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Efficiency of Adjuvant Therapies in the Management of Medication-Related Osteonecrosis of the Jaws: A Case Series and a Literature Review

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Abstract **Original Research Article**

Introduction: Medication-related osteonecrosis of the jaw (MRONJ) is a challenging condition with no established gold standard treatment. This article presents a case series that explores a minimally invasive surgical protocol combined with various adjuvant treatments to manage MRONJ in oncologic patients. ***Patient and Methods*:** Seven patients diagnosed with MRONJ, with mandibular involvement at stages 2 and 3 were included in the case series. The treatment protocol consisted of pre-operative steps, including oral cavity sanitation, hygiene motivation, and pre-operative medical treatment. Using operative techniques, the surgical protocol involved fluorescence-guided bone debridement, curettage, and bone smoothing. Adjuvant treatments such as platelet-rich fibrin, buccal fat pad grafts, Pentoxifylline and tocopherol combination, and low-level laser therapy were used. Follow-up assessments were conducted at regular intervals, and the outcomes were evaluated. ***Result:*** Improved cicatrization and symptom relief in most cases, with complete healing achieved in all patients. ***Conclusion***: The study highlights the outcome of the use of adjuvant therapies in the management of MRONJ, however, further research is needed in order to acknowledge the potential of adjuvant therapies for MRONJ treatment and establish a standardized protocol.

Keywords: Bisphosphonates, Minimally Invasive Surgical Procedure, Pentoxifylline, Tocopherol, Platelet-rich fibrin, osteonecrosis of the jaws, Angiogenesis Inhibitors.

1. INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a rare condition caused by antiresorptive medications such as bisphosphonates, denosumab, or antiangiogenic treatments [1].

Whilst different treatments (therapeutic or palliative) have been described for MRONJ management, it is still a matter of controversy in the oral and maxillofacial communities that a gold standard treatment has not yet been defined.

A wide variety of MRONG treatment strategies have been proposed, ranging from nonsurgical medical treatments such as antimicrobial mouth rinses, systemic antibiotics, hyperbaric oxygen therapy, pentoxifylline, and teriparatide to surgical interventions such as curettage, sequestrectomy, bone debridement, and surgical resection [2, 3].

According to some studies, both medical conservative and surgical approaches might be optimized by adding unconventional adjuvant therapies to improve the healing process [3].

Therefore, this case series aims to expose the MRONJ minimally invasive surgical protocol associated with the use of various adjuvant treatments and evaluate its outcome with oncologic patients.

2. PATIENTS AND METHODS

2.1. Study design

An interventional case series was conducted at Farhat Hached Sousse university hospital's Oral Medicine Oral Surgery unit between 2017 and 2020.

2.2. Inclusion criteria

- Oncologic patients who were treated with intravenous injectable Bisphosphonates and diagnosed with MRONJ.

- Mandibular localization with stages 2, and 3 of MRONJ according to AAOMS staging [3].
- No history of radio-therapy of the jaws or obvious metastatic disease of the jaws.

2.3. Non-inclusion criteria

Contraindication of surgical treatment for patients who were in the final stage of the disease due to comorbidities.

2.4. Treatment protocol

2.4.1. Pre-operative steps

- Oral cavity sanitation.
- Hygiene motivation: learning good teeth brushing methods and prescription of local antiseptics based on chlorhexidine 0.2%.
- Pre-operatory medical treatment consisted of:
  - Antibiotic association of amoxicillin (2g /day) with metronidazole (1.5g/day) was prescribed 10 days before surgery. In case of penicillin allergy, macrolides (Pristinamycine: Pyostacine, 1g /day) were administrated.
  - Curative vitamin D supplementation: 1 ampoule of 200,000 IU / month for 3 months in case of vitamin D deficiency.
  - Pre-operative administration of tetracycline at a rate of 200 mg/day (DOXYCYCLINE®) for 10 days as part of the indication of fluorescence-guided bone debridement.
  - Pentoxifylline 800 mg /day and Tocopherol (Vit E) 400 mg/day for 3 months.

Pentoxifylline was not prescribed to patients treated with platelet aggregation inhibitors or anticoagulants for other cardiovascular diseases and was stopped 2 days before surgery to avoid the risk of intraoperative bleeding.

2.4.2. Surgical protocol

After informed consent and medical evaluation, patients were operated under local anesthesia.

Our surgical protocol was based on fluorescence-guided necrotic bone removal (Figure 1), it was carried out using a certified fluorescence lamp using tetracycline (DOXYCYCLINE®), and the necrotic bone resection was performed using conventional rotating instruments or piezoelectric bone surgery.

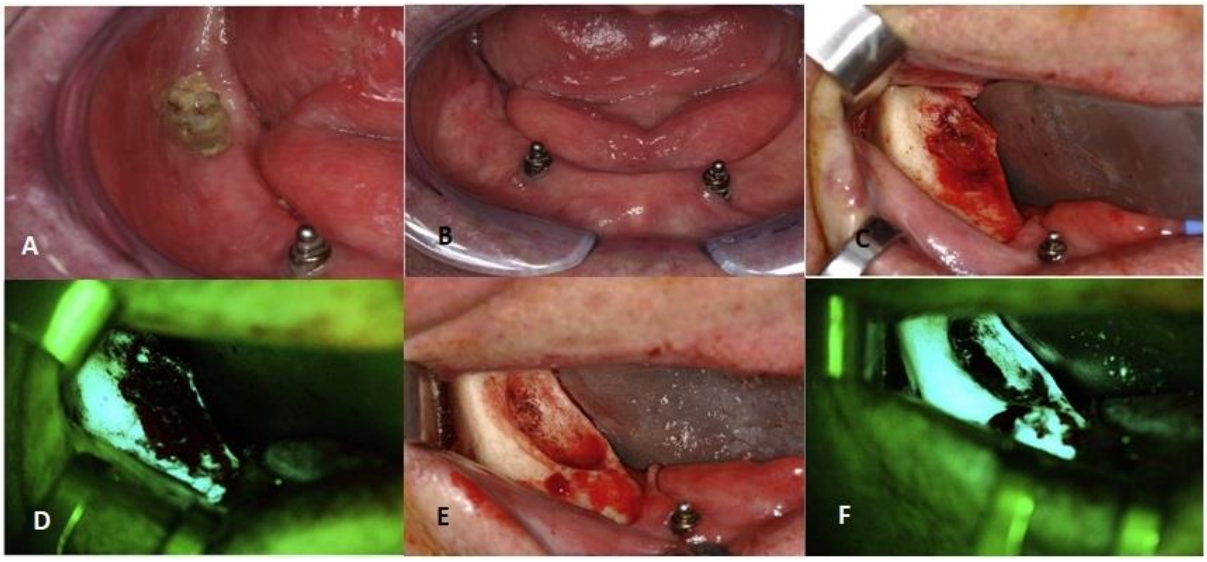

Figure 1: Fluorescence guided bone curettage of stage 2 MRONJ in a 74-year-old male patient with prostate cancer antecedents and intravenous zoledronate treatment over 2 years

The illustration depicts the exposed necrotic bone and putrid exudation of the right mandible (regio 47/48) (A) and one year after fluorescence-guided surgery (B). During surgery, there was necrotic bone with diminished fluorescence in the lingual aspect of the mandible (C and D). After the complete removal of the necrotic bone parts and smoothening of sharp bony edges, the fluorescence was homogenously green (E and F).

Surgical treatment:

1. Disinfection of the site and anesthesia.
2. Reflection of a full-thickness mucoperiosteal flap.
3. Bone debridement (piezoelectric surgery/conventional methods).
4. Sharp bony edges smoothening.
5. Setting up the adjunctive treatment to optimize healing results
   - PRF (Figure 2)
   - Buccal Fat Pad (Figure 3)
6. Wound closure using one or double-layer wound closure (tension-free flap required).

