

Table 1: Irradiation parameters of PBM therapy and aPDT.

	PBM	Protocol	aPDT	Protocol
Pre	Red (R) and Infrared (IR)	2J per point, each point at 1 cm apart around the lesion 2 to 5 times a week	Yes	6J per point: 2 vestibular; 2 lingual, 1 at the center of the lesion. E = 30J 3 times a week
Trans	No	-	Yes. After necrotic bone removal and before suturing	6J per point: 2 vestibular; 2 lingual, 1 at the center of the lesion. E = 30J
Post	Red (R) and Infrared (IR)	R: 2J per point, 3 points IR: 2J per point, 2 points 3 times a week	Yes	6J per point: 2 vestibular; 2 lingual, 1 at the center of the lesion. E = 30J 2 to 3 times a week

PBM: Photobiomodulation; aPDT: antimicrobial Photodynamic Therapy

Table 2: Protocols of the photonics therapies pre, trans and post-surgery.

Author, year	No of patients	Study design	Sex/age (years)	Drug associated with MRONJ/Finality	-Stage of MRONJ/Classification	Treatment	Main results
Minamisa ko, et al., 2016	1	Case Report	M/85	Alendronic acid/ bone thinning of both knees	Stage 2/AAOMS	-Clindamycin -Oral hygiene guidance -Chlorhexidine gluconate gel 0.12% -Weekly and undertaken to superficial bone debridement, aPDT and LLLT application for 12 months, until clinical healing of bone exposure accounting a total of 37 sessions.	-Healing of bone exposure -No recurrence in 6 months

Poli, et al., 2018	1	Case Report	F/62	Clodronate/osteoporosis	Stage 1/AAOMS classification	-Amoxicillin 1 g every 8 h for 20 days, starting 3 days before surgery -Mouth rinsing with 0.2% chlorhexidine twice daily -Surgery under local anesthesia -Transoperative aPDT -Ibuprofen 600 mg every 8 h for 3 days post-operative -Weekly applications of low-level-laser therapy for 6 weeks	-A complete resolution of the disease was observed in terms of the maintenance of mucosal closure without any signs of residual infection, fistulae or exposed necrotic bone at the surgical site. -Clinical healing was corroborated by a radiological evaluation showing no radiographic signs of MRONJ and smooth margins at the 6-month follow-up
Poli, et al., 2019	11	Case series	F = 8, M = 3/65-79 years old (72.5 -mean age)	Bisphosphonates (Alendronate and Clodronate) or Denosumab /osteoporosis/ mean duration of antiresorptive treatment was 39.2 (24-72 months)	MRONJ prevention	- 15 mL 0.2% chlorhexidine digluconate solution twice daily for one month, starting 2 weeks before the surgery -Professional oral hygiene procedures were performed to remove plaque and calculus one week before	-The follow-up ranged from 6 months to 1 year - No patients showed prodromal manifestations of MRONJ -No case of MRONJ was recorded up

						surgery -Amoxicillin for 20 days, starting 3 days before surgery -Transoperative aPDT -Ibuprofen and topical application of ice packs postoperative -Weekly low-level laser therapy for 6 weeks.	to the latest follow-up visit.
Tataroti, et al., 2020	17 - MRONJ treatment 18 - MRONJ prevention	Prospective study	MRONJ treatment: M = 12.5% F = 87.5% Mean age = 73.37 MRONJ prevention: M= 0% F= 100% Mean age = 68.94	MRONJ treatment: Oral bisphosphonates (75%) and intravenous - Zoledronic acid (25%) / osteoporosis (62.5%), osteopenia (12.5%), Breast cancer (18.75%), others (6.25%) MRONJ prevention: Oral bisphosphonates (72.2%) and intravenous - Zoledronic acid (28.8%) / osteoporosis (61.1%), osteopenia (11.11%), Breast cancer (22.22%), others (5.55%)	Stages 0-3 / AAOMS classification	MRONJ treatment: -Amoxicillin or Clindamycin in cases of inflammation/infections -Preoperative aPDT until the reduction of signs and symptoms of infection -Surgically bone necrotic remotion -APDT inside surgical wound weekly until healing -Antibiotics pre or postoperatively for no longer than 7 days -Daily mouth rinsing with 0.12 % chlorhexidine digluconate -PBM when patients presented complaints of pain or signs of post-operative edema MRONJ prevention:	Treatment protocol: -Seventeen patients presented with MRONJ underwent aPDT protocol and sixteen of them showed total regression of lesions -Follow-up of 3-36 months Preventive protocol: - None presented signs of MRONJ after a follow-up -Follow-up of 6-29 months

