

Medication-Related Osteonecrosis of the Jaw (MRONJ) Treatment: An Update

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Abstract

The current management of medication-related osteonecrosis of the jaw (MRONJ) is still a controversial topic. Non-surgical modalities based on antibiotics, mouth-rinses and superficial debridement in early stages have shown partial improvement; however, complete resolution has rarely been achieved. Surgical management such as superficial and deep sequestrectomies and radical resections of MRONJ advanced lesions and recently, combined therapies, have been used. The purpose of this literature review was to show different modalities currently being used for its management, including original articles, case series, case reports and Randomized Clinical Trials (RCT), published in the English language in the last five years. Surgical management for advanced lesions continues to be the gold standard but combined therapy showed an increase in the clinical success rates and it will become a new approach to the treatment protocol for patients suffering initial (I and II) or advanced stages of MRONJ.

Keywords: *Bisphosphonates-Associated Osteonecrosis of the Jaw; Surgical Treatment; Non-Surgical Treatment; Osteonecrosis; Alendronate; Pamidronate; Denosumab; Zoledronic Acid*

Introduction

Medication-related osteonecrosis of the Jaw (MRONJ) is a pathological condition presenting exposed bone, intra or extra oral fistulae as consequence of use of antiresorptive or antiangiogenic drugs. It is important to exclude radiotherapy in the region of the necrotic bone [1].

Furthermore, it is considered inability of the alveolar bone to respond to injury and therefore its incapacity to heal after surgical procedures, i.e. tooth extraction. The surrounding microbiota causes local infection and exposure of bone for at least 8 weeks after first clinical detection [2].

Management of MRONJ lesions

The treatment of MRONJ may vary according to the clinical presentation, stages and symptoms. Thus, it ranges from non-surgical management with antibiotic therapy, oral bactericidal mouthwashes, to surgical procedure and/or debridement of wide, extensive lesions [3].

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), with reference to the stage of progression of this pathological condition, it has been classified into four stages and its management would be established according to its stage [1].

Stage 0: No bone exposure. Conservative management is indicated, in addition to the use of the Low-level laser therapy (LLLT) that stimulates the bone repair process by raising the rate of osteoblastic proliferation, in addition to stimulating lymphatic and blood (capillary) vessel growth. Assessing the evolution of the condition is necessary to prevent its aggravation.

Stage 1: Presence of bone exposure or fistula, without clinical infection. Antiseptic washing and topping with adhesive paste should be performed, 3 times daily. If clinical regression does not occur after 8 weeks, surgical debridement will be indicated.

Stage 2: There is bone exposure with pain and signs of infection. After 2 weeks of drug therapy to reduce the inflammatory process,

surgical debridement is indicated and should be performed as conservatively as possible, but to the maximum extent necessary for a complete removal of the affected bone. Antibiotics, anti-inflammatory medications are administered.

Stage 3: Presence of osteolysis extending beyond the alveolar bone region (i.e. lower border of the mandible, maxillary sinus and zygoma in the maxilla) may present pathological fracture or extra-oral fistulas. Marginal or segmental osteotomies are recommended for severe cases. The surgical method is indicated only if it can improve the patient's quality of life. If the patient rejects the surgical procedure, a conservative approach could be adopted to control the symptoms and prevent the progression of osteonecrosis.

An European Position Paper regarding management of MRONJ lesions (Workshop of European task force on medication-related osteonecrosis of the jaw-Current challenges) suggested that therapeutic modalities should be divided into two groups: non-surgical and surgical treatment due to the inconsistency of terms established in the literature, such as "conservative treatment" that might include a number of different interventions ranging from topical antimicrobial mouthwashes to removal of superficial loose sequestra [4].

Surgical and non-surgical management

Surgical treatment could achieve high success rates when correctly indicated, according to a recent study conducted by a Brazilian oncological center, in which complete clinical recovery was observed in the majority of patients (40 of 46 MRONJ lesions included in the study, corresponding to 87% of the sample), [5]. As a conclusion of this study, surgical management will be the first choice to increase clinical success, defined as complete resolution with mucosal recovery and healing with wound closure. Moreover, an extensive surgical approach should be considered as an option for patients who are in a good clinical condition (Figure 1A-1J).