7. Bio-stimulation with Low-level laser therapy (LLLT) (A diode laser was used with a wavelength of 809 nm)

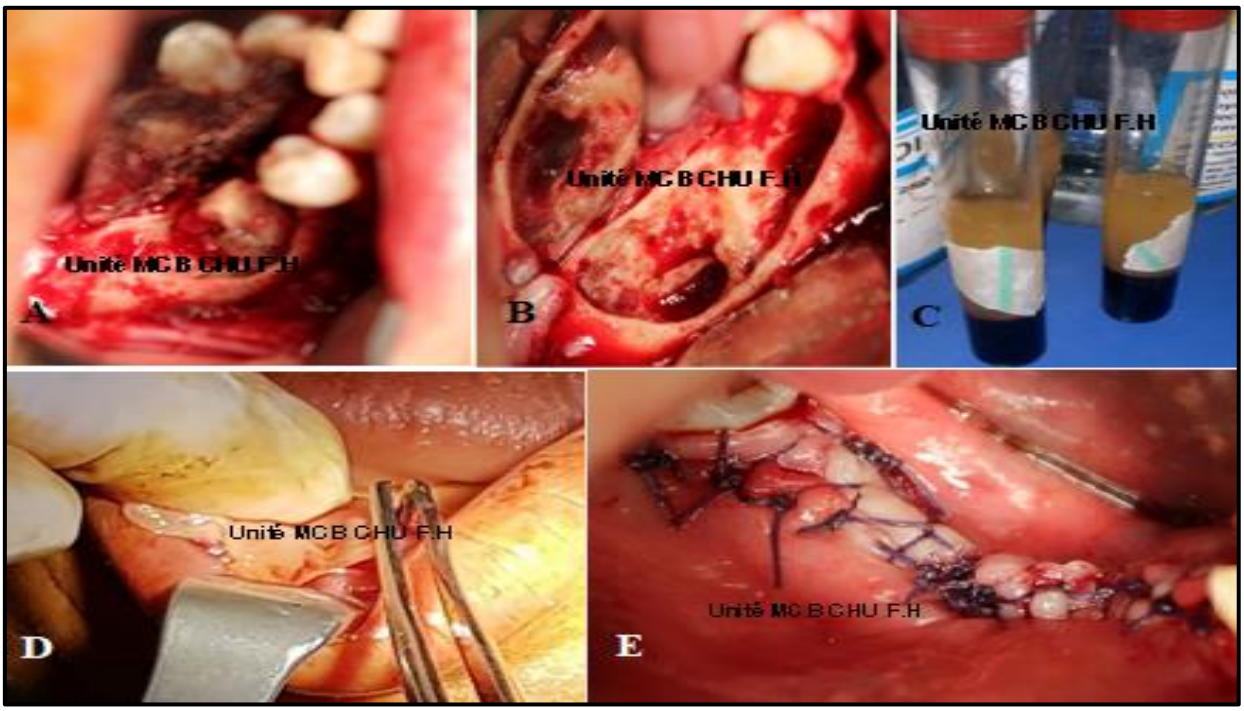

Figure 2: Surgical management with PRF as adjuvant treatment for a 56-years-old female patient (O.H)

Surgical steps: (A) Intraoperative view of the bone sequestration; (B) Intraoperative clinical view after removal of necrotic bone; (C) Preparation of autologous PRF to optimize mucosal and bone healing; (D) PRF placement; (E) Postoperative intra-oral clinical view after mucosal double-layer wound suture.

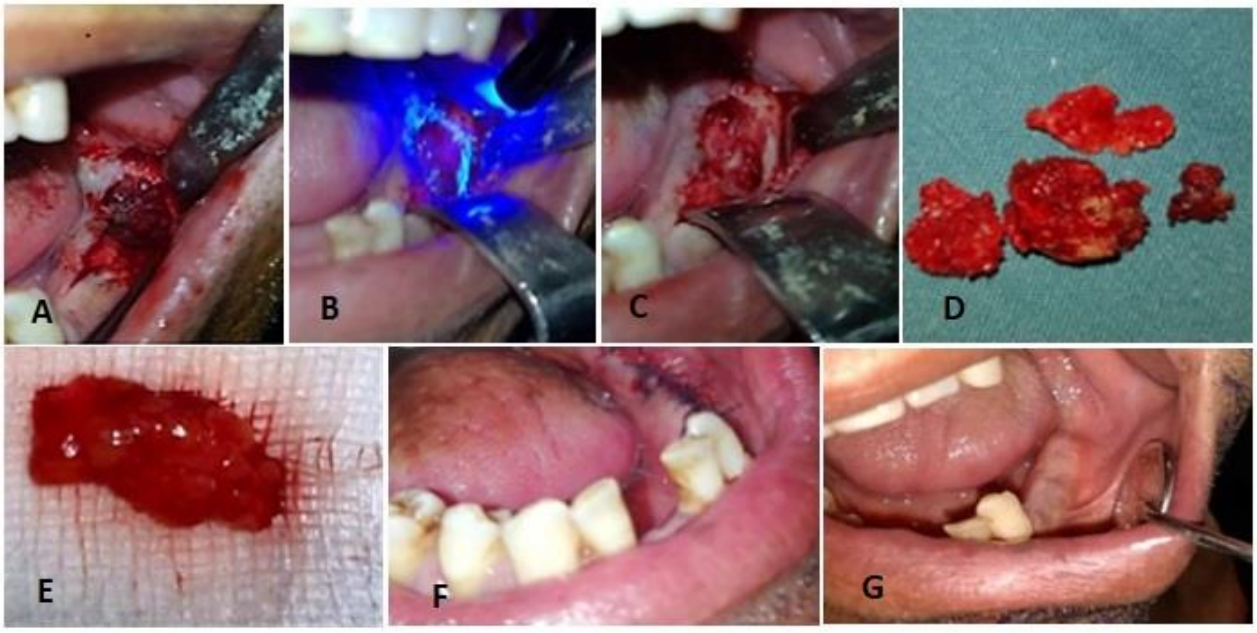

Figure 3: Surgical management with BFP as adjuvant treatment for a 44-years-old male patient

Surgical steps: (A) Granulation tissue under the bony fragment (B) Tetracycline fluorescence guided surgery to distinguish necrotic and viable bone (C) Removal of the sequestrum and necrotic bone (D) Curettage of the infected site (E) Harvesting of the free fat pad graft (F) Tension-free flap fixation (G) Complete wound healing without bone exposure 2 weeks post-operatory.

2.4.3. Post-operatory follow-up

- Continue the antibiotics use: Metronidazole 1.5g / d for 10 days and amoxicillin 2g / d until mucosal healing. Maintenance of local antiseptic care until complete mucosal healing
- Resumption of medical treatment based on Pentoxifylline 800 mg /day and Vitamin E 400 mg /day for three months.
- The patient was checked up after 10 days, 1, 3, 6, and 12 months.

The first appointment was after 10 days of the surgery to remove sutures then a clinical follow-up at 1, 3, 6, and 12 months.

Radiological control is performed at 6 months at least to assess ossification, osteolysis, or sequestration.

3. RESULTS

Table 1 shows the characteristics of included patients. Four men and three women diagnosed with MRONJ were included, with a mean age of 58.5 years (range 44 to 66).

Table 1: Descriptive characteristics of the included patients

Age (years)	**58, 5**
Sex	
Male	4
Female	3
Smokers	0
Cancer	
Multiple Myeloma	3
Breast cancer	3
Prostate cancer	1
The mean number of IV BPs injections	18 ± 1
Comorbidities	
Diabetes	1
Hypertension	3
Chemotherapy	6
Corticosteroids	4
Cardiovascular Disease	1

Table 2 resumes the stages and sites of the MRONJ as well as the inducing factors, and the clinical and radiological findings.

- The majority of patients were in stage II (6/9)
- The most reported inducing factor was teeth extraction (7/9)
- The clinical findings included painful bone exposure and purulent discharge; the most reported radiological findings were; Osteolysis with or without osteocondensation, Bone sequestration, and bone sclerosis.

Table 2: MRONJ characteristics

MRONJ CHARACTERISTICS		**NUMBER OF CASES**
Stage	**II**	**6**
	III	**1**
Inducing factors	**Teeth extractions**	**5**
	Periodontal disease	**1**
	Spontaneous	**1**
Clinical signs	**Bone exposure**	**2**
	Purulent discharge	**4**
	Bone exposure + purulent discharge	**1**
Radiological findings	**Osteolysis**	**2**
	Osteolysis + osteocondensation	**5**
	Unhealed socket	**4**
	Bone sequestration	**5**
	Bone sclerosis	**1**

Table 3 exposes the interventional data of the treated MRONJ sites with the used protocol.

A total of 11 surgical acts were performed, associated with Fluorescence guided bone debridement divided to:

- Seven cases with double-layer wound closure

- Four cases with one-layer wound closure

Different adjuvant treatments associated with the surgery were used either alone or combined.

Depending on the used surgical methods, the early outcomes assessed were;

Improvement in five cases with partial healing, reduction of the previously exposed bone, and symptoms (mainly pain).

Improvement then healing in two cases with the persistence of a slight bone exposure that disappeared afterward.

