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Clinical Practice Guidelines in Dental Management of Medication Related Osteonecrosis of Jaw (MRONJ)

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ABSTRACT

Medication-related osteonecrosis of the jaw (MRONJ) is a condition characterised by areas of necrotic bone in the maxillofacial region following exposure to antiresorptives or anti angiogenic agents. Bisphosphonates and denosumab are the most common drugs and are used to treat patients with metastatic bone cancer or osteoporosis. The major adverse effect of these drugs is that it exclusively affects the maxillofacial region leading to exposed necrotic jawbone accompanied with soft tissue infection and fistula formation. The condition is potentially painful and affects the quality-of-life Dentists play an important role in prevention, diagnosis and effectively managing the condition. Proper planning and executing the dental treatment are very essential as dentoalveolar surgeries also increase the risk of MRONJ. Thus, this study aims to describe a new clinical practice guideline with the available literature to establish a multidisciplinary standard approach to improve the patient's quality of life.

Key words: Osteonecrosis, Antiresorptives, Hypercalcemia, Oral surgery, Dentist

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INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is defined as an uncommon condition that occurs after exposure to agents which are used to prevent bone complications namely the bisphosphonates or treatment with angiogenesis inhibitors [1]. Major cases of MRONJ manifest as bone exposure in the maxillofacial region while cases with no clinical bone exposure have also been reported [2-5].

Antiresorptives medications commonly used are bisphosphonates and Rank-ligand inhibitors. Bisphosphonates are smaller molecules which lodges in the hydroxyapatite-binding sites present on bone surfaces. When osteoclasts begin to resorb this bone, the liberated bisphosphonates bind to farnesyl pyrophosphate synthase which is present inside the osteoclasts leading to apoptosis [6-8]. Bisphosphonates are prescribed in both intravenous and oral formulations depending on their purpose. Intravenous are used in management of hypercalcemia of malignancy, skeletal-related events (SRE) associated with bone metastases such as breast cancer, prostate cancer and lung cancers and multiple myeloma [9-12] while oral bisphosphonates are used for osteopenia, paget's disease, osteogenesis imperfecta [13].

Denosumab is a human monoclonal antibody and mode of action is different from bisphosphonates. It basically targets and binds to nuclear factor k-B (RANK) ligand (RANKL); thereby preventing the activation of RANK present on the surface of osteoclasts and osteoclast precursors. Inhibition of the RANKLRANK interaction impedes osteoclast formation, function, and survival thus bone resorption is reduced [14]. Denosumab are used to reduce risk of vertebral, non-vertebral, and hip fractures in osteoporotic patients skeletal-related events (SRE) associated with bone metastases [15].

Anti-angiogenic agents have angiogenesis inhibitors which interferes with the formation of new blood vessels by binding to various signaling molecules thus disrupting the

angiogenesis-signaling cascade [16] and are used in management of renal cell carcinoma, gastrointestinal stromal tumor, neuroendocrine tumor, hepatocellular carcinoma, thyroid cancer ,metastatic colorectal cancer, non-squamous, non-small cell lung cancer ,glioblastoma and cervical cancer [17].

The epidemiology and pathophysiology of MRONJ are not clearly explained. Current studies states that there is necrosis which may be a result of suppression of bone turnover, inhibition of angiogenesis, toxic effects on soft tissue, inflammation or infection [18]. Etiology of the disease is multifactorial which can be influenced by genetic and immunological factors [19].

MRONJ mostly occurs following a dental treatment that impacts the bone and may also occur spontaneously [20]. Signs and symptoms are soft tissue infection and swelling, delayed healing following a dental extraction or other oral surgery procedures, pain, numbness, paraesthesia or exposed bone [21]. They may also experience pain or altered sensation in the absence of exposed bone. In some cases, MRONJ may be only an incidental finding as the patient may be asymptomatic [22].

Prior to commencement of antiresorptives and angiogenic drugs dental screening and adequate treatment are essential to reduce the risk of MRONJ [23,24]. It is also the responsibility of the physician to educate the patient about MRONJ and the importance of a complete oral health examination prior to commencing, during and after the treatment with those drugs, in order to eliminate any infective outbreaks of MRONJ [25]. It is the role of the dentist to remove the risk factors and stress the importance of maintaining good oral hygiene with regular dental visits. Thus, this study aims to describe a new clinical practice guideline with the available literature to establish a multidisciplinary standard approach in order to improve the patient's quality of life.

Our recent research portfolio slides numerous articles in reputed journals [26-30]. Based on this experience we planned to pursue Clinical practice guidelines in dental management of Medication-related osteonecrosis of the jaw (MRONJ).

DIAGNOSIS AND STAGING

The American Association of Oral and Maxillofacial Surgeons proposes the following criteria for the diagnosis of MRONJ [31]:

Current or any previous treatment with antiresorptive or antiangiogenic agents.

Bone exposure or an intraoral or extraoral fistula in the maxillofacial region through which the bone can be probed and is present for more than eight weeks.

No obvious metastatic disease or radiation history to the jaws.

Radiographic findings are variable and may include

Altered bony trabeculae with mottled osteosclerotic changes.

Bone sequestra and osteolytic changes.

Thickened lamina dura and narrowed periodontal ligament space.

Persistent rarefaction at the site of dental extractions (≥ 6 months after extraction).

At risk- No clinical or radiographic changes consistent with MRONJ in patients who have been treated with either oral or IV bisphosphonates.

Stage 0- No clinical evidence of necrotic bone, but radiographic changes, symptoms, and nonspecific clinical findings consistent with MRONJ assuming other possible odontogenic causes have been excluded.

Stage 1-Asymptomatic, exposed bone, or fistulae that probes to bone, with no evidence of infection.

Stage 2-Exposed and necrotic bone, or fistulae that probes to bone, with pain, erythema, and infection with or without purulent drainage.

Stage 3-Exposed and necrotic bone or a fistula that probes to bone with pain, erythema, and infection and one or more of the following: Exposed and necrotic bone extending beyond the region of alveolar bone resulting in pathologic fracture, extra-oral fistula, oral antral or oral nasal communication or osteolysis.

Clinical practice guidelines for dental treatment

Pre-treatment phase.

In-treatment phase.

Post treatment phase.

Established MRONJ.

Pretreatment phase

Salgerollo et al. in his study of 773 patients reported the need for educating and maintaining good oral hygiene in patients who are about to commence their treatment with anti-angiogenic and antiresorptive drugs [32]. Scottish guideline also emphasis the need for patient education regarding the benefits, adverse effects of the drugs and importance of oral hygiene [33].

Discussion with patients

Inform the patient risk of MRONJ and it is usually caused due to their anti-resorptive and anti-angiogenic drugs.

Discuss the benefits of anti-resorptive and anti-angiogenic drugs and thus it should be continued.

Healthy diet with reduced sugar containing food.

Maintaining good oral hygiene.

Using fluoride toothpaste and mouthwash.

Avoid smoking and alcohol.

Periodic dental checkups.

Inform patients with dental implants placed prior to commencement with the drugs, of the small risk of MRONJ at those sites and ensure excellent oral hygiene at implant site(s) [1].

Immediate reporting of pain/swelling, loose teeth, exposed bone, pus/discharge, non-healing sores or lesions, altered sensation, tingling, numbness [34].

Dental treatment

Long standing dental caries and periodontal infections can lead to periapical infections which may poses a risk for necrosis [35,36]. Literatures have reported that 11.2% of necrosis was related to periodontal surgeries [36]. Extractions are an invasive dental procedure and all teeth with poor prognosis must be removed [37]. Bone necrosis following a dentoalveolar surgery is due to lack of normal healing of the bone and its surrounding tissue because of low cellular proliferative capacity [38]. Thus, it is essential to achieve primary wound closure in these patients.

Appropriate radiographs for diagnosis of any infections and pathology.

Extract any teeth of poor prognosis.

Elective dentoalveolar surgery can be performed.

Dental prophylaxis, caries control, conservative & restorative therapy.

Ill-fitting/ damaged dentures should be adjusted or replaced.

Dental implants should be avoided.

Prescribe high fluoride toothpaste.

Initiation of therapy must be delayed until oral health is optimized (i.e) until the dental extraction site has mucolized (14-21 days) or when there is adequate osseous healing [39].

In treatment phase

Bisphosphanates and denosumab are treated for both oncogenic and non-oncogenic causes. The risk assessment for treatment is greatly influenced by the type of underlying medical condition. Dental extractions or dental procedures that impact the bone is considered as a risk factor of developing MRONJ in patients consuming these drugