Masterclass in Clinical Practice

Implant Dentistry

with
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Dental implants and medication related osteonecrosis of the jaw (MRONJ)

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Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse drug reaction, consisting of progressive bone destruction in the maxillofacial region. In 2014 the nomenclature was changed from bisphosphonate-related osteonecrosis of the jaw (BRONJ) to MRONJ, to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive and antiangiogenic therapies.[1] Surgical trauma has been reported as one of the most important possible risk factors for the development of MRONJ. Therefore, the safety of dental implant placement in these patients has been the subject of controversial debate for several years and remains an ongoing source of uncertainty for dental practitioners.[2]

Definition of MRONJ

A diagnosis of MRONJ is based on the following criteria:

- Current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications.
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks.
- No history of radiation therapy to the jaws or metastatic disease to the jaws.[3]

A case of MRONJ is shown in Fig. 1. This 72 year-old female presented with an area of exposed bone on the left posterior lingual surface of the mandible for the past 3 months. Her medical history includes breast cancer, osteoarthritis, osteoporosis, back, hip and knee operations and the patient was receiving intravenous bisphosphonate therapy.

A staging system (stages 0-3) has been developed for MRONJ based on the symptoms, clinical and radiological findings. Treatment strategies for MRONJ varies depending on the stage.[3] Figures 2a-b show a case of MRONJ in a cancer patient who received intravenous BPs.

Antiresorptive and antiangiogenic medications: classification of drugs and pathophysiology

Antiresorptive medications, such as bisphosphonates (BPs), denosumab and angiogenesis inhibitors, have been widely used for treatment of osteoporosis, hypercalcemia caused by malignancies and skeletal-related events (bone pain and pathological fractures provoked by multiple myeloma and solid tumours). These medications have a unique risk factor for surgical interventions, as they all can induce MRONJ. Recently introduced medications such as neutralising antibodies to TNF-α, CD20 and sclerostin, and other

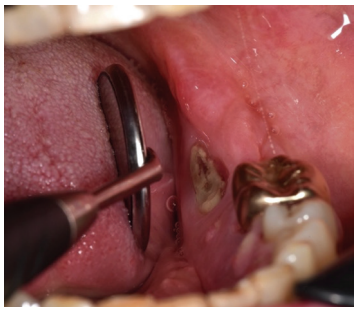

Figure 1: Clinical presentation of MRONJ after removal of a molar tooth

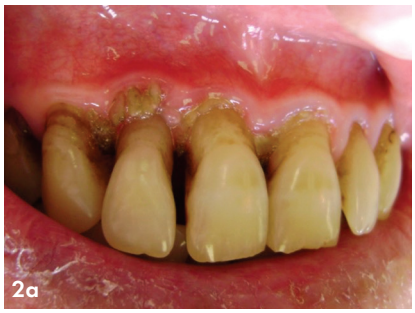

Figure 2a: Necrotic bone becoming exposed in a cancer patient with MRONJ after BP treatment

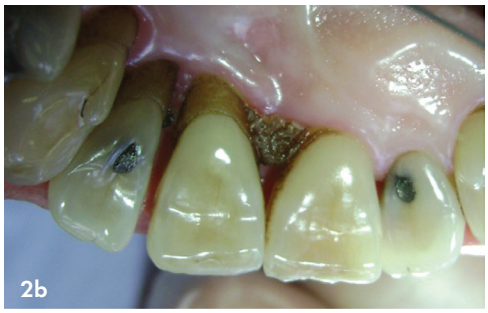

Figure 2b:Palatal view of necrotic bone between central incisors in same patient

molecular targeted drugs have also shown risk of inducing MRONJ[4], which implies that the number of MRONJ patients will increase due to more extensive use of antiresorptive medications for treatment of systemic diseases.