The Delayed outcomes show complete healing in all the cases accompanied by slight hypoesthesia in just one case and a relapse in four cases after a mean period of 12.5 months presented as purulent bone fistula or bone exposure.

The mean follow-up time after treatment was one year. All patients show complete healing as the final result of the treatment where 6 patients were still alive and only 1 had died due to the underlying oncologic disease.

Table 3: The treatment approaches of the MRONJ patients.

Cases	Stage	Surgical protocol	Wound closer		Adjuvant treatments					
		F.G.B.D	1 layer	2 layers	PRF	Piezo	PENTOCLO	BFP	VIT D	LLLT
1	II	■		■	■	■				
2	II	■		■		■		■		
3	II	■		■	■		■			
4	II	■	■		■	■				
		■		■	■	■				
5	II	■		■		■		■	■	
6	III	■		■	■	■	■	■	■	
7	II	■	■		■					
		■	■		■		■		■	
		■	■		■	■	■			
		■		■			■	■		■

Abbreviations: F.G.B.D: fluorescence guided bone debridement; PRF: platelet rich fibrin; piezo: piezoelectric surgery; PENTOCLO: Potentiation by Clodronate; BFP: Buccal Fat Pad; VIT D: vitamin D; LLLT: low level laser therapy

4. DISCUSSION

4.1. Background

MRONJ management continues to be a subject of debate and controversy. Various treatment protocols have been put forward; however, a consensus has yet to be reached regarding the most effective approach [4, 5].

Previously, surgical treatment was restricted only to stage 3 MRONJ according to the previous AAOMS position paper (2009) [18], for stage 1 and stage 2 the treatment was limited to medical therapy such as antibiotics, oral antibacterial mouth rinse, and pain killers.

However, in the 2014 AAOMS position paper [6, 7], edited by Ruggiero *et al*., (2015) surgery can be performed at every MRONJ stage, ranging from conservative curettage to major resection/reconstruction of the necrotic portion. Moreover, the different ways in which the disease manifests may influence the decision as to whether to perform surgery. Therefore, if the patient's underlying condition allows a surgical intervention, conservative surgical removal of lesions is frequently advocated as the elective technique for all stages [8, 9].

In our case series, conservative surgical treatment was employed for all stages of MRONJ. Patients underwent fluorescence-guided bone debridement, curettage, and bone smoothing procedures using operative manual and instrumental techniques.

To achieve an enhanced surgical outcome, several key factors must be considered, including administering pre and postoperative antibiotics, thoroughly removing necrotic bone, meticulous wound closure, and using adjuvant therapies.

Complete mucosal wound closure aims to ensure that delayed and compromised jaw bone healing can occur without interruption. Mucoperiosteal flaps closed with numerous stitches seem to be safe and reliable. However, it is recommended to perform double-layered wound closure whenever possible and this was presented in most of our surgical interventions [10].

4.2. Significance of Adjunctive Treatments

While adjuvant therapies have shown promise in aiding the recovery of patients with MRONJ [3, 11] their specific impact on alleviating the condition remains unverified, and a standardized protocol has yet to be established. These additional measures encompass a range of options, including the use of Pentoxifylline in conjunction with tocopherol, advanced techniques like

piezosurgery, the application of photobiomodulation, platelet concentrates, and the consideration of buccal fat pad grafts. These therapies can be administered concurrently with or after surgical treatment, and in certain cases, they can even be employed independently.

4.2.1. Piezosurgery

Piezosurgery minimizes soft tissue trauma, preserves the inferior alveolar nerve, and removes necrotic bone, potentially avoiding invasive bone resection with rotary instruments 12. Ultrasonication, unlike conventional surgery, achieves local decontamination by destroying suspended microorganisms through intense cavitation during ultrasonic motion [13].

4.2.2. PENTOCLO protocol

Pentoxifylline, a methylxanthine derivative, is used to manage peripheral vascular diseases. It reduces blood viscosity, improves red blood cell flexibility, dilates blood vessels, and enhances erythrocyte distensibility [14]. Additionally, pentoxifylline possesses anti-inflammatory and antioxidant effects by reducing neutrophil activation and decreasing plasma levels of tumor necrosis factor-a, interleukin-1 (IL-1), and IL-6 [15]. Tocopherol is a powerful antioxidant that scavenges oxygen radicals, protecting cell membranes, reducing inflammation, inhibiting procollagen gene expression, and mitigating damage from free radicals and necrosis [16]. When combined with pentoxifylline, tocopherol is believed to enhance wound healing and minimize scar formation [17]. Previous use of this combination has shown promising results in managing osteoradionecrosis, leading to significant improvement in symptoms [18].

In the conducted case series, five patients were treated with pentoxifylline/tocopherol associated with surgical interventions, either alone or combined with other adjuvant treatments.

4.2.3. PRF

PRF is a promising adjuvant to the management of MRONJ. The sustained presence of the PRF clot preserves a fibrin matrix that releases growth factors, promoting tissue healing and stimulating angiogenesis. This helps control the progression of MRONJ [19, 20]. A prospective study conducted by Kim *et al*., in 2014 demonstrated promising results in treating MRONJ with Leukocyte-PRF. Among the patients who underwent surgical resection, 77% showed complete resolution, 18% experienced delayed resolution, and 6% showed no resolution [21]. PRF is easy to prepare, cost-effective, and carries no patient risk, based on experiential evidence. However, further research is needed to establish its efficacy in tissue healing definitively.

4.2.4. BFP

The BFP was once considered a structure with no defined function. However, in the past three decades, it has proven valuable in oral and maxillofacial surgery [22]. The pedicled BFP offers benefits like double-layer protection, abundant adipose-derived stem cells, and high vascularization, which have been widely used in bone engineering due to their ability to differentiate into various cell types [23, 24]. Remarkably, the free BFP can heal effectively even without a blood supply, progressing through the healing process without causing tissue necrosis [25]. The healing process BFP commonly involves fibrosis with rapid and complete epithelialization of the graft within two weeks' post-surgery, while free BFP takes around four months to heal [25, 26]. The BFP thus allows compensating for tissue loss caused by bone exposure and provides an opportunity to cover the site without leaving the bone exposed, ensuring proper mucosal and osseous healing. Successful treatment of Stage 3 MRONJ cases has been reported using BFP and mucoperiosteal flaps [27, 28]. Following these studies, our patients achieved complete healing in four sites using a free BFP graft and mucoperiosteal flap.

4.2.5. LLLT

LLLT is an increasingly utilized and innovative medical approach with potent antimicrobial and bio-stimulating effects on oral tissues. Research extensively documents the effects of different laser wavelengths on bone, skin, and mucosal metabolism. LLLT stimulates cell proliferation, promotes lymphatic and blood vessel formation, improves bone mineralization, and facilitates bone and soft tissue healing [29-31]. In recent years, LLLT has been employed as adjuvant therapy for treating medication-related osteonecrosis of the jaw (MRONJ), demonstrating positive results in analgesia, reduction of edema formation, cell bio-modulation, and acceleration of the wound healing process [30].

LLLT was used only once in this study with a patient who relapsed 3 times in 4 years and needed every time a surgical re-intervention with different adjuvant treatments. Therefore, in the last surgical intervention, LLLT was used in combination with a PBFP, and complete wound healing was achieved till the last check-up. The patient showed improvement in the clinical symptoms as an early outcome and complete healing after one year of the surgical act.

5. CONCLUSION

In the absence of a standardized protocol for treating MRONJ, diverse adjuvant therapies have been investigated in combination with surgery to improve treatment outcomes. These adjuvant therapies are cost-effective, safe, well-tolerated, and reproducible, administered over varying durations from weeks to months, depending on the specific treatment. Although a standardized strategy for each adjuvant therapy is yet to be established, their effectiveness in MRONJ patients has been observed. Further interventional and prospective studies of adjuvant therapies' effect on

MRONJ is necessary to advance the development of a standardized treatment protocol.

6. Highlights

- Customized treatment approaches are crucial when dealing with Medication-Related Osteonecrosis of the Jaw (MRONJ).
- Adjuvant therapies like pentoxifylline, platelet-rich fibrin, and low-level laser therapy show promise in improving patient outcomes.
- With the absence of standardized MRONJ management protocols, this study emphasizes the need for ongoing research to establish evidence-based guidelines.

Authors' Contributions

TM study design, draft, and manuscript editing
GB patient management, study design, draft, and manuscript editing
Both first and second author have the same contribution to this article's redaction

All authors read and approved the final manuscript.

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