

Medication-Related Osteonecrosis of Jaw (MRONJ)

Subjects: Dentistry, Oral Surgery & Medicine

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Medication-related osteonecrosis of the jaw (MRONJ) is a serious adverse reaction of antiresorptive and antiangiogenic agents, and it is also a potentially painful and debilitating condition.

Keywords: ONJ ; osteonecrosis ; treatment ; therapy ; surgery ; staging

1. Introduction

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 has not yet been defined. In brief, this standard would involve the three main categories of MRONJ: (a) non-invasive procedures (ranging from pharmacological to laser treatment) ^{[1][2]}, (b) invasive techniques (i.e., conservative or aggressive surgical approaches) ^[3] and (c) a combination of (a) and (b) (i.e., surgery plus one of the aforementioned non-invasive procedures) ^[4]. Non-invasive procedures include: medical treatment, intraoral vacuum-assisted treatment ^[5], the use of pentoxifylline (associated or not with tocopherol ^[6] ^[7]), Er:YAG laser ablation, and Nd: YAG/diode laser biostimulation ^{[8][9][10]} and teriparatide ^{[11][12][13][14]}. Only partial and delayed healing has been reported with non-invasive techniques, to the exclusion of low-level laser treatment (LLLT) and, in certain cases, teriparatide. Furthermore, there is a paucity of high-impact studies in the literature, which would demonstrate effective positive outcomes ^[15].

Surgical treatments comprise: (i) conservative approaches, such as bone debridement, and sequestrectomy, and (ii) invasive, more aggressive procedures, such as re-sectioning the affected bone and jawbone reconstruction, where indicated. Several studies have yielded very positive results for surgical treatment in MRONJ treatment, especially if performed in the early stages of the disease ^{[16][17][18][19]}.

Many in the field consider that the term 'treatment' is often used inappropriately, in that it is not possible for the disease to heal completely or for the majority of MRONJ patients to arrive at a state of remission. Thus, and as documented in the MRONJ literature, treatment goals are mainly concerned with managing pain, controlling for any infection of the soft and hard tissues and reducing the progression or occurrence of bone necrosis ^[4]. Over and above every consideration, the authors of this paper hold that maximizing a patient's quality of life has to be a key feature of every protocol requiring MRONJ treatment.

2. Studies

In order to be included in the systematic review outlined in this paper, studies had to include results from: prospective, non-randomized and randomized clinical trials, retrospective cohort studies and case series ($n \geq 10$), which investigated the role of surgical (conservative or aggressive) techniques with or without combined procedures (surgery plus a non-invasive one) and with a follow-up ≥ 6 months. Studies were excluded if they constituted a Commentary, Review, Editorial or Protocol. Case series ($n < 10$) or case reports were excluded from the pooled analysis, and the studies were limited to research regarding human beings.

Furthermore, other data sources (from international meetings and indexed dentistry journals such as Journal of Dentistry, Journal of Oral Maxillofacial Surgery, Journal of Dental Research) were scanned as a source of grey literature.

Screening and eligibility were assessed independently by two reviewers (F.C. and O.D.F.), who were in agreement regarding the results. The Titles of papers and Abstracts were initially screened for relevance and possible eligible results, and thereafter full texts were retrieved. Finally, the reviewers combined their results to create a corpus of selected papers to assess for final eligibility. According to the aim of this review, the resulting papers were allocated to four experimental categories: (1) conservative surgery, (2) aggressive surgery, (3) a conservative plus non-invasive procedure and (4) aggressive surgery plus non-invasive protocols. **Table 1** and **Table 2** summarize the eligible studies.

Table 1. Summary of the characteristics and the results of the studies concerning MRONJ surgical therapies.