						-24h preoperative course of antibiotic (Amoxicillin or Ampicillin or Clindamycin) - Transoperative aPDT after tooth extraction and weekly until tissue repair -Daily mouth rinsing with 0.12 % chlorhexidine digluconate -PBM after complaints of pain or signs of post operative edema	
Martins, et al., 2021	1	Case Report	F/66	Zoledronic acid/bone metastasis	MRONJ prevention	-Amoxicillin -Mouthwashes with 0.12% chlorhexidine - PBM - Transoperative aPDT and 3 times a week during the first 2 weeks and once a week until the complete wound healing	-Entire region of the suture covered by pseudomembrane -Dry socket development with necrotic bone exposure with 20 days, that rapidly regressed without any further treatment Complete heal in 30 days, with no sign or symptom of inflammation and infection - During the follow-up of 7 months, there was neither development of bone necrosis and

							sequestration nor oral infection focus
Silva, et al., 2023	1	Case Report	F/62	Alendronate/osteoporosis	Stage II/NR	-Doxycycline 10 days preoperative -Remotion of bone sequestration -Transoperative aPDT and PBM once a week -PBM	-Good tissue repair, with the entire wound covered with reddish tissue, demonstrating vitality of the entire tissue -After 3 months, the patient presented complete epithelial repair, with full coverage of the exposed areas and with significant resolution of the pain -In the 1-year follow-up, a normal mucosal aspect was observed, without bone exposure and absence of painful symptoms
MRONJ = medication-related osteonecrosis of the jaw / NR = not reported / AAOMS = American Association of Oral and Maxillofacial Surgeons / aPDT = antimicrobial photodynamic therapy/ PBM = photobiomodulation							

Table 3: Characteristics of cases reporting combined aPDT and PBM for the treatment/prevention of MRONJ.

Author, year	No of patients	Study design	Sex/age (years)	Drug associated with MRONJ/Finality	-Stage of MRONJ/Classification	Treatment	Main results
Castro, et al., 2016	2	Case series	1.F/46 2.F/51	1.Alendronate/70 mg per week for 6 years/osteoporosis, Prednisone 20 mg per day/lupus erythematosus 2.Alendronate/70 mg per week	1.Stage 3/NR 2.Stage 2/NR	1.-Amoxicilin + Potassium Clavulanate and Metronidazole, -Surgical debridement - Transoperative aPDT -PRF in the bone defect -Same antibiotic therapy post-operative 2. - Clindamycin -Surgically remotion of necrotic bone -Post-operative antibiotic -New surgical intervention due to the persistence of the exposed bone and infection -aPDT trans-operative -PRF in the bone defect	1.14 days of follow-up showed full coverage of bone tissue by mucosa and absence of infection and 10 months later a complete healing of the operated area, with the presence of bone neoformation and absence of symptoms was detected 2. A 14 month follow-up of indicated complete recovery of the operated area, significant bone neoformation, full coverage of bone tissue by healthy mucosa and absence of symptoms
Almeida, et al., 2021	1	Case report	F/75	Zoledronic acid/breast cancer	Stage 2/AAOMS	-Clindamycin -Mouthwash with 0.12% chlorhexidine digluconate - Necrotic bone curettage -APDT	- After 12 sessions, complete regression of the lesion with an absence of painful symptoms or presence of purulent secretion was

