

DOWNGRADING ADVANCED STAGE MEDICATION RELATED OSTEONECROSIS OF JAW (MRONJ) USING PEDICLED FLAP- TECHNICAL REVIEW WITH CASE REPORT

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ABSTRACT DOI: [https://doi.org/10.25241/stomaeduj.2019.6\(3\).art.6](https://doi.org/10.25241/stomaeduj.2019.6(3).art.6)

Introduction: Medication related osteonecrosis of the jaw (MRONJ) is a locally destructive, and potentially devastating disease process that occurs in patients with a history of antiresorptive or antiangiogenic therapy. A widely accepted practice of surgical intervention in the management of advanced stage MRONJ involves segmental resection of the affected bone.

Aim: We propose to downgrade the stage with pedicled flaps for eradication of biofilm and vascular coverage with load sharing or load bearing constructs of the skeleton. As patients that receive antiresorptive or antiangiogenic therapy often have multiple medical comorbidities, this limits their surgical options and precludes them from being able to undergo expansive segmental resections or microvascular free tissue transfers and are left with palliative measures, thus compromising their care.

Summary: Either concept of MRONJ progression- bone metabolism or vascular breakdown is treated with immediate advancement of a pedicled local tissue flap and is performed for soft tissue coverage, thus providing a new vascular envelope and decreasing soft tissue toxicity to halt furtherance of the disease. Submental island flaps, nasolabial flaps, pedicled buccal fat pad flaps, and facial artery musculomucosal flaps have demonstrated success for longer than two years. This technique addresses downgrading MRONJ stage II and III in the mandible as a possible long-term treatment. This unreported innovative approach consists of marginal resection of the involved alveolar bone, while preserving the affected basal bone and subsequently provides reinforcement with a titanium bone plate, decreasing the chance of pathologic fracture.

Keywords: MRONJ; Flap; Pedicled flap; Medication related osteonecrosis of the jaw; Bisphosphonate related osteonecrosis of the jaw.

1. Introduction

Medication related osteonecrosis of the jaw (MRONJ) is defined as exposed or probable bone in the maxillofacial region without resolution in 8-12 weeks in persons with a history of treatment with an antiresorptive or antiangiogenic therapy who have not received radiation therapy to the jaws [1]. This is an iatrogenic process with an elevated potential for morbidity and decreased quality of life. MRONJ typically occurs in patients with a history of long-term bisphosphonate, RANK ligand inhibitor, or angiogenesis inhibitor use with

a precipitating trauma to the maxilla or mandible, such as a dentoalveolar procedure [1,2]. MRONJ has a spectrum of presentation, as represented in its staging [1]:

MRONJ Staging

At Risk: No apparent necrotic bone in patients who have been treated with oral or IV bisphosphonates.

Stage 0: No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms

Stage 1: Exposed and necrotic bone for more than 8 weeks, or fistulae that probes to bone in patients

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Peer-Reviewed Article

Citation: Chandra SR, Tyler H, Coropciuc R-G, Politis C. Downgrading advanced stage Medication Related Osteonecrosis of Jaw (MRONJ) using pedicled flap- Technical review with case report. *Stoma Edu J.* 2019;6(3):193-198.

Received: September 08, 2019

Revised: September 18, 2019

Accepted: September 24, 2019

Published: September 25, 2019

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Table 1. Summary of the stages 0-3 on the left column; middle column is the current and the right column proposes the modification in management especially in the stage 2 & 3.

MRONJ Staging	Standard Treatment Strategies	Proposed Treatment Strategies
At Risk: No apparent necrotic bone in patient who have been treated with oral or IV bisphosphonates.	- No Treatment indicated - Patient education	No changes
Stage 0: No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms	Systemic management - Analgesics - Antibiotics	No changes
Stage 1: Exposed and necrotic bone, or fistulae that probe to bone in patients who are asymptomatic and have no evidence of infection	- Antibacterial mouth rinse - Clinical follow-up - Patient education and review of indications for antiresorptive and antiangiogenic therapies.	No changes
Stage 2: Exposed and necrotic bone, or fistulae that probe to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	- Symptomatic treatment with oral antibiotics - Oral antibacterial mouth rise - Pain control - Debridement to relieve soft tissue irritation and infection control	- Symptomatic treatment with oral antibiotics - Oral antibacterial mouth rise - Pain control - Debridement of alveolar bone and immediate advancement of a pedicled local tissue flap
Stage 3: Exposed and necrotic bone or fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed or necrotic bone extending beyond the region of the alveolar bone, resulting in pathologic fracture, extra-oral fistula, oroantral/ oronasal communication, or osteolysis extending to the inferior boarder of the mandible or sinus floor.	- Antibacterial mouth rinse - Antibiotic therapy and pain control - Surgical debridement /resection for linger term palliation of infection and pain	- Antibacterial mouth rinse - Antibiotic therapy and pain control - Surgical debridement / resection of alveolar bone, leaving basilar bone intact, placement of a supra or subperiosteal titanium bone plate and immediate advancement of a pedicled local tissue flap

Table 2. The table highlights the advantages to the vascular flap coverage to MRONJ management.

Advantages of Vascular Coverage
1. Improved blood supply to underlying bone
2. Improved medication delivery to underlying bone
3. Eradication of chronic biofilm colonization
4. Decreased inflammation
5. Halts disease progression

who are asymptomatic and have no evidence of infection

Stage 2: Exposed and necrotic bone, or fistulae that probe to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage

Stage 3: Exposed and necrotic bone or fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed or necrotic bone extending beyond the region of the alveolar bone, resulting in pathologic fracture, extra-oral fistula, oroantral/oronasal communication, or osteolysis extending to the inferior boarder of the mandible or sinus floor.

Table 3. Key notable points prior to sequestrum removal and vascular coverage of MRONJ.

Critical Steps Prior to Vascular Soft Tissue Coverage
1. Obtain cultures
2. Review imaging to determine the presence of pathologic fracture or need for internal fixation
3. Biopsy for recurrence of neoplastic process. Example– recurrence of multiple myeloma

To date, there is no consensus on the MRONJ stage III treatment protocol.

The current management options range from the non-invasive, antibacterial mouth rinse, systemic treatment with oral antibiotics, and close follow up, to invasive management of potentially extensive debridement/resection of the maxilla or mandible. Conservative therapy is defined as no surgical intervention. This category includes the use of antibacterial mouth rinses and antibiotics and the removal of sequestra without local anesthetics. Ozone therapy and hyperbaric oxygen therapy are considered conservative therapeutic approaches, even though for neither of these evidence-based



Figure 1. MRONJ and bony sequestrum of right mandible in patient with history of antiangiogenic therapy.



Figure 2. Resection of necrotic alveolar bone is done, basal bone retained can be reinforced by plating (load bearing or sharing as needed) and submental island flap harvested using the same neck incision.

proof of benefit is available. Conservative surgical therapy is defined as a sequestrectomy, without resection or removal of non-sequestered bone. Whenever no mucoperiosteal flap is used a sequestrectomy is considered limited surgical therapy. Invasive surgical treatment includes anything from a sequestrectomy (starting with the use of mucoperiosteal flaps), with a resection of the affected bone up to the bleeding margins of bone, to segmental mandibulectomies and reconstructions with pedicled or microvascular free flaps.

Conservative management alone is insufficient to achieve full mucosal healing, but can be useful to stabilize disease progression in patients unfit for surgery. The use of hyperbaric oxygen therapy has no role in MRONJ grade III. The conservative surgical approach provides better results than a purely conservative approach: 75% achieve an improved condition, and of these, 54% achieve full mucosal healing. However, this group consists of a relatively small number of patients (n=48, distributed over four studies) [3,4,5]. The best treatment results for MRONJ stage III are observed in patients treated with invasive surgery. Invasive surgery without microvascular flap reconstruction yields a full mucosal healing rate of 85%, when six studies are combined [6-11]. This approach outperforms the 54% healing rate achieved with the limited surgical approach. This finding suggests that extensive bony resection up to the bleeding margins is more efficient than a sequestrectomy to achieve full mucosal healing in MRONJ stage III. Invasive surgery with microvascular flap reconstruction yields even better results, with a full mucosal healing rate of 97% [12,13]. However, many patients cannot undergo this kind of procedure, due to underlying comorbidity [14]. Bisphosphonate, RANK ligand inhibitor, and angiogenesis inhibitors are most commonly used for cancer-related conditions, and thus these patients

typically have numerous medical co-morbidities that often do not allow them to undergo extensive debridement/resection of the affected bone and reconstruction. Patients who are not able to undergo their indicated surgical treatment typically suffer deterioration of MRONJ and their antiresorptive or antiangiogenic therapy is often discontinued. This leaves the patient vulnerable to advancement of their cancer-related condition and their inadequate treatment allows for progression of MRONJ leading to involvement of previously unaffected bone, pathologic fractures and extra-oral and oronasal/oroantral fistula development. Soft tissue toxicity has been proposed in the pathogenesis of MRONJ. The mechanism is thought to involve the toxic effects of deposited bisphosphonates to local soft tissue and this might contribute to osteonecrosis of the jaw (ONJ) [2,15,16]. The inhibition of a variety of cell types to grow on bone surfaces previously treated with bisphosphonates has been demonstrated [17]. However, no tissue toxicity has been reported with RANK-L inhibitors. Given these considerations, we have developed a less invasive technique for the treatment of MRONJ while providing a vascularized soft tissue envelope and down grading the disease, irrespective of the cause of MRONJ.

2. Technique

The current standard practice in the treatment of MRONJ is to resect the affected portion of the jaws until the necrotic portion has been removed and bleeding bone is encountered [18]. As MRONJ is

a generalized affliction of the skeleton, the idea of debridement is to eradicate the biofilm of the exposed bone and aid in soft tissue coverage. In patients with progressive or advanced stages of the disease, large amounts of the supporting basilar bone is often removed, creating a loss of structure and scaffolding for the surrounding soft tissues. In these cases, we propose solely removing the affected alveolar portion of the bone, leaving the affected portions of basilar bone intact (Table I). Due to the inherent lack of strength of the necrotic basilar bone, a supra or subperiosteal titanium bone plate is placed spanning the length of the affected portion of the jaw.

This plate is anchored with bicortical locking screws on the proximal and distal aspects of the span. From there, soft tissue coverage is provided by way of a pedicled local flap (Table II), Depending on the location and size of the soft tissue defect, a flap is raised and rotated over the soft tissue defect, creating a tension-free closure. Submental island flaps, nasolabial flaps, pedicled buccal fat pad flaps, and facial artery musculomucosal flaps can be used to cover the defect.

Local pedicled flaps also help in oroantral fistulas and tori coverage. So far three patients with stage III MRONJ have been treated with this technique with a minimum follow-up of 13 months. All patients kept the necrotic basilar bone, protected by a lower border reconstruction plate, and no intraoral fistula recurred during the follow-up period. The technique is depicted in Figures 1-2.

3. Discussion

MRONJ has several proposed hypotheses of pathophysiology, including bone remodeling inhibition, inflammation and infection, angiogenesis inhibition, and immunity dysfunction.

Given the fact that MRONJ occurs in patients with a history of antiresorptive and antiangiogenic therapies and a host of different backgrounds most authors agree that the MRONJ pathogenesis is likely multifactorial.

One of the earlier noted hypotheses was that bisphosphates, especially nitrogen-containing bisphosphonates, caused direct soft tissue toxicity, inducing apoptosis and decreased proliferation of oral epithelial cells [2,15]. In vitro studies demonstrate that nitrogen containing bisphosphonates localize to epithelial tissue and bone and that alendronate is associated with esophageal irritation, requiring

special precautions during administration [19]. One of the facets to our proposed technique is to provide a new soft tissue envelope by way of advancing a pedicled flap. This not only provides a more robust blood supply to the underlying bone, but it allows for increased delivery of medications. It also eradicates the chronic colonization of debris and biofilm that causes persistent inflammation. Our observations show that this technique has been able to halt furtherance of the disease.

As previously discussed, MRONJ has a spectrum of presentation, as represented in its staging. Multiple studies have suggested treatment of the early stage MRONJ as more significant debilitation to the quality of life and pathological fractures happen in advanced stages of MRONJ. By removing the overlying infected soft tissue, debriding the alveolar bone and providing a new soft tissue coverage, this technique successfully downgrades MRONJ to a less severe state so that local measures, such as antibacterial mouth wash, are able to keep the symptom manageable.

Several other authors agree that a new vascular soft tissue coverage is essential to the long-term treatment of MRONJ (Table III) [20]. Commonly clinic based plain panoramic imaging in outpatients and cone beam computed tomographic imaging may be adequate to monitor bone status if there is appropriate soft tissue coverage.

Bone isotope studies are more specific for the turnover with biocontamination of the exposed bone. Additionally, osteoporosis from bacterial biofilm burden of the area is reduced from good vascularized soft tissue coverage as proposed here.

4. Conclusion

This technique demonstrates a novel approach to MRONJ treatment. Our more conservative technique of alveolar bone debridement, leaving the basilar bone intact, placement of a titanium bone plate for reinforcement and advancement of a local tissue flap for soft tissue coverage is ideal for patients who are unable to undergo a microvascular free tissue transfer or who should not terminate their antiresorptive or antiangiogenic therapy.

Conflict of Interest

All authors have no conflict of interest to declare.

Funding

No sources of funding were obtained for this study.

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Questions

1. MRONJ in which there is exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage is:

- a. MRONJ stage 0;
- b. MRONJ stage 1;
- c. MRONJ stage 2;
- d. MRONJ stage 3.

2. Denosumab (monoclonal antibody) inhibits maturation of osteoclasts by binding to and inhibiting:

- a. RANK-Ligand;
- b. Osteoprotegerin;
- c. WNT-ligand;
- d. Sclerostin.

3. One of following treatments does not belong to the standard of care in MRONJ:

- a. Hyperbaric oxygen;
- b. Antibiotics;
- c. Sequestrectomy;
- d. Regional or distant soft tissue flaps.

4. XGEVA® is a:

- a. Nitrogen containing bisphosphonate;
- b. Non-nitrogen nitrogen containing bisphosphonate;
- c. Diphosphonic acid;
- d. Fully human monoclonal antibody to RANKL.



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