For MRONJ treatment, establishing an accurate treatment protocol has become a challenge to the supportive care professionals who treat this condition. Conservative debridement consists of removal of the superficial necrotic bone; primary closure of the wound is mandatory. Radical debridement involves the removal of large amounts of bone tissue and primary closure of the wound must be achieved, in order to obtain a complete mucosal recovery. Indeed, there are techniques used as adjuvant therapies to surgery, known as combined therapy, which has improved the results of surgical treatment relative to reducing the period of time for wound healing, with ongoing treatment involving the placement of somatic grafts or bone grafting at pathological sites treated [1,6].

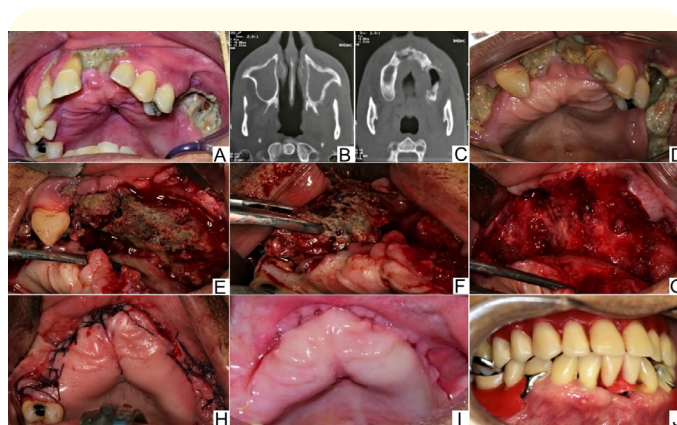


Figure 1A-1J: Extensive surgical debridement for patients suffering bilateral MRONJ lesion caused by intake of zoledronic acid for breast cancer treatment.

Photobiomodulation (PBM) has been shown to be a promising non-surgical modality for treating the primary stages of MRONJ lesions (stage I and II) [6], such as using lasers with wavelength in the red (630 - 700 nm) and infrared regions (700 - 904 nm), for biostimulating the surrounding tissues, decreasing pain and discomfort. Thereby, the repair and healing of the affected bone was improved with the purpose of increasing the disease-free survival rates [3,7,8].

Moreover, photodynamic therapy (PDT), in which the interaction of a photosensitizer with low level laser (LLL) creates reactive oxygen species (ROS) that function as the bactericidal agent, and as auxiliary treatment during surgical management (Figure 2A-2H), have obtained improvement in clinical success rates [2,6]. However, there are few reports in the current literature regarding the association of the two therapies with the conventional surgical treatment of MRONJ, the direct effect and synergistic efficacy of the different therapeutic alternatives and performing routine surgery with the complete or partial resolution of the established clinical condition (MRONJ) [9].

Aim of the Study

This brief review aimed to describe and compare the main recent studies, in which patients with MRONJ lesions have been treated with non-surgical and surgical approaches.

Review of the Literature

A literature review was performed using the Medline, PUBMED and Web of Science databases; a search for original articles in the English language was performed. Articles that were published in the last five years from 2015 to 2020 were retrieved, using the

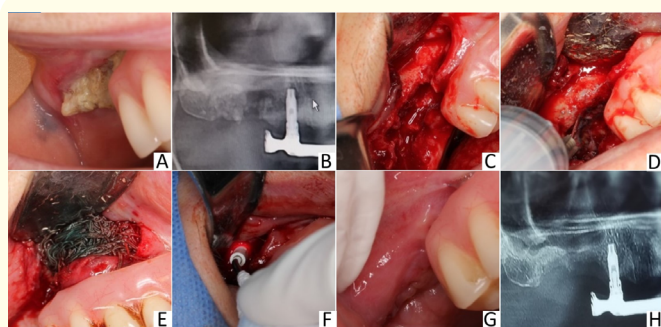


Figure 2A-2H: Combined therapy based on surgical debridement and antimicrobial photodynamic therapy (aPDT) for treating MRONJ lesion classified as Stage II in the right maxilla caused by intake of alendronate oral bisphosphonate during five years.

key words “medication-related osteonecrosis of the jaw”, “surgical treatment”; “non-surgical treatment”; “MRONJ approaches”; “bisphosphonates”; “denosumab”; “conservative treatment”; “combined therapy”. We selected 25 articles were selected from our current research of the MRONJ treatment literature review and keywords, which included clinical trials, systematic reviews; multicenter studies retrospective studies, cases series, cases reports, written in English language, published during 2015 until 2020. The description of principal characteristics and results of each study are shown in the Table 1.

Discussion

Medication-related osteonecrosis of the jaw (MRONJ) is an adverse reaction to several drugs used to control and manage bone metabolic disorders and malignancies of the bone tissue. The main medications are bisphosphonates and denosumab; these antiresorptive agents inhibit the normal resorption activity of osteoclasts [5,10,11].

Reports in the current literature discussed the capacity of denosumab to create an environment with less formation of blood vessels in the surrounding tissue [2,10,11]. Treatment of MRONJ was usually found to be difficult and continued to be controversial, because up to now, no accurate therapeutic strategy to ensure the complete resolution of this condition has been found. The main goal of each therapeutic modality has been to establish infection control, diminish the progression of bone necrosis and pain [12].

The recent European Position Paper (Workshop of European task force on medication-related osteonecrosis of the jaw-Current challenges, 2019) about the treatment of MRONJ lesions, disclosed

data about the proper use of non-surgical treatment to reduce acute symptoms (pain) and local infection. However, paper pointed out the importance of surgical treatment to ensure long-term mucosal healing, because in several cases progression was shown after non-surgical management, and not resolution of the condition [4].

Non-surgical management is used in the primary stages of MRONJ (I and II) and the current literature has recommended this modality to treat these types of lesions [1], exhorting its use to avoid extensive surgical procedures with the purpose of preserving the remaining bone and soft tissues. In a recent study, published in 2018, a retrospective cohort study was conducted with 106 patients who had 117 sites of MRONJ revealed by clinical examination. The research group evaluated the effectiveness of nonsurgical therapy using local wound care in management of these lesions. Patients showed complete recovery (complete resolution of the disease was found in the clinical and radiographic parameters) of 71% of lesions, with an additional 22% of the lesions undergoing improvement in the disease. A complementary finding was that the wound care score was statistically associated with disease and time of resolution. This suggested the need for continuous oral care, specifically local care of MRONJ lesion wounds, which was extremely important for resolution of the disease in patients with established MRONJ diagnosis [13].

Among other non-surgical treatment modalities, other authors have described the use of drug therapies, targeting the fact that the etiology of osteonecrosis of the jaws is multifactorial; and specifically, in the case of the decrease in local blood flow, they saw the possibility of using pharmacological vasodilators. Thus, a recent study performed, primarily began to evaluate the clinical relevance of Pentoxifylline (vasodilator) and tocopherol (vitamin E) in the treatment of MRONJ lesions. A systematic review with a total of 14 patients, of whom 12 had bone exposure, 1 had a bone spike and 1 had no exposure, were treated with pentoxifylline 400 mg twice daily and tocopherol in varying doses (500 mg twice daily vs 400 mg twice a day vs 400 IU twice a day). A reduction in all clinical signs and symptoms could be seen after 13 months of follow-up, [14].

Autogenous platelet concentrate (APC) or platelet rich fibrin (PRF) and Leukocyte-Platelet-Rich Fibrin (L-PRF), which is known to have numerous growth factors, used as adjuvant therapy has been researched in MRONJ management [15-17]. A recent systematic review, evaluating 302 of these lesions, concluded that in 87.8% of these, a complete response was obtained after conventional surgical treatment followed by the use of APC/PRF. In contrast, surgical treatment only showed complete success in 63.8% of the lesions.