							observed in the region -New lesion after 2 weeks treated with the same protocol, with complete regression of the lesion
Schussel, et al., 2022	1	Case report	F/69	Pamidronate/ 90 mg monthly for more than 5 years and Thalidomide/multiple myeloma	Stage 3/AAOMS	-Systemic antibiotic therapy (Amoxicillin and Metronidazole) -PENTO protocol (Pentoxifyline and Tocopherol) for 30 days -0.12% chlorhexidine gluconate mouthwash -APDT weekly in the first 2 months and then every fortnight -Debridement of the necrotic bone	-Reduction in the areas of bone exposure with improved food intake and taste sensation -Need for an antibiotic prescription for 3 more cycles during the 12-month follow-up period -To further increase the adjuvant effect of aPDT, the PENTO protocol was also prescribed for 6 months -Since adjuvant therapies will not be able to heal MRONJ completely, the patient will remain in follow-up to control the condition
MRONJ = medication-related osteonecrosis of the jaw / NR = not reported / AAOMS = American Association of Oral and Maxillofacial Surgeons / aPDT = antimicrobial photodynamic therapy/ PBM = photobiomodulation							

Table 4: Characteristics of cases reporting aPDT for the treatment/prevention of MRONJ.

Author, year	Treatment	Laser type/Wavelength (nm)	Photosensitizer	Spot size (cm ²)	Power	Power density	Energy density	Exposure time	Energy/point (J)	Energy (J)
Castro, et al., 2016	-APDT	Low-level laser/660 nm	37.5 mg/L toluidine blue dye (TBO)	0.04 cm ²	40 mW	NR	100 J/cm ²	100 s	4J	32 J
Minami sako, et al., 2016	-APDT -PBM	Diode low-level laser/660	0.01% methylene blue	NR	100m W	-	142 J/cm ²	40 s	4J	NR
		Diode low-level laser/808 nm	-						4J	
Poli, et al., 2018	-APDT -PBM (same apparatus)	A hand-held diode laser/660 nm	0.5-mL solution of 10 mg/mL phenothiazine chloride dye consisting of Methylenthioniniu mchlorid based on methylene blue compound	NR	100 mW	60 mW/c m ²	3.6 J/cm ²	60 s	NR	10.8 J
Poli, et al., 2019	-APDT (preventive) -PBM (same apparatus)	A hand-held diode laser/660 nm	0.5-mL solution of 10 mg/mL phenothiazine chloride dye consisting of Methylenthioniniu mchlorid based on methylene blue compound	NR	100 mW	60 mW/c m ²	3.6 J/cm ²	60 s	NR	varied depending on the extension of the surgical area
Tataroti, et al., 2020	-APDT -PBM (preventive and curative)	Diode laser/660 nm	0.01 % methylene blue	0.028c m ²	0.1 W	3.57 W/c m ²	321 J/cm ²	90 s	9J	27 J
		Diode laser/808 nm	-	0.028c m ²	0.1 W	3.57 W/c m ²	107 J/cm ²	30 s	3J	12 J
Almeida, et al., 2021	-APDT	Hand duo laser device/660 nm	0.01% methylene blue gel	0.03c m ²	0.1 W	NR	300 J/cm ²	90 s	9J	9 J
Martins, et al., 2021	-APDT -PBM	Twin Laser - Diode laser - 660 nm	2% methylene blue	NR	40 mW	NR	NR	NR	4,8J	NR
		Twin Laser -	-				NR		0,2 J - 1 J/ point	

		Diode laser/660 nm and 808 nm								
Schusse l, et al., 2022	-APDT	Low power laser	0.005% methylene blue	NR	NR	NR	NR	30 s	NR	NR
Silva, et al., 2023	-APDT -PBM	Red light /660 nm	1 mL of methylene blue	NR	35 mW	NR	NR	180 s	6J	NR
		Infrared light/880 nm	-		35 mW		NR	60 s	2.1J	
NR = not reported / aPDT = antimicrobial photodynamic therapy/ PBM = photobiomodulation										

Table 5: Reported parameters of combined aPDT and PBM for the treatment/prevention of MRONJ.

Discussion

Medication-Related Osteonecrosis of the Jaw (MRONJ) is of great severity, especially in cancer patients, because it affects their quality of life, due to its morbidity. For this reason, for patients with MRONJ lesions, the goal of treatment is to control the infection, minimize progression of the necrosis and promoting tissue repair to close the oral mucosa on the top of the lesion [1,6]. In this way, phototherapies performed with low-level laser (PBM and aPDT) emerges as an alternative and conservative approach for the management of osteonecrosis [12,14,25-34] and have been used successfully in the clinical cases presented. Since, through aPDT, it is possible to promote decontamination of the lesion and, with PBM, it is possible to modulate inflammation, accelerate hard / soft tissue repair and promote analgesia, thus improve the quality of life of patients [12,14,25-34].

