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Surgical extraction with photobiomodulation as an adjunctive modality in patients at-risk for medication-related osteonecrosis of the jaw: retrospective study

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Abstract

Aim The study aims to retrospectively assess and share the experience of the use of photobiomodulation (PBM) as an adjunctive to surgical extraction in patients at-risk for medication-related osteonecrosis of the jaw (MRONJ) due to a treatment history with bone-modifying agents.

Methods The department database and medical records were examined in the period between 2016 and 2023. The inclusion criteria were; at-risk patients for MRONJ with current or previous treatment with bone-modifying agents, with or without a history of antiangiogenic agents administration, who underwent single or multiple dental extractions, subjected to PBM preventive protocol, and without a diagnosis or history of MRONJ development. The PBM protocol consisted of four sessions, two sessions before the intervention and two sessions after the intervention. The PBM parameters (per session) were; total power of 0.6 W, time of 15 min, frequency of 30 kHz, and total energy of 577.4 J.

Results A total of 62 patients (58 females and 4 males) fulfilled the inclusion criteria with a mean age of 67.5 years. Complete healing without the development of MRONJ was shown in 50 (80.65%) patients, and the development of MRONJ was shown in 12 (19.35%) patients. The statistical analysis revealed a higher risk of MRONJ in patients with a history of administration of zoledronic acid ($p=0.029$) and in patients undergoing corticosteroid therapy ($p=0.039$). While a lower risk was observed in patients in treatment for thyroid pathology ($p=0.055$).

Conclusions The majority of the included at-risk MRONJ patients showed complete healing after surgical extraction with the use of PBM as an adjunctive modality. Corticosteroid treatment as a systemic risk factor and zoledronic acid as a drug-related risk factor show significant associations with the development of MRONJ.

Keywords Diode laser, Medication-related osteonecrosis of the jaw, Osteonecrosis, Photobiomodulation, Surgical extraction

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Background

Medication-related osteonecrosis of the jaw (MRONJ) is a complex pathology with several unclear issues regarding its pathogenesis and management. According to the joint committee of the Italian Society of Maxillofacial Surgery (SICMF) and the Italian Society of Oral Pathology and Medicine (SIPMO), the definition of MRONJ has been recently established to be "an adverse drug reaction that results in progressive destruction and necrosis of maxillary and/or mandibular bones in patients who are exposed to drugs with an established increased risk of the disease, without being subjected to a recent radiotherapy" [1]. Oncological patients and patients with osteometabolic diseases are mostly affected by MRONJ. These patients are usually exposed to antiresorptive medications (i.e. bisphosphonates or denosumab) and/or antiangiogenic medications (e.g. bevacizumab, aflibercept; inhibitors of tyrosine kinases (TKIs), mammalian target of rapamycin (mTOR) inhibitors) [2].

Dental extractions and/or invasive surgical procedures have been usually described as a main risk factor in approximately 73% of reported MRONJ cases [3]. However, recent research has reported the detection of necrotic bone during dental procedures without considering these procedures as the triggering event [4]. In addition, there is growing evidence that suggests considering the presence or absence of infection (i.e. periodontal infections and/or periimplantitis) as a triggering event rather than considering only the dental extraction [5, 6]. A recent study has demonstrated a decrease in the risk of MRONJ with the extraction of teeth with a higher susceptibility to infection [7]. It seems that bone infection is the most important risk factor rather than considering only dental extraction and surgical procedures [7, 8]. Other risk factors should be also considered such as drug-related factors, systemic, and local risk factors.

According to the recent position papers of the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the joint committee of SICMF and SIPMO, preventive dental measures are still the first line of management of MRONJ [1, 9]. Systemic and local antibiotics are widely recommended as prophylaxis with minimally traumatic surgical procedures in at-risk patients for MRONJ. This recommendation is to prevent possible bone infection after surgical intervention [2, 8–10].

However, there is no standardized protocol regarding the prophylactic antibiotic regimens (i.e. drug type, administration timing, dosage, quantity, and administration method) till now [8, 11]. This issue should be investigated and resolved in order to avoid the increased risk of developing antibiotic resistance. In addition, minimal exposure to antibiotic therapy is recommended for this kind of patients in order to avoid compromising the general health of these already fragile patients [8, 12].

Therefore, several systemic and local adjunctive modalities have been proposed in order to minimize the use of prophylactic antibiotic therapy and to promote wound healing; such as hyperbaric oxygen therapy, parathyroid hormone (PTH, teriparatide), autologous platelet concentrates, ozone therapy, and photobiomodulation (PBM) [8, 13–15].