Thus, the authors concluded that the use of APC could help in the treatment of MRONJ because it is a local immunomodulatory factor [18].

As previously described, non-surgical treatment is indicated for cases of osteonecrosis in the early stages of the disease, being used mostly in Stage I and II. However, a recent case report described the non-surgical treatment of an advanced stage III lesion, with bone exposure, pain and fistula in the molar region on the right side, associated with cellulitis in the mandibular symphysis. The patient was first treated with antibiotics (Ampicillin/Sulbactam 750 mg every 12 hours for 45 days) as a treatment for osteomyelitis. Subsequently, the 65-year-old patient was treated with Teriparatide rhPTH - an anabolic agent promoting bone metabolism - and 5 months later, she showed no radiographic and clinical evidence of the pathology. We suppose that this case report could lead to new perspectives being considered with regard to non-surgical treatment, because this medication has shown promising results, however, its use has not yet been approved globally for patients with different comorbidities, such as oncological patients [19].

In a study conducted in the period 2003 to 2017, 15 patients diagnosed with MRONJ in stage III were treated. Thirteen patients underwent surgical intervention characterized by removal of bone sequestration and osteoplastic surgical procedures of the lesions, which had devitalized bone; and two patients were treated with antibiotics and soft diet. Eleven of the patients treated with surgery showed complete healing of the pathological fracture or pseudoarthrosis and no complaints and functional deficits were registered [20].

For the treatment of stage III MRONJ, there is still an ongoing debate about the conservative and the aggressive modalities show in different previous studies. The conservative group [1,3,13,21] recommended reduction of the bone trauma inherent to the surgical procedure and suggested continuing with a conservative approach for as long as possible. Whereas, the latter group suggested aggressive and extensive surgical resections and reconstructions of the jaw, for example, with the use of a vascularized osteocutaneous fibular free flap [10,20,22,23].

A study carried out a survey of 17 patients relative to using the non-surgical method in patients showing stage I MRONJ. Treatment consisted of irrigation with (0.12%) chlorhexidine digluconate three times per day and application of chlorhexidine gel. Eleven patients developed total repair of the affected area, and seven

patients had an average improvement of 64.7% in recovery of the lesions. No clinical worsening occurred in any patient. The authors emphasized that surgical treatment was restricted to patients with an advanced stage of the disease [24].

A recent prospective study evaluated 361 patients and treatment planning was established based on the stage of MRONJ presented. Two thousand and two patients were treated by the conservative method with oral antiseptics, antibiotic therapy and debridement of exposed bone sequestration; 37 were submitted to surgery due to worsening of the clinical conditions with non-surgical management; and 122 were treated with invasive surgery, with removal of the necrotic bone, or marginal mandibulectomy, or partial maxillectomy, varying according to the pathological condition. Total regression of the osteonecrosis was obtained in 25.2% of patients who underwent conservative treatment and in 76.7% of those who underwent surgical treatment [10].

Among the 106 patients evaluated in a prospective study, 85 patients from Group 1 were submitted to the surgical approach, with procedures ranging from surgical debridement to bone resection, and 21 patients (Group 2) were treated conservatively. For Group 1, in those with MRONJ in stages I and II, 100% of the lesions recovered, and in stage III, 86.5% recovered. In Group 2, there was no total recovery of any lesion; only one patient in stage II and one patient in stage III improved as the lesions reverted to stage I and II, respectively. There was worsening in one patient from stage II to III and in the others, the disease remained in a stable condition [25].

Currently, there are other surgical approaches to manage MRONJ in advanced stages, such as the use of autologous bone marrow mesenchymal stem cells (MSCs) as adjuvant therapy with the necrosectomy procedure. A prospective study showed promising results with the use of both treatments, because it was found that MSCs promoted wound healing and induced new bone formation after 12 to 54 months of follow-up in six patients who had been submitted to this surgical approach. The clinical success was assessed according to the clinical and radiographic parameters used in these two periods [22].