Treatment	Study	Study Type	Pts	Intervention	Outcome	Follow-Up
Conservative Surgery	De Souza Pova et al., 2016	Case report	N = 1 Onc Stage 1	Removal of the exposed necrotic bone and primary wound closure	Complete healing and new bone formation in the surgical site	26 months
	Ribeiro et al., 2015	Case report	N = 1 Ost Stage unspecified	Surgical removal of whole necrotic bone, extraction of all compromised teeth	Complete healing	12 months
	De Souza Faloni et al., 2011	Case report	N = 1 Ost Stage 2	Conservative debridement of the necrotic bone and of part of the surrounding healthy bone, as a margin of safety	Complete healing	8 months
	Pechalova et al., 2011	Case series	N = 3 Onc Stage unspecified	Conservative surgical debridement	Complete healing	Average of 4 months
	Martins et al., 2012	Retrospective clinical study	N = 5 Onc Stage 1,2	Sequestrectomy and/or ostectomy and/or osteoplasty until bone marrow bleeding	60% patients completely healed	6 months
	Jung et al., 2017	Case series	N = 7 Ost Stage 2,3	Patient underwent conventional surgery, and the bone defects were filled with absorbable collagen plugs.	Complete healing and new bone formation in the surgical site	3 months
	Atalay et al., 2011	Retrospective clinical study	N = 10 Onc Stage	The affected bony tissues were curetted from the surface of the bone using bone curettes and round tungsten carbide burs. The necrotic bone was completely removed until the vital bone tissues and vessel spots appeared	40% patients completely healed	6 months
	Vescovi et al., 2012	Retrospective clinical study	N = 17 Onc + Ost Stage 1,2,3	Conservative surgical treatments consisted of sequestrectomy of necrotic bone, superficial debridement/curettage, or corticotomy/surgical removal of alveolar and/or cortical bone	53% patients completely healed	9 months
	Vescovi et al., 2011	Prospective clinical study	N = 17 Onc + Ost Stage 1,2,3	Conservative surgical treatments included sequestrectomies, superficial debridement/curettage and corticotomies/surgical removal of surrounding alveolar and/or cortical bone	65% patients completely healed	12 months
	Freiberger et al., 2012 ⁵	Randomized control trial	N = 19 Onc + Ost Stage 1,2,3	Surgical debridement of the necrotic bone	33% patients completely healed	24 months
	Fortuna et al., 2012	Single-center prospective open-label clinical trial	N = 26 Onc Stage 2,3	Systemic and topical antibiotic therapy following by sequestrectomy	73% patients completely healed	Average of 10 months
	Lee et al., 2014	Case series	N = 30 Ost + Onc Stage 1,2,3	Minor surgical debridement was performed after irrigation, in which the necrotic bone fragments were removed	Complete healing	Average of 16 months

Treatment	Study	Study Type	Pts	Intervention	Outcome	Follow-Up
Conservative Surgery with Buccal Fat Pad Closure	Schubert et al., 2012	Prospective study	N = 54 Onc + Ost Stage 1,2,3	Complete electrical or manual removal of the osteonecrosis until points of bleeding from the bone can be macroscopically detected.	88.8% patients completely healed	6 months (72%)
	Graziani et al., 2012	Retrospective cohort multicenter study	N = 227 Ost + Onc Stage 1,2,3	Local debridement was comprised of all surgical interventions, such as sequestrectomy, soft tissue debridement and curettage, that did not require bone surgery beyond the regular margins	49% patients completely healed	6 months
	Duarte et al., 2015	Case report	N = 1 Onc Stage 2	The extensive necrotic bone area was surgically removed, resulting in oral sinus communication. A buccal fat pad was used to cover the defect	Complete healing	3 months
	Gallego et al., 2012	Case series	N = 3 Onc + Ost Stage 1,2,3	Sequestrectomy and bone debridement. The overlying mucosa was sutured over the defect with reconstruction with buccal fat pad.	Complete healing	Average of 12 months
	Berrone et al., 2015	Case series	N = 5 Onc Stage 3	Removal of the necrotic bone and primary closure of the oroantral communication using a buccal fat pad flap.	Complete healing	Average of 12 months
	Lopes et al., 2015	Retrospective observational cohort study	N = 46 Onc + Ost Stage 2,3	Removal of all necrotic bone until bleeding was obtaining at the bony margins, conscious smoothing of all sharp bone edges and primary closure of the wound.	87% patients completely healed	10 months
	Hayashida et al., 2017	Multicenter retrospective study	N = 38 Onc + Ost Stage 1,2,3	One group received conservative surgery, removal of only the necrotic bone and extensive surgery, defined as removal of the necrotic and surrounding bone (marginal mandibulectomy or partial maxillectomy).	76.7% patients completely healed	Average of 15 months