The effectiveness of PBM as an adjunctive modality has been demonstrated in the management of several oral conditions, such as oral mucositis, oral lichen planus, temporomandibular joint disorders, and minimizing pain and edema after surgical extraction of lower third molar [16–19]. PBM is the therapeutic use of non-ionizing forms of light and/or infrared light in low powers on living cells. The exact mechanism of action is not fully understood [20]. Several studies have demonstrated that PBM can induce several physiological pathways, leading to anti-inflammatory, analgesic, and bio-modulatory effects, which lead eventually to repair damages caused by injuries or diseases [19].

PBM has also been proposed as an adjunctive/supportive to surgical management of MRONJ [21–23]. Some studies have reported the beneficial effect of PBM application as a palliative modality for some non-operable MRONJ cases [24]. Other studies have demonstrated the positive effect of PBM as an adjunct with or without other adjuncts such as autologous platelet concentrates in the surgical approach to managing MRONJ [15, 22, 25, 26]. Recently, an animal study was conducted to observe the preventive effect of PBM on the onset of MRONJ after surgical extraction, and the results were promising [27].To the best of our knowledge, few clinical studies have investigated PBM as an adjunctive to surgical extraction in at-risk patients for MRONJ. The aim of the study is to retrospectively assess and share our experience using PBM as an adjunctive to surgical extraction in at-risk patients for MRONJ due to a treatment history with bone-modifying agents (BMAs) and to demonstrate the risk profile of these patients by documenting the drug-related risk factors and commonly recommended systemic-related risk factors.

Methods

A single-centre retrospective study was conducted on patients referred to the Department of Oral and Maxillofacial Sciences, Sapienza University of Rome. The study is part of a task force project of different medical specialities called "MoMax" (Oral Medicine and Maxillofacial) project, that provides medically compromised and oncologic patients with multidisciplinary team care. This project can be considered one of the reference centres in Italy for at-risk patients or with established MRONJ.

Table 1 The inclusion and exclusion criteria of the study

Inclusion criteria	Exclusion criteria
- At-risk patients for medication-related osteonecrosis of the jaw (MRONJ) with current or previous treatment with bone modifying agents (BMAs).	- Patients with a confirmed diagnosis of MRONJ.
- Patients with or without a history of antiangiogenic agents (AAs) administration.	- At-risk patients for MRONJ with a history of radiotherapy in the head and neck region.
- Patients underwent single or multiple dental extractions.	- At-risk patients for MRONJ with current or previous treatment only of AAs.
- Patients subjected to photobiomodulation (PBM) preventive protocol.	- At-risk patients for MRONJ with age < 18 years old.
- Patients without a diagnosis or history of MRONJ development.	

All the study procedures were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All the patients signed an informed consent for participation in the research.

Data collection

The department database and medical records were examined in the period between 2016 and 2023. The inclusion criteria were; at-risk patients for MRONJ with current or previous treatment with BMAs with or without a history of antiangiogenic agents (AAs) administration, underwent single or multiple dental extractions, subjected to PBM preventive protocol, without a diagnosis or history of MRONJ development. The exclusion criteria were patients with a confirmed diagnosis of MRONJ, a history of radiotherapy in the head and neck region, with current or previous treatment only of AAs, and/or age < 18 years old (Table 1).

The collected data were age, gender, tobacco status and consumption amount, alcohol status and consumption amount, drug (BMAs and AAs) related data, systemic risk factors, other concomitant pathologies, and site and number of extractions. The included patients were categorized into two main groups; (1) "with MRONJ" and (2) "without MRONJ", in order to evaluate the effect of different considered variables on the treatment outcome. The patients were furtherly categorized into subgroups according to the other considered variables.

For the tobacco status and consumption analysis, the patients were categorized into non-smokers, ex-smokers, and smokers. The consumption amount was calculated in pack-years. The smoker and ex-smoker patients were categorized accordingly into patients with consumption amounts ≤ 20 pack-years and > 20 pack-years. For the alcohol status and consumption, the patients were categorized into drinkers and non-drinkers, and the consumption amount was measured in the number of drinks/week.

The collected data related to the BMAs administration were; agent type (bisphosphonates, denosumab, or both), number of medications, route of administration (oral, subcutaneous "SQ", intravenous "I.V.", intramuscular "I.M.", or more than one), and duration of treatment (months).

Table 2 The list of the collected data from the department database of the included patients of the study

Collected data category	List of collected data
1) General patient information	- Age
	- Gender
	- Tobacco status and consumption amount (pack-years)
	- Alcohol status and consumption amount (drinks/week)
2) Local-related risk factors	- Site of extraction
	- Number of extractions
3) Drug-related risk factors	- Agent type (bisphosphonates, denosumab, or both)
	- Total number of administered medications
	- Route of administration (oral, subcutaneous "SQ", intravenous "I.V.", intramuscular "I.M.", or more than one)
	- Duration of treatment (months)
4) Systemic-related risk factors	- Underlying pathology (oncological, osteoporosis, cancer treatment-induced bone loss (CTIBL), or osteogenesis imperfecta)
	- Chemotherapy
	- Radiotherapy
	- Corticosteroids
	- Diabetes mellitus
	- Thyroid pathology
	- Hypertension
	- Other concomitant pathologies
5) Treatment outcome	- Presence/absence of medication-related osteonecrosis of the jaw (MRONJ)

The collected systemic risk factors were; underlying pathology (oncological, osteoporosis, patients with cancer treatment-induced bone loss (CTIBL) or osteogenesis imperfecta), chemotherapy, radiotherapy, corticosteroids, diabetes mellitus, thyroid pathology, hypertension, and other concomitant pathologies (Table 2).

For the individual risk assessment and evaluation of its impact on the treatment outcome, it was considered the proposed categorization of at-risk patients for MRONJ by the SIPMO-SICMF Expert Panel [1]. The patients were categorized into; (1) patients receiving high-dose (HD) BMAs and (2) patients receiving low-dose (LD)

BMA therapy. The first group of patients receiving HD-BMAs were categorized into; (1) HD-BMAs R_+ "without history of systemic risk factors" and (2) HD-BMAs R_{++} "with history of systemic risk factors". While the second group of patients receiving LD-BMAs were categorized into; (1) LD-BMAs R_0 "with BMA therapy for less than 3 years without systemic risk factors" and (2) LD-BMAs R_x "with BMA therapy for more than 3 years and/or with a history of systemic risk factors".

Management protocol of at-risk patients for MRONJ

All Patients with current or previous treatment with BMAs and/or AAs referred to the department for performing single or multiple surgical extractions were considered at-risk patients for MRONJ and were subjected to a predetermined protocol. Comprehensive clinical and radiographic examination were performed and full medical and clinical history were collected. In patients with current treatment with BMAs and/or AAs, the prophylactic drug holiday, according to the recommendations of the SIPMO-SICMF Expert panel, was performed following the authorization by the treating physician/prescriber [1]. All the patients were subjected to systemic antibiotics (1 g amoxicillin/clavulanic acid and 250 mg metronidazole) starting three days before the surgical extraction, two times a day, and till the seventh day after the intervention. In addition, a mouthwash of 0.2% chlorhexidine gluconate was prescribed for the same period of the systemic antibiotic. All the patients were subjected to intraoral PBM application at the site of the intervention. The patients were provided with the authorization to resume the BMAs and/or AAs in case of complete wound closure at one month follow-up. All the patients were subjected to periodic recalls "every 4 months" to confirm the oral hygiene measures and the absence of any source of infection.

Table 3 Photobiomodulation (PBM) parameters in patients at-risk for medication-related osteonecrosis of the jaw (MRONJ)

Manufacturer	FISIOLINE
Model identifier	Lumix® C.P.S. ® Dental (Multidiodic laser)
Number and type of emitters	Three wavelengths, visible and infrared GaAs
Wavelength	650 nm, 810 nm, and 910 nm
Pulse mode	For visible 650 nm: continuous mode, for 810 nm: continuous modulating, and for 910 nm: 30 kHz
Spot size	0.5cm^2
Exposure duration	15 min
Application technique	Scanning in a defocused mode
Total irradiation energy per session	577.4 J
Number and frequency of treatment sessions	Total of four sessions, two sessions before the intervention (6 days before and 2 days before) and two sessions after the intervention (2 days after and 6 days after)

PBM protocol of at-risk patients for MRONJ

The intraoral PBM application was performed by a multidiodic (Lumix C.P.S. Dental, FISIOLINE, Verduno, Cuneo, Italy) emitting simultaneously 650 nm, 810 nm, and 910 nm wavelengths. The PBM protocol consisted of four sessions, two sessions before the intervention (6 days before and 2 days before) and two sessions after the intervention (2 days after and 6 days after). The site of the intervention "surgical extraction" was irradiated in scanning and non-contact mode (at ~ 1 cm distance). The PBM parameters (per session) were total power of 0.6 W, time of 15 min, frequency of 30 kHz, and total energy of 577.4 J. Multiple PBM applications, at the same session, were performed with the same parameters in case of multiple programmed extractions at a distance from each other. Table 3 shows the used laser parameters.

Statistical analysis

An Excel sheet was created for the collected data of the included patients. A power analysis was carried out using the G*Power software, version 3.1.9.7 [28]. The power analysis results indicated a minimum number of 60 patients to achieve a statistical power of 0.80 and a statistical significance of 0.05. The statistical analysis was performed by the SPSS statistical processing software (Statistical Package for Social Science, Armonk, NY, USA), release 25.0. The distributions of scores in continuous variables (including age, duration of treatment (months), and number of extracted teeth) were evaluated using the Shapiro test, in order to assess their normality. The association between each patient characteristic and the development of MRONJ was evaluated using the chi-square test, for variables calculated on a nominal or ordinal scale (Fisher's exact test), the t-test for independent samples, and the Mann-Whitney test for metric variables. The odds ratio (OR) was calculated with a 95% confidence interval (95% CI) for all the associations. The results were considered significant when the p-value was < 0.05.

Results

A total of 62 patients (58 females and 4 males) fulfilled the inclusion criteria of the study with a mean age of 67.5 years. The patients were distributed according to the primary pathology as follows: 25 (40.32%) osteoporotic patients, 18 (29.03%) oncologic patients, 18 (29.03%) patients with CTIBL, and 1 (1.61%) patient with osteogenesis imperfecta. A total of 44 (70.97%) patients received LD-BMAs and 18 (29.03%) patients received HD-BMAs. The mean duration of the treatment of the related drug was 53.60 ± 43.1 months. The

average number of performed teeth extractions was 2.3 ± 1.9 teeth, maxillary teeth in 24 (38.71%) patients, mandibular teeth in 24 (38.71%) patients and both in 14 (22.58%) patients. A complete healing without the development of MRONJ was shown in 50 (80.65%) patients, and the development of MRONJ was shown in 12 (19.35%) patients. Table 4 shows a general overview of the included patients.

Analysis of patients' risk profile

The risk profile of patients with developed MRONJ was compared with patients without MRONJ (Table 5). In the assessment of the drug-related factors, the patients with a history of administration of zoledronic acid showed a higher risk of MRONJ with statistical significance ($p = 0.029$). In addition, a higher risk was observed in patients with an I.V. route of administration with statistical significance ($p = 0.029$).

Table 4 General overview of the included at-risk patients for medication-related osteonecrosis of the jaw (MRONJ)

Characteristics				*n* (%)
Gender	Female			58 (93.55)
	Male			4 (6.45)
Age	≤ 60			16 (26.81)
	> 60			46 (74.19)
Primary pathology	Osteoporosis			25 (40.32)
	Oncological			18 (29.03)
	Osteogenesis imperfecta			1 (1.61)
	Patients with CTIBL			18 (29.03)
Individual risk assessment	LD-BMAs		LD-BMAs R_0	7 (15.91)
			LD-BMAs R_x	37 (84.09)
	HD-BMAs		HD-BMAs R_+	7 (36.84)
			HD-BMAs R_{++}	11 (57.89)
Administrated agent type	Bisphosphonates			40 (64.52
	Denosumab			18 (29.03
	Both			4 (6.45)
Route of drug administration	Oral			25 (40.32)
	S.Q.			17 (27.42)
	I.M.			2 (3.23)
	I.V.			11 (17.74)
	More than one			7 (11.29)
Duration of treatment	≥ 3 years			39 (62.90)
	< 3 years			23 (37.10)
General medical conditions	Bone metastasis			5 (8.06)
	Diabetes mellitus			7 (11.29)
	Thyroid Pathology			13 (20.97)
	Chemotherapy			14 (22.58)
	Radiotherapy			19 (30.65)
	Corticosteroids			8 (12.90)
	Other concomitant pathologies			13 (20.97)
Tobacco status	Non-smokers			46 (74.19)
	Ex-smokers			9 (14.52)
	Smokers			7 (11.29)
Tobacco consumption amount (pack years)	Ex-smokers	≤ 20 pack years		9 (14.52)
		> 20 pack years		0
	Smokers	≤ 20 pack years		4 (6.45)
		> 20 pack years		3 (4.84)
Alcohol status	Non Drinkers			62 (100)
	Drinkers			0
Extraction site	Maxilla			24 (38.71)
	Mandible			24 (38.71)
	Both			14 (22.58)