A similar study evaluated the surgical treatment of maxillary MRONJ using two different wound closure techniques after the removal of bone sequestra: a single-layer closure with mucoperiosteal flap, and double-layer closure with buccal fat pad flap (BFPF) and mucoperiosteal flap. The study found that patients submitted to sequestrectomy, with the surgical site covered with mucoperiosteal

flap obtained complete mucosal healing (complete epithelization of the surgical site in absence of inflammation and pain) in 76.7% of the lesions. Whereas, 85.7% of the lesions obtained complete mucosal healing when were covered with BFPF. Both techniques are reliable for MRONJ treatment, however, the use of BFPF is indicated in cases of MRONJ- related oroantral communications [26].

Previous studies and case reports have shown the efficacy of synergistic application of conventional treatment (antibiotic therapy + surgical debridement), PBM and photodynamic therapy in the early stages of the disease (stage 1 and 2) [2,6,27].

The results were positive when LLLT was used for rapid healing of the surgical wound, associated with increased proliferation of fibroblasts and chondroblasts, collagen synthesis, stimulation of osteogenesis, improvement in the bone cell differentiation capacity and mechanisms of repair. In addition, LLLT has been found to increase local and regional blood flow, stimulating endothelial cell proliferation - and as previously described - resulting in improved analgesia [2,27].

A recent systematic review [28] evaluated the clinical results obtained with the use of different types of laser therapy before (for reducing preoperative pain), during (as a surgical technique for removing necrotic tissue) and after treatment (resulting in analgesia and controlling postoperative inflammation) of MRONJ lesions.

The results presented were favorable with regard to the use of laser therapy exclusively after the surgical treatment of MRONJ when compared with its use in the preoperative period, for the control of pain and inflammation.

Randomized prospective cohort clinical studies with high-quality methodological design should be conducted for accurate clinical evaluation of the properties of laser therapy with regard to its use in the trans- surgical stage as the main surgical tool (High level of laser therapy - Er: YAG laser), and the possible synergism when used with low-power laser therapy and its concomitant application with other therapies such as platelet- rich plasma (LLLT + PRP) in the previously described modality that has shown promising results: the combined therapy for the management of MRONJ lesions in the different stages of the disease, [28,29].

Whereas, PDT has a mechanism of action based on the bactericidal effect caused in the site submitted to treatment with the aim of decreasing the local microbiota. Previous studies [2,30,31] have shown a decrease in bacterial communities in periodontal pockets after the application of this therapeutic modality. In addition to producing the formation of reactive oxygen species, PDT may favor and stimulate proliferation of the periodontal ligament cells and fibroblasts of the surrounding periodontal supporting tissues, with the purpose of maintaining the teeth anchored to the bone [32].

Table 1: Main last studies describing non-surgical or surgical approach to manage MRONJ lesions (2015-2020)

N ^o	Author	Number of patients	Age (mean)	Sex	Sites (Number and place)	Study type	Treatment	Follow-up period	Results (%)
1	Fortunato et al. (2020)	410	-	-	Maxilla Mandible	Systematic review	Surgical management with application of platelet concentrates (APC)	9 years	Surgical: 63,8% of resolution Surgical + APC: complete response: 87,8% Partial response: 6,7%
2	Li et al. (2020)	354	-	-	Maxilla Mandible	Systematic review	Surgical: laser treatment. Non-surgical: laser-assisted treatment plus platelet-rich plasma.	?	Results of the studies that were deemed to be high-to-low quality and to have high-to-low statistical power suggested that there may be considerable clinical improvement in MRONJ by using laser-assisted treatment
3	Mourão et al. (2020)	11	67,7	F: 9 M: 2	Maxilla: 4 Mandible: 7	Case report	Surgical: with the adjunct of Platelet-rich Fibrin (PRF)	12-36 months	Complete resolution
4	Poli et al. (2019)	11	65-79	F: 8 M: 3	Maxilla: 6 Mandible: 7	Case series	Surgical: dental and implants removal Non-surgical: Applications of low-level laser therapy	6 months - 1 year	Complete resolution