Bisphosphonates

BPs are potent inhibitors of osteoclast-mediated bone resorption, mainly acting by inhibiting protein prenylation in osteoclasts. When attached to hydroxyapatite within the bone matrix, BPs are encountered by active osteoclasts causing these cells to lose their ruffled border appearance, resulting in apoptosis of osteoclasts.[5] BPs have a wide therapeutical range including the management of cancer-related conditions, prevention of osteoporosis-related fractures and other metabolic bone diseases such as Paget`s disease and osteogenesis imperfecta.[3] Regarding the risk of developing MRONJ, it may depend on the route of administration (greater for intravenous versus oral), duration of the exposure and lifetime cumulative dose. The most often BPs administered orally – include alendronate (Fosamax®), risedronate (Actonel®) or parenterally (zoledronic acid [Reclast®]) and ibandronate (Boniva®).

Denosumab

Denosumab is a monoclonal antibody that binds the receptor activator of nuclear factor kB ligand (RANKL), blocking attachment to the receptor activator of nuclear factor kB (RANK), thus inhibiting osteoclast differentiation, which results in reduction of osteoclastic activity and bone resorption. [6] By preventing the activation of RANK, denosumab supresses the increased osteoclast activity in solid tumours with osseous metastases. Additionally, it prevents osteolysis and tumour progression in giant cell tumours of the bone that express RANKL and osteoclast-like giant cells that express RANK receptor.[7] Unlike BPs, denosumab does not bind to the bone and its effects on bone modelling mostly diminish within 6 months of treatment cessation.[3]

Angiogenesis inhibitors

Angiogenesis inhibitors have an impact on blood vessel formation and the signalling cascade. These agents bind to vascular endothelial growth factor (VEGF) leading to the interruption of vascular formation and, possibly, bone necrosis.[8] This group of medications include tyrosine kinase inhibitors (i.e. sunitinib), monoclonal antibody targeting VEGF (i.e. bevacizumab), the mammalian target of rapamycin inhibitors (i.e. everolimus) and VEGF decoy receptors (i.e. aflibercept). By interfering with tumour neo angiogenesis and consequent inhibition of collateral blood flow development, these medications cause the shrinkage of tumours. This antiangiogenic effect has similar consequences to the blood flow in jaws, resulting in MRONJ.[8]

Risk Factors for MRONJ

To estimate the risk for medications associated with MRONJ, the primary parameter to be considered is the therapeutic indication for treatment (eg, malignancy or osteoporosis/osteopenia). The risk of MRONJ is considerably higher in the malignancy group than in the osteoporosis group. Regardless of indications for therapy, the duration of antiresorptive therapy is a risk factor for developing MRONJ.[3]

Dentoalveolar operations are the most common identifiable predisposing factor for developing MRONJ. Studies report that among patients with MRONJ, tooth extraction was identified as the predisposing event in 62 to 82 percent of cases.[3] The risk of developing MRONJ among patients who have been exposed to antiresorptive medications for other dentoalveolar operations such as dental implant placement or periodontal procedures is unknown. The risk for MRONJ after implant placement among patients treated with denosumab has been reported to be 0.5 percent. These procedures should therefore be performed with caution in cancer patients exposed to antiresorptive therapies and osteoporosis patients should be informed of potential risks, including development of MRONJ, early and late implant failure.[3]

MRONJ is more likely to appear in the mandible than the maxilla but can appear in both jaws. Furthermore, pre-existing inflammatory dental disease such as periodontal disease or periapical pathology is considered a risk factor. Age and sex are variably reported as risk factors for MRONJ, with advanced age at higher risk. The higher prevalence of MRONJ in the female population is likely a reflection of the underlying disease for which the agents are being prescribed (eg, osteoporosis, breast cancer).[3]

Corticosteroids are associated with an increased risk for MRONJ. There are concerns that corticosteroids increase the risk for MRONJ when given in conjunction with antiresorptive agents. Comorbid conditions such as anemia and diabetes are inconsistently reported to be associated with an increased risk for MRONJ. Cancer type and tobacco use are variably reported as risk factors.[3]

Prevention of MRONJ in the dental implant patient

Dental implants have become the standard of care for replacing missing teeth. The success of this is due to the predictable bone healing around titanium and zirconia implants. Bone healing on dental implants is a process called osseointegration and refers to the direct healing of bone to the implant surface as seen under light microscopy. It therefore follows that anything interfering with bone healing, may interfere with the osseointegration process. BPs may interfere with the process of osseointegration.[9] In a recent systematic review it was shown that intravenous BPs versus oral treatment could have a much higher failure rate of dental implants (almost 9% compared to 1%).[10] It is therefore important to obtain a detailed history from the patient, alternatively from the treating oncologist in cancer patients as they tend to be treated with intravenous BPs.