Cancer treatment-induced bone loss (CTIBL); High-dose bone-modifying agents (HD-BMAs); Intravenous (I.V.); Intramuscular (I.M.); Low-dose bone-modifying agents (LD-BMAs); Subcutaneous (SQ)

Table 5 Comparison of the risk profile between patients with developed medication-related osteonecrosis of the jaw (MRONJ) and patients without MRONJ

Characteristics		Without MRONJ	With MRONJ	p-value
Gender: n (%)				
Female		46 (92)	12 (100)	0.578
Male		4 (8)	0	
Age: mean (SD)		67.3 (11.61)	68.3 (16.7)	0.363
≤ 60: n (%)		13 (26)	3 (25)	1.000
> 60: n (%)		37 (74)	9 (75)	
Primary pathology: n (%)				0.268
Osteoporosis		23 (46)	2 (16.67)	0.101
Oncological		13 (26)	5 (41.7)	0.305
Osteogenesis imperfecta		1 (2)	0	1.000
Patients with CTIBL		13 (26)	5 (41.67)	0.305
Individual risk assessment: n (%)				0.142
LD-BMAs	LD-BMAs R_0	5 (13.51)	2 (28.57)	0.307
	LD-BMAs R_x	32 (86.49)	5 (71.43)	
HD-BMAs	HD-BMAs R_+	6 (46.15)	1 (20)	0.596
	HD-BMAs R_{++}	7 (53.85)	4 (80)	
Administrated agent type: n (%)				
Bisphosphonates		32 (64)	8 (66.67)	0.916
Denosumab		15 (30)	3 (25)	
Both		3 (6)	1 (8.33)	
Related drug: n (%)				0.102
Zoledronic acid		6 (12)	5 (41.67)	**0.029**
Alendronic acid		10 (20)	2 (16.67)	1.000
Ibandronic acid		5 (10)	1 (8.33)	1.000
Risedronic acid		5 (10)	0	0.573
Clodronic acid		3 (6)	0	1.000
Neridronic acid		1 (2)	0	1.000
Denosumab		15 (30)	2 (16.67)	0.484
More than one drug		5 (10)	2 (16.67)	0.645
Route of drug administration: n (%)				0.242
Oral		22 (44)	3 (25)	0.330
S.Q.		15 (30)	2 (16.67)	0.484
I.M.		2 (4)	0	1.000
I.V.		6 (12)	5 (41.67)	**0.029**
More than one		5 (10)	2 (16.67)	0.612
Duration of treatment (months): mean (SD)		55.3 (45.7)	46.7 (30.96)	0.796
≥ 3 years: n (%)		32 (64)	7 (58.33)	0.748
< 3 years: n (%)		18 (36)	5 (41.67)	
General medical conditions: n (%)				
Bone metastasis		4 (8)	1 (8.33)	1.000
Diabetes mellitus		4 (8)	3 (25)	0.125
Thyroid pathology		13 (26)	0	0.055
Chemotherapy		10 (20)	4 (33.33)	0.442
Radiotherapy		15 (30)	4 (33.33)	1.000
Corticosteroids		4 (8)	4 (33.33)	**0.039**
Other concomitant pathologies		11 (22)	2 (16.67)	1.000
Tobacco status: n (%)				
Non-smokers		35 (70)	11 (91.67)	0.261
Ex-smokers		8 (16)	1 (8.33)	
Smokers		7 (14)	0	
Tobacco consumption amount (pack years): n (%)				

Table 5 (continued)

Characteristics		Without MRONJ	With MRONJ	p-value
Ex-smokers	≤ 20 pack years	8 (16)	1 (8.33)	1.000
	> 20 pack years	0	0	
Smokers	≤ 20 pack years	4 (8)	0	1.000
	> 20 pack years	3 (6)	0	
Alcohol status: n (%)				
Non-drinkers		50 (100)	12 (100)	1.000
Drinkers		0	0	
Extraction site: n (%)				0.394
Maxilla		18 (36)	6 (50)	0.511
Mandible		19 (38)	5 (41.67)	1.000
Both		13 (26)	1 (8.33)	0.267
Number of extracted teeth: mean (SD)		2.32 (1.89)	2.3 (2.2)	0.977

Cancer treatment-induced bone loss (CTIBL); High-dose bone-modifying agents (HD-BMAs); Intravenous (I.V.); Intramuscular (I.M.); Low-dose bone-modifying agents (LD-BMAs); Standard deviation (SD); Subcutaneous (SQ)

In the assessment of systemic risk factors, a higher risk of MRONJ was observed in patients on corticosteroid therapy with significance ($p = 0.039$). A lower risk was observed in patients on treatment for thyroid pathology with marginal significance ($p = 0.055$).

For a better understanding of the role of each considered risk factor on the development of MRONJ, the ORs and their 95% CI were calculated. It revealed the presence of significant risk in patients in corticosteroid therapy with an OR of 5.750 (95% CI 1.1888–27.8111, $p = 0.0296$) and in patients with I.V. route of administration with an OR of 6.1111 (95% CI 1.1251–33.1939, $p = 0.036$) (Table S1).

Comparing LD-BMAs with HD-BMAs patients, it revealed that LD-BMAs patients were older with statistical significance ($p = 0.0019$). This was a predicted result, where LD-BMAs patients were mainly in treatment for osteoporosis or for CTIBL. It also revealed that most HD-BMAs patients had a history of radiotherapy ($p = 0.0018$), where 11 patients (61.11%) out of 19 patients with a history of radiotherapy were subjected to HD-BMAs. This result was quietly predicted as HD-BMAs patients are mainly oncological patients. No patient was included in the study subjected to radiotherapy on the head and neck region. In addition, it was revealed that most HD-BMAs patients were in treatment with zoledronic acid ($p = 0.0001$), in contrast, most LD-BMAs patients were in treatment with alendronic acid ($p = 0.013$).

Discussion

PBM has been introduced in recent years, alone or in combination with other methods, for the management of MRONJ. In this study, the majority of included at-risk patients showed complete healing ($n = 50$, 80.65%). This may be due to the positive impact of PBM on modulating the cell metabolism and improving the wound healing process. In the literature, there are large differences in the incidence of MRONJ after tooth extraction. These may be attributed to the complex nature of MRONJ and the presence of many risk factors. In a recent systematic review evaluating the incidence of MRONJ following tooth extraction, it was observed the presence of a significant heterogeneity of data in the literature. It was revealed that the incidence of MRONJ after tooth extractions ranged between 11.4% and 50% in cancer patients who were subjected to high doses of BMAs. On the other hand, it was observed that the incidence of MRONJ without tooth extraction ranged between 3.4% and 9.3% [29]. In a study by Yamazaki et al., the risk ratio of high-dose intravenous medications when compared with low-dose oral administrations was 14.6 (95% CI 1.7–125.8) [30].

The PBM exact mechanism of action is still not completely understood. Several mechanisms have been proposed to explain the biostimulant effect of PBM on soft and hard tissues [31]. The biostimulant effect can be explained through its capability to enhance the vitality and motility of irradiated cells. The irradiated photons activate the cytochrome c-oxidase (COX), an essential element of the electron transport chain (ETC), in the inner mitochondrial membrane of the irradiated cells. The activation of COX enhances the production of cellular energy and stores it in the high-energy bond of adenosine triphosphate (ATP). In addition, the irradiated photons prompt the increase in the release of reactive oxygen species (ROS) and the release of nitric oxide (NO). The release of these molecules prompts the activation of several nuclear genes, through the mechanism of the "second messenger" (e.g., nuclear factor-kappa B (NF-kB)), which eventually leads to enhancement in the production of growth factors. Moreover, the extracellular release of NO after irradiation may improve the microcirculation due to being a potent vasodilator [32–34]. These enhanced cellular processes may play a role in the repair of tissues suffering from poor cellular proliferation because of the privilege of an acidic medium after injury [19].

Another mechanism is proposed regarding the biostimulant effect of PBM on bone tissues. It has been found that laser irradiation expands the organic matrix of bone, and this consequently leads to an increase in the differentiated osteoblastic cells and an improvement of bone formation activity [35–37].

Some studies have reported the analgesic effect of PBM and referred that to its ability to modify the central uptake and release of serotonin and acetylcholine, stimulate the production of endorphins, and inhibit the release of bradykinin [38]. Also, it has been reported that the appropriate dose of PBM may affect the vessels' permeability and lead to better control of the influx of proinflammatory cytokines [39]. This may be also another explanation for the less acute inflammatory condition on the irradiated tissues after injury [19].

PBM can be applied in three different modalities for the management of MRONJ; for preventive purposes, antalgic "palliative", or as an adjunct to conventional surgical treatments with or without hemoderivatives. Several systematic reviews have been conducted to evaluate the efficacy of lasers in the management of MRONJ. Most of them have observed the efficacy and superior results of PBM combined with other conventional surgical/medical therapies. However, they have noticed the lack of high-quality randomised controlled trials and they have recommended performing further studies with detailed protocol parameters and patient characteristics. Among the included studies in these systematic reviews, few studies have been found evaluating the application of PBM for preventive purposes in at-risk patients for MRONJ [21, 22, 40, 41]. An animal study conducted on Wistar rats received intraperitoneal injections of zoledronic acid for 4 weeks, the preventive effect of PBM and ozone application was evaluated after tooth extraction. PBM and ozone groups showed a statistically significant difference in bone formation when compared with the control group and no difference was observed between ozone and PBM groups [27].

In a recent systematic review, two clinical studies have been included that have used PBM for preventive purposes as an adjunctive modality with surgical extraction in at-risk patients for MRONJ [22, 42, 43]. One study has used PBM in combination with photodynamic therapy (PDT) in at-risk patients undergoing dental extraction. The laser preventive protocol in this study consisted of (1) PDT in the sockets immediately after extraction and weekly till complete resolution in case of incomplete healing. (2) two PBM applications; the first application was immediately after extraction with the following parameters per point; 660 nm, power of 100mW, time of 90s, and energy of 9 J. The second application was performed weekly in case of the presence of pain or edema in combination with PDT socket application till the complete resolution; with the following parameters per point; 808 nm, power of 100mW, time of 30s, energy of 3 J. The authors reported that nine out of 18 included patients (50%) were subjected to PBM postoperatively due to the presence of clinical inflammatory signs and there was the need to apply more than two sessions in two patients [42].

The other study used PBM in combination with autologous platelet concentrates. The PBM was applied on the socket postoperatively. Seven sessions have been performed using Nd: YAG laser (1064 nm) with the following parameters; power of 1.25 W, frequency of 15 Hz, and time of 1 min repeated 5 times in each session. The authors reported complete healing in all the included patients ($n = 44$) [43]. The relatively better results of these studies when compared to our study may be attributed to the use of another adjunct (PDT or autologous platelet concentrates) and/or the difference in the characteristics of the included patients.

There are two challenging issues for evaluating and conducting a study on PBM as an adjunctive modality for the reduction of the risk of MRONJ. The first issue is related to defining an effective dose of PBM. Many laser parameters should be considered and precisely adjusted as inadequate doses may affect the results. This may consequently lead to difficulty in conducting studies and establishing a standard protocol for PBM in general applications and in particular for the management of MRONJ. Due to the abovementioned issue, there is a growing stream in the literature to encourage reporting PBM applications with a detailed standardized description of the protocol. This would be helpful for future studies and meta-analyses for achieving a standardized protocol for each PBM application [44].

The second challenging issue is that MRONJ is a complex medical condition and is considered a multifactorial condition [1, 2, 5]. The SIPMO-SICMF Expert Panel has recently suggested to categorize the at-risk patients and patients with established MRONJ according to the dose of BMAs. Moreover, it has been also suggested to subdivide them based on the presence or absence of several risk factors. It is believed that categorization and understanding the risk profile of the patients would be one of the ways to achieve an adequate strategy for risk reduction where the decision-making for the risk reduction and the management of MRONJ can be mostly changed by a better understanding of the profile of the patients [1, 45].

Several systematic reviews, studying the incidence of MRONJ and evaluating the efficacy of treatment protocols in general and in particular laser-assisted treatment protocols, have observed a lack of detailed description of the profile of the included patients [22, 31, 40, 41, 46]. This observation may lead to false negative or false

positive results of the analysis of different proposed protocols for the management of MRONJ.

In this study, an analysis of the risk profile of the included patients has been conducted, where it is believed that a detailed description of the risk profile of the at-risk patients or with established MRONJ would be helpful for future related studies and meta-analysis. The analysis revealed the presence of a possible higher risk in patients treated with zoledronic acid and patients treated with corticosteroids. These results follow the literature, where they have been already considered among the reported risk factors of MRONJ [47, 48]. In a study by Hata et al., the 8-year cumulative incidence of MRONJ in patients with zoledronic acid was 32.1%, while the 3-year cumulative incidence was 9.1% [47]. In another study, the 3-cumulative incidence was 29.2% [49]. In our study, seven of the included patients had been subjected to the zoledronic acid for more than 3 years and 4 of them showed MRONJ development after surgical extraction.