5	Tartaroti et al. (2020)	18	68,94	F: 18 M: 0	Mandible: 10 Maxilla: 8	Case series	Surgical with adjuvant therapies such as: PDT and PBM therapy protocols	6-29 months	87.5 % patients required sequestrectomy and healed after removal of necrotic bone. (12.5 %) re-epithelialization occurred after necrotic bone spontaneously detached from the region leaving a healthy mucosal bed, without pain or bone sequestration.
6	Heifetz-Li et al. (2019)	14	66,7	F: 9 M: 5	Maxilla Mandible	Systematic review	Non-surgical: Local application pentoxifyline and tocopherol	13 months	Complete resolution: 100% free from pain
7	Sarmiento et al. (2019)	1	65	F: 1	Mandible: 1	Case report	Non-surgical: solution of Teriparatide	5 months	Complete resolution
8	Valente et al. (2019)	15	64	F: 9 M: 6	Mandible: 9 Maxilla: 6	Retrospective clinical study	Surgical: sequestrectomy Non-surgical: debridement and leukocyte-platelet-rich fibrin (L-PRF)	6 years	Resolution: 73,3% Nonresolution: 26,7%
9	Aljohani et al. (2018)	72	72	F: 46 M: 26	Maxilla: 72	Case series	Surgical: (Mucoperiosteal flap and Buccal fat pad)	6 months	Complete mucosal healing (covered with mucoperiosteal flap): 76.7% Complete mucosal healing with BFPF: 85.7%
10	Favia et al. (2018)	106	70.2	F: 74 M: 32	Maxilla: 34 Mandible: 73	Retrospective study	Group 1: Surgical (Antibiotics +debridement and sequestrectomy) + tension-free wound closure with a mucoperiosteal flap. Group 2: Non-surgical: mouth-rinses, antibiotics and PBM	18 months	Group 1: Complete resolution: 100% (Stages I and II) 86,5% (Stage III) Partial resolution: 13,5% (Stage III) Group 2: -No lesions showed complete healing, but remained stable
11	Hadaya et al. (2018)	106	71.7	F: 63 M: 20	Maxilla: 43 Mandible: 74	Retrospective cohort study	Non-surgical: Local wound care (to perform with a cotton swab and chlorhexidine 0, 12%)	1, 2 and 3 months	Complete resolution; 71% Partial resolution: 22%
12	Hasegawa et al. (2018)	89	64.5	F: 51 M: 34	Mandible		Surgical debridement and wound primary closure	8 months	Complete resolution: 76.7%
13	Merigo et al. (2018)	21	72.6	F: 16 M: 05	Mandible: 15 Maxilla: 6		Combined Therapy: Surgical: Piezosurgery, Laser Er. YAG Non-surgical: platelet-rich plasm, PBM (808nm)	9.6 months	Complete resolution: 92.85% Partial resolution; 7.15%
14	Nisi et al. (2018)	53	71.9	F: 53	Maxilla: 12 Mandible: 39 Maxilla plus Mandible: 2	Prospective study	Combined Therapy: Surgical: Conservative surgical supragingival debridement Non-Surgical: mouth-rinses-antibiotics	24 – 48 months	Complete resolution: 45 patients (91,8%) Partial resolution: 8 patients (8.2%)
15	Pichardo et al. (2018)	15	71.8	F: 8 M: 7	Mandible: 15	Observational study	Surgical: Sequestrectomy followed by intermaxillary fixation	24months	Complete resolution: 73% Partial resolution (free of complaints and able to function): 27%
16	Yamada et al. (2018)	275	75	F: 178 M: 97	Mandible: 193 Maxilla: 75 Others: 7		- Non-Surgical: 140 - Surgical: Sequestrectomy: 62 patients Sequestrectomy with bone resection: 72 patients	12 months	Complete resolution: 49.8% (137 patients) Stage I: 39.8% Stage II: 26.3% Stage III: 19% Modality treatment:

						Unknown: 1 patient		Non-surgical: 17.2%
								Sequestrectomy: 34.5%
								Extended surgery with bone and segmental resection: 40.7%
17	Fornaini et al. (2017)	01	60	M: 01	Mandible	Randomized controlled trial Combined therapy: Surgical + Adjuvant therapies Antibiotics Laser Er: YAG (surgical debridement) Platelet-Rich Plasma PBM	48 months	Complete resolution (wound closure) for the 2 years follow up
18	Hayashida et al. (2017)	361	73.7	F: 238 M: 123	Mandible: 237 Maxilla: 124	Non-surgical : 2002 patients Surgical treatment: 159 patients	15-81 months	I. Complete resolution - Non-surgical: 25.2% - Surgical: 76.7% II. Partial resolution: - Non-surgical: 10.9% - Surgical: 18.2% III. Stable disease: - Non-surgical: 46.0% - Surgical: 4.4% IV. Progressive disease: - Non-Surgical: 17.8% - Surgical: 0.6%
19	Momesso et al. (2017)	01	65	F: 01	Maxilla	Combined therapy: Surgical + Adjuvant therapies Removal of necrotic bone. PBM Antibiotics	6-12 months	Complete healing of the affected area (6 months follow-up) and after 12 months a patients were rehabilited.
20	Voss et al. (2017)	06	65.2	F: 5 M: 1	Mandible: 6	Surgical: Sequestrectomy followed by Mesenchymal stem cells.	12-54 months	Satisfactory healing with no signs of wound: 100%
21	Minamisako et al. (2016)	01	85	M: 1	Maxilla	Combined Therapy: Surgical: Conservative debridement Non-surgical: Antibiotics, LLLT, PDT.	12 months	Complete resolution (wound closure) after 12 months follow-up
22	Bodem et al. (2015)	17	63.6	F: 11 M: 6	Mandible: 15 Maxilla: 2	Non-surgical : Mouth rinses with Chlorhexidine (CHX) and daily CHX gel application.	10.8 months	Complete resolution: 45.8% (11 patients)
23	Del Fabbro et al. (2015)	362	-	-	Maxilla Mandible	Systematic review Surgical: in combination with APC	-	The adjunct of APC in MRONJ treatment significantly reduced osteonecrosis recurrence with respect to control
24	Lopes et al. (2015)	33	65.6	F: 25 M: 8	Mandible: 25 Maxilla: 20	Surgical debridement and coadjuvant antibiotics	6 – 10 months	Complete resolution: 87%(40 patients) Partial resolution: 6.5% (3 patients) None: 6.5% (3 patients)
25	Vascovi et al. (2015)	1	-	-	Maxilla: 1	Case report Surgical: laser treatment	7 months	Complete mucosal healing was evident, and the patient was free of symptoms

Abbreviation: F, Female; M, Male; PBM, photobiomodulation; LLT, low-laser therapy; PDT, photodynamic therapy; CHX, chlorhexidine

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Conclusion

This brief review of current literature described new modalities for the accurate treatment of different stages of MRONJ, and several studies have indicated that surgical management was still the gold standard for the treatment of advanced stages (II and III) in patients suffering from this pathological condition.

The association of two or more approaches that involved non-surgical and surgical procedures showed an increase in the clinical success rates of patients who underwent treatment. Moreover, the synergism of these treatment modalities might lead to improvement in the prognosis and quality of life of MRONJ patients. Results of clinical and radiographic parameters should be considered criteria with predictive value in establishing complete or partial resolution of the disease after an extensive period of follow-up.

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Conflict of Interest

There are not conflicts of interest for this article to declare.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent

This article does not contain any studies with human participants or animals performed by any of the authors.

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