Treatment	Study	Study Type	Pts	Intervention	Outcome	Follow-Up
Aggressive Surgery	Hewson et al., 2012	Case report	N = 1 Onc Stage 3	Radical surgical excision of all diseased bone and nasio-labial flap reconstruction.	Complete healing	6 months
	Ghazali et al., 2013	Case report	N = 1 Ost Stage 3	Hemimandibulectomy and an osteocutaneous fibula flap reconstruction	Complete healing	24 months
	Shintani et al., 2015	Cohort study	N = 4 Ost + Onc Stage 1,2,3	Segmental resection and immediate reconstruction with a reconstruction plate were performed.	3/4 patients completely healed	12 months
	Lee et al., 2014	Case report	N = 10 Ost + Onc Stage 1,2,3	Large necrotic bone segment was removed by an ultrasonic bone saw. A bone file or rongeur was used for rounding the sharp bone edge. Then, the bone defect was closed by sutures or COE pack.	Complete healing	Average of 8 months
	Hanasono et al., 2013	Case series	N = 13 Onc Stage2, 3	Segmental mandibulectomy and microvascular free flap reconstruction.	Complete healing	Average of 15 months
	Graziani et al., 2012	Retrospective cohort multicenter study	N = 120 Ost + Onc Stage 1,2,3	Re-sective procedures were defined as corticotomy, surgical removal of the lesion and extended bone removal without prejudice for the continuity of the mandible/maxilla.	68% patients completely healed	6 months
	Hayashida et al., 2017	Multicenter retrospective study	N = 121 Onc + Ost Stage 1,2,3	Extensive surgery, defined as removal of the necrotic and surrounding bone (marginal mandibulectomy or partial maxillectomy).	86.8% patients completely healed	Average of 15 months

Table 2. Summary of the characteristics and the results of the studies on MRONJ surgery plus non-invasive procedures.

Study	Study Type	Population	Intervention	Outcome	Follow-Up
Conservative surgery plus (+) non-invasive procedures					

Study	Study Type	Population	Intervention	Outcome	Follow-Up	
1. Surgery + Blood Component	Gönen et al., 2017	Case report	N = 1 Onc Stage 3	Sequestrectomy + PRF	Complete resolution	18 months
	Soydan et al., 2014	Case report	N = 1 Onc Stage unspecified	Curettage + PRF	Complete resolution	6 months
	Maluf et al., 2016	Case series	N = 2 Onc Stage 2	Resection of the necrotic tissues, curettage and osteotomy + L-PRF	Partial healing	6 months
	Dincă et al., 2014	Retrospective clinical study	N = 10 Onc Stage 2	Sequestrectomy or curettage + PRF	Complete resolution	1 month
	Nørholt et al., 2016	Prospective study	N = 15 Onc + Ost Stage 2,3	Curettage + L-PRF	93.3% patients completely healed	20 months
	Anitua et al., 2013	Case report	N = 1 Onc Stage unspecified	Curettage + PRGF	Complete resolution	12 months
	Bocanegra-Pérez et al., 2012	Prospective descriptive study	N = 8 Onc + Ost Stage 2	Curettage + PRP	Complete resolution	14 months
	Mozzati et al., 2012	Retrospective clinical study	N = 32 Onc Stage 2	Conservative surgery + PRFG	Complete resolution	From 48 to 50 months
	Tsai et al., 2016	Case report	N = 1 Ost Stage 3	Surgical debridement, sequestrectomy + PRF	Complete resolution	10 months
	Pelaz et al., 2014	Cohort study	N = 5 Ost Stage 3	Sequestrectomy and curettage + PRF	Complete resolution	An average of 20 months
	Park et al., 2017	Prospective study	N = 25 Onc + Ost Stage 1,2,3	Conservative surgery + L-PRF	36% patients completely healed	4 months
	Fernando de Almeida Barros Mourao C et al., 2020	Case series	N = 11 Ost Stage 2	Surgical removal of necrotic bone + PRF membranes	Complete healing	24 months
	Giudice A et al., 2020	Case report	N = 1 Ost Stage 3	Surgical removal of necrotic bone + PRF membranes	Complete healing	60 months
	Bouland C et al., 2020	Case report	N = 2 Ost + Onc Stage 2 and 3	Surgical removal of necrotic bone + SVF and L-PRF membranes	Complete healing	18 months
2. Surgery + Blood Component + Photodynamic Therapy	De Castro et al., 2016	Case series	N = 2 Ost Stage 2,3	Surgical debridement + PDT + PRF	Complete resolution	An average of 12 months
3. Surgery + Blood Component + Bone Morphogenetic Protein	Park et al., 2017	Prospective study	N = 30 Onc + Ost Stage 1,2,3	Conservative surgery + combined L-PRF and recombinant human BMP-2 (rhBMP-2)	60% patients completely healed	4 months