Prevention of MRONJ has been shown to be possible in patients receiving BPs. In their systematic review, Gelazius et al (2018) showed that discontinuing BPs 3 months before implant placement and starting again 3 months post-surgery could prevent MRONJ. These patients were also covered with antibiotic treatment post-surgery.[10] Other studies have also shown treatment of dental implant patients on BP's is possible without complications.[11, 12]

There are however many variables/comorbidities such as periodontal disease, smoking, uncontrolled Diabetes, dental infections, corticosteroids and immunosuppressive conditions.[10] A careful medical history and clinical examination is imperative for prevention of complications in patients taking BPs.

Predicting MRONJ: Avoidance strategies

Due to the severity of MRONJ and the lack of successful treatment regimens once MRONJ develops, it is important to understand the most successful avoidance strategies:

- *CTX (Carboxy-terminal collagen crosslinks) test or as it is known in South Africa rather, Beta-Crosslaps:*

Over the past decades, serum levels of C-terminal telopeptide cross-link (CTX), a bone remodelling by-product has been punted as a reliable test to predict MRONJ. There seems to be no consensus however that this test is conclusive in predicting MRONJ, although a figure above 0.150 ng/ml is seen as safe with little to no risk and below 0.100 ng/ml is high risk.[13, 14, 15] The sensitivity of this has been shown to be 37.5% and specificity 57.7% but most patients who developed MRONJ had low CTX levels.[16] In the absence of other more reliable tests, it is still being used. A figure well above 150ng/ml indicates close to normal levels and safe for dental surgery, whereas one well below 100ng/ml should serve as a contra-indication for dental surgery.

- *Drug Holiday:*

This has been shown to increase the CTX levels and may prevent MRONJ, especially if the drug holiday is 3-6 months or longer.[9, 10] BPs should be discontinued 3-6 months before surgery and started again 3-6 months after surgery. Others have found that a short drug holiday has no benefit.[16]

- *Antibiotic cover:*

Antibiotic cover before, during and after surgery (Amoxicillin and Clavulanic acid) has been shown to prevent MRONJ, especially if used with a drug holiday.[9]

Conclusions

MRONJ is a serious complication after dental surgery, and especially so if the procedure was an elective one such as dental implant surgery. Clinicians should assess each case very carefully to identify comorbidities such as periodontal disease, smoking, diabetes, dental infections and immunosuppression.

It follows that factors such as bone type, presence and thickness of gingiva at implant site, healthy periodontium and smoking that may affect success rates in healthy individuals, will have so much more effect in patients on medication making them susceptible to MRONJ. Performing two stage dental implant placement compared to one stage, may also help, even if it is anecdotal. With the healing protected from oral bacteria in two stage surgery, it may just be the help that is needed for uneventful healing. Using implants with a proven design to prevent peri-implant bone loss, such as

a cone-in-cone abutment connection will lower changes of developing peri-implantitis which would be a risk for MRONJ.

Clinicians should make use of the Beta-Crosslaps blood test, but should caution patients that it is not a fool-proof test, merely an indicator. If the value is below 150ng/ml, it is recommended not to perform elective dental implant surgery. Should a patient request treatment with the full knowledge of potential complications, a drug holiday should be discussed with the treating physician, two stage placement protocol followed and elimination of all comorbidities performed before surgery. Antibiotic cover (Amoxicillin and Clavulanic acid) should be considered (unless a penicillin allergy is present), starting before surgery and continued post-surgery for a few days. Alternatives such as ciprofloxacin may be considered if a patient is allergic to penicillin.

Until such time that more definitive studies are done to provide guidance for this complex clinical dilemma, we will have to manage it as best possible with the knowledge set out above. Common sense should prevail.

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