Some limitations should be acknowledged for better interpretation of the results; (1) This study is a single-center study, and a multicentric study with a larger sample size would lead to more concrete results. (2) The absence of a control group and the retrospective nature of the study hindered the ability to evaluate completely the effectiveness of this PBM protocol in preventing MRONJ. (3) The study was based on department medical records, some essential data in particular the accumulated dose were not available. The type, administration duration (starting and ending date), route of administration, and reason of administration were the only available data. (4) In addition, some local risk factors were not evaluated due to its retrospective nature, such as dental/periodontal condition of the extracted teeth, status of removable denture (if present), and presence or absence of peri-implantitis and anatomical condition (e.g. torus, exostosis, pronounced mylohyoid ridge). Analysing these local risk factors may lead to a better understanding of the risk profile of the patients and may explain the ineffectiveness of PBM in some cases.

In addition to considering the limitations of this study, some suggestions can be considered for future studies for better evaluation of PBM and even other treatment strategies in at-risk patients for MRONJ; they may include; determining more restricted and specific inclusion criteria of the at-risk patients, reporting the detailed parameters of PBM protocol as it has been recommended in the literature, considering detailed analysis of the outcomes at the clinical and/or radiographic level, and considering the risk profile of patients as it has been recently recommended in literature of MRONJ patients and reporting all the data that would be helpful for future analysis for evaluating the PBM, different treatments, and above all better understanding of the disease.

Conclusion

The majority of the included at-risk MRONJ patients showed complete healing after surgical extraction with the use of PBM as an adjunctive modality. Corticosteroid treatment as a systemic risk factor and zoledronic acid as a drug-related risk factor have been significantly associated with the development of MRONJ. There is a need for further studies that investigate the effectiveness of PBM in the risk reduction of MRONJ with a detailed description of the risk profile of MRONJ patients.

Abbreviations

PBM	Photobiomodulation
MRONJ	Medication-related osteonecrosis of the jaw
SICMF	Italian Society of Maxillofacial Surgery
SIPMO	Italian Society of Oral Pathology and Medicine
TKIs	Inhibitors of tyrosine kinases
mTOR	mammalian target of rapamycin
AAOMS	American Association of Oral and Maxillofacial Surgeons
PTH	Parathyroid hormone
BMAs	Bone-modifying agents
AAs	Antiangiogenic agents
ORN	Osteoradionecrosis
SQ	Subcutaneous
I.V.	Intravenous
I.M.	Intramuscular
CTIBL	Cancer treatment-induced bone loss
HD BMA	High-dose bone-modifying agent
LD BMA	Low-dose bone-modifying agent
HD-BMAs R_+	Patients subjected to HD BMA and without history of systemic risk factors
HD-BMAs R_{++}	Patients subjected to HD BMA with history of systemic risk factors
LD-BMAs R_0	Patients subjected to LD-BMAs for less than 3 years without systemic risk factors
LD-BMAs R_x	Patients subjected to LD-BMAs for more than 3 years and/or with history of systemic risk factors
OR	Odd ratio
95% CI	95% confidence interval
COX	Cytochrome c-oxidase
ETC	Electron transport chain
ATP	Adenosine triphosphate
ROS	Reactive oxygen species
NO	Nitric oxide
NF-kB	Nuclear factor-kappa B
PDT	Photodynamic therapy

Supplementary Information

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Supplementary Material 1

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Author contributions

Conceptualization, G.T., A.M., A.D.V., G.P., and U.R.; Methodology, G.T., A. M., A.D.V., G.P., F. R., F.G., and U.R.; Software, A. M., L.B., G.V., F. R., and F.G.; Validation, G.T., A.D.V., G.P., and U.R.; formal analysis, A.M, L.B. and G.V.; Investigation, A.M., L.B., G.V.; Resources, G.T., A.D.V., G.P., and U.R.; Data curation, A.M., L.B., and G.V.; Writing—original draft preparation, G.T. and A.M.; Writing—review and editing, G.T., A.M., A.D.V., G.P., F.R., L.B., G.V., F.G., and U.R.; Supervision, G.T. and U.R; Project administration, G.T., A.D.V., G.P., and U.R. All authors have read and agreed to the published version of the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the authors on reasonable request.

Declarations

Ethics approval and consent to participate
All the study procedures were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards with the approval of the Local Ethical Committee of Sapienza University of Rome (Prot. n. 775/17, Ref. EC: 4687). All the patients signed an informed consent for participation in the research.

Consent for publication
Not applicable.

Competing interests
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