Study	Study Type	Population	Intervention	Outcome	Follow-Up	
4. Surgery + Teriparatide	Lee et al., 2010	Case report	N = 1 Ost Stage 2	Sequestrectomy + teriparatide	Complete resolution	6 months
5. Surgery + Teriparatide + Bone Morphogenetic Protein	Jung et al., 2017	Cohort study	N = 6 Ost Stage 2,3	Conservative surgery and absorbable collagen plugs soaked by rhBMP-2 into the bone defect plus daily subcutaneous injection of 20 mg teriparatide for 1–4 months.	Complete resolution	3 months
6. Surgery + Bone Morphogenetic Protein	Jung et al., 2017	Cohort study	N = 4 Ost Stage 2,3	Conservative surgery and absorbable collagen plugs soaked by rhBMP-2 into the bone defect.	Complete resolution	3 months
7. Surgery + Blood Component + Autologous Bone Marrow Stem Cells	González-García et al., 2013	Case report	N = 1 Onc Stage 2	Removal of the necrotic bone+ bone marrow stem cells + beta tricalcium phosphate + demineralized bone matrix + PRP	Complete resolution	6 months
	De Santis et al., 2020	Case report	N = 2 Onc Stage 2	Debridement of the exposed necrotic bone followed by bone marrow stem cells injection	Complete healing and new bone formation in the surgical site.	13 months
8. Surgery + LLLT	Da Guarda et al., 2012	Case report	N = 1 Onc Stage unspecified	GaAlAs diode laser every 48 h for 10 days + antibiotic therapy + curettage	Complete resolution	6 months
9. Surgery + Blood Component + Laser Phototherapy	Altay et al., 2014	Retrospective clinical study	N = 11 Onc Stage 2,3	Pre- and post-operative antibiotic administrations + GaA-IAs diode laser	Complete resolution	12 months
	Atalay et al., 2011	Retrospective clinical study	N = 10 Onc Stage 1,2	Conservative surgery + low-level laser therapy application (Er:YAG and Nd:YAG)	70% patients completely healed	12 months
	Vescovi et al., 2012	Retrospective clinical study	N = 45 Onc + Ost Stage 1,2,3	Conservative surgery + laser Nd:YAG	89% patients completely healed	6 months
	Vescovi et al., 2011	Prospective clinical study	N = 62 Onc + Ost Stage 1,2,3	Conservative surgery + laser LLLT	73% patients completely healed	17 months.
	Martins et al., 2012	Retrospective clinical study	N = 14 Onc Stage 1,2,3	Conservative surgery + continuous indium-gallium-aluminum-phosphide diode laser. The LPT treatment started on the first visit and continued daily until mucosal healing was observed.	86% patients completely healed	12 months
10. Surgery + Ozone	Agrillo et al., 2012	Retrospective study	N = 94 Onc + Ost Stage unspecified	Curettage or sequestrectomy + Ozone therapy (3 min sessions 2/week) + pharmacological therapy	90% patients completely healed	An average of 6 months