Our results in the presented clinical case are like those observed by Tartaroti, et al., 2020 who used aPDT in a series of cases, applied once a week during the pre, trans and post-surgical phases of treatment. The objectives were to reduce the signs and symptoms of infection, to decrease the microbial load in the surgical wound and to prevent recontamination, until the complete closure of the lesion. However, in the Tartarotti, et al., study PBM was used only when patients had pain or edema in the post-surgical phase until symptom remission [14], whereas in our protocol, the PBM was applied in pre- and post-surgery in all cases. Furthermore, trans-surgical aPDT was performed, like most cases reported in the literature, including for MRONJ prevention [14,27,28,31,33]. This approach appears important for disease prevention due to the effectiveness of aPDT in reducing colony-forming units of *Actinomyces* [35], the main bacterial pathogen isolated from MRONJ lesions [36].

The parameters used for aPDT varied between studies, whereas Tartaroti, et al., applied energy per point of 9 J, in our protocol a smaller energy (6J) was applied [14,26-33]. With these smaller energies the decontamination occurred in lesser irradiation times per point, which is much more comfortable for the patients. Another important finding of both studies was the presence of granulation tissue formed between the necrotic bone and the base of the lesion, which facilitated the sequestrectomy, which occurred either spontaneously or with ease detachment during the surgery, revealing a healthy-looking soft tissue bed on the surgical site. This pattern of spontaneous sequestrectomy of bone necrotic with subsequent mucosal closure was also observed in a patient with osteoradionecrosis after 4 sessions of aPDT [37]. In addition to obtaining closure of the MRONJ lesion, perhaps this finding that facilitated the implementation of conservative surgical treatment was the most interesting result of the protocol presented here.

In the conduction of the clinical case here presented, it was decided to use the association of aPDT and PBM in all stages of the MRONJ treatment as a strategy to intentionally induce the formation of granulation tissue because of an immunological response to the foreign body, evidencing the appearance of bone sequestration. This response was already somewhat expected by previous clinical experiences of our research group, published, for example, in Pedroni, et al., which showed the same favorable results and granulation tissue formation associated with bone sequestration in an oncologic patient with osteoradionecrosis treated with the same protocol [25]. Those findings were expected based on the biological responses to the photonic therapies, since they control the infection by decreasing the microorganism's bioburden [25,38]. Moreover, these therapies are able to speed up the

repair process of the mucosa, improve the release of growth factors and bone tissue repair, as they induce the proliferation and differentiation of fibroblasts, stem cells and leading to increase of local angiogenesis, regulating bone production and mineralization in addition to its analgesic effect due to the release of endogenous opiates [22,23,39,40-42]. All these effects of PBM and aPDT may explain the formation of the granulation tissue underneath the necrotic bone in such prominent way, by increasing blood vessels formation and proliferation of fibroblasts, which facilitated the removal of the necrotic bone and further tissue healing.

The implementation of the phototherapies in the protocols here presented lead to complete regression of the lesion, with no recurrences. In addition, the protocols based on phototherapies (PBM and aPDT) favored the surgical procedure by controlling infection, stimulating the rapid formation of granulation tissue, which promoted the detaching of the bone sequestrations allowing the identification of healthy tissue in the surgical bed and allowing a more conservative surgical procedure. In addition, these therapies can also be used to control infection in debilitated patients who are not eligible for surgery [30].

Conclusion

It is important to emphasize the need for understanding the basis of these photonic therapies to determine their appropriate applications within the biological therapeutic window, with individualized protocols, avoiding inhibitory doses. Nevertheless, considering the limitations of this study of a single clinical case, but based on the positive outcome by applying the proposed photonics protocol, one can infer that the combination of PBM and aPDT in the pre, trans and post-surgery showed to be efficient in the treatment of MRONJ lesion. It would be important to test this protocol in a larger number of patients, perhaps in a randomized clinical trial, to confirm our results, which would be relevant in the management of MRONJ lesions in the future.

Conflict of Interests

The authors declare no conflict of interest in this publication.

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