Study	Study Type	Population	Intervention	Outcome	Follow-Up	
11. HBO + Surgery *	Fatema et al., 2013	Case report	N = 1 Onc Stage 2	Antibiotics therapy, irrigation, pre-operative HBO therapy for 20 sessions, conservative minor surgical debridement and again post-operative HBO therapy for ten sessions.	Complete resolution	Unspecified
	Al-Zoman et al., 2013	Case series	N = 3 Onc Stage 2,3	HBO therapy, oral/parenteral antibiotic, analgesics, conservative surgery (debridement of bone sequestra) and daily rinsing with chlorhexidine mouthwash.	Complete resolution	12 months
	Freiberger et al., 2012	Randomized control trial	N = 24 Onc + Ost Stage 1,2,3	40 HBO treatments at 2.0 atm for 2 h twice per day and conservative surgical debridement of the necrotic bone.	52% patients completely healed	24 months
12. Ozone + Surgery*	Ripamonti et al., 2012	Case report	N = 1 Onc Stage unspecified	Antibiotic + antimycotic therapy for 10 days. Local ozone gas (total of 15 applications). Conservative surgery (sequestrectomy).	Complete resolution	36 months
	Brozoski et al., 2020	Case series	N = 2 Onc + Ost Stage 2	Weekly irrigation with aqueous ozone solution on bone-exposed region + daily mouthwashes of ozone solution. After 3 and 6 months: conservative surgery (debridement and sequestrectomy)	Complete resolution	An average of 24 months
13. Teriparatide + Surgery *	Doh et al., 2015	Case report	N = 1 Ost Stage 2	After 4 months of daily teriparatide therapy conservative surgery (sequestrectomy). The TPTD therapy was terminated 6 months after the initial treatment.	Complete resolution	20 months
	Kwon et al., 2012	Case series	N = 6 Ost Stage 2,3	Daily Teriparatide (20 µg/day) 1–3 months + conservative sequestrectomy/marginal/aggressive segmental resection	Complete resolution	3 months
	Kakehashi et al., 2015	Case series	N = 10 Ost Stage 2,3	Daily teriparatide (20 µg/day) ranged from 4 to 24 months. In some cases, surgery was performed to obtain the healing.	Partial resolution	From 4 to 24 months (duration of teriparatide therapy until mucosal healing)
Aggressive surgery plus non-invasive procedures						
1. Surgery + Bone Graft + Bone Morphogenetic Protein	Rahim I 2015	Case report	N = 1 Ost Stage 3	Partial mandibulectomy + bone graft from the iliac crest + rhBMP-7	Complete resolution	60 months
2. AF-Guided Surgery + LLLT	Vescovi P 2015	Case report	N = 1 Onc Stage 3	Osteotomy with Er:YAG laser + AF visualization to guide the osteoplasty. Intraoral irrigations with povidone iodine solution + application of Nd:YAG laser + weekly applications of LLLT for 3 weeks after intervention	Complete resolution	7 months

* Procedures administered prior to surgery.

Data collection was independently performed by two authors (F.C. and A.G.), and their results were reviewed by a third author (O.D.F.) to check for accuracy.

Aggressive surgery plus non-invasive procedures (auxiliary treatment): only two papers (case reports) discussed the results of aggressive surgery protocols with auxiliary treatment ^{[20][21]}.

The overall 6-month total resolution rate (a) and the 6-month improvement rate (b) were: 74% (CI 95%; 64–83%) and 87% (CI 95%; 78–94%), respectively. The following was reported for (a): 80% (CI 95%; 68–90%) for invasive surgery alone (**Figure 2a**). 69% (95% CI; 53–84%) for invasive surgery plus non-invasive procedures (**Figure 2b**).

The following was reported for (b): 81% (CI 95%; 67–92%) for invasive surgery alone (**Figure 3a**). 92% (CI 95%; 88–94%) for invasive surgery plus non-invasive procedures (**Figure 3b**).

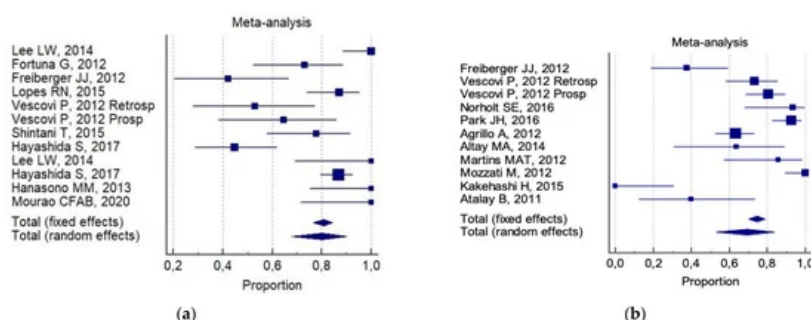


Figure 2. Forest plot results of pooled results about complete resolution in (a) invasive (conservative/aggressive) treatments, and (b) invasive (conservative/aggressive) treatments + non-invasive treatments.

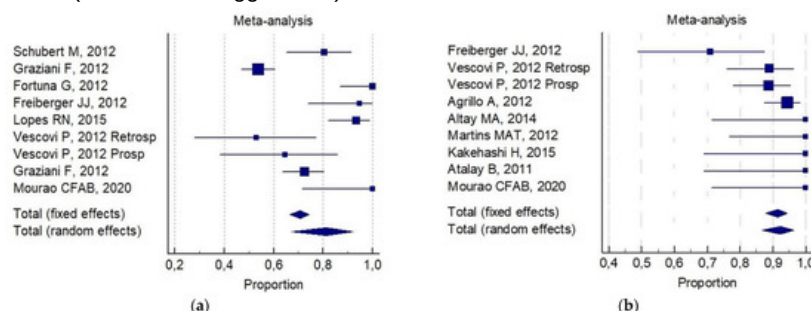


Figure 3. Forest plot results of pooled results about complete resolution in (a) invasive (conservative/aggressive) treatments, and (b) invasive (conservative/aggressive) plus non-invasive treatments.

Of interest, a significant statistical difference was observed in the 6-month improvement rate, on comparing combined conservative surgery (mean = 91%) versus only surgical (conservative alone and aggressive alone) techniques (mean 77%, $p = 0.05$). There was no significant difference for any group with respect to the 6-month total resolution rate (82% versus 72%, respectively). No reliable data were available for an analysis of aggressive surgery plus a non-invasive procedure with respect to all the selected indicators.

4. Referring

Referring to the systematic review described herein, the associations between conservative surgery plus blood components, and laser or photodynamic therapy, appear to contribute much to: newly formed bone, the full coverage of bone tissue with healthy mucosa and the absence of symptoms and other signs of necrotic progression. This is due to the analgesic, anti-inflammatory and biomodulatory effects of blood components, and this protocol has been shown to be effective on average over a 6-month follow-up period with a success rate of 86%.

The association of autologous bone marrow stem cells with conservative surgery and blood components has been reported only in one case study, with a success rate of 100% on average over a 6-month follow-up period. The CT scan revealed the diminution of osteolytic lesions with complete bone regeneration of the medial cortex of the lower jaw and a total resolution of symptoms.

The use of surgery has also been associated with teriparatide (TPTD) treatment (prior to or after conventional surgical treatment) for MRONJ in osteoporotic patients. TPTD stimulates trabecular and cortical thickness, and trabecular connectivity and bone size bone formation by increasing osteoblast number and activity. Although successful results using TPTD treatment have been reported in the literature, its safety and efficacy are currently awaiting comprehensive evaluation. The treatment time during which it can be safely administered is strictly limited to less than 2 years in one lifespan [22][23][24]. A success rate of 83% on average over an 11-month follow-up period has been reported for the surgical treatment plus TPTD treatment (or vice versa) of MRONJ: any surgical wound completely healed with X-rays indicating stable alveolar bone. No inflammatory signs and symptoms have been reported to date.

As a pre-surgical treatment, HBO has successfully treated MRONJ lesions, thereby: improving the quality of life of afflicted patients [25][26][27], increasing wound healing, and reducing edema, inflammation and pain. HBO followed by surgical treatment had a success rate of 84% on average over an 18-month follow-up period, with: the complete healing of MRONJ lesion, total mucosal coverage, a cessation in the signs of infection and notable symptomatic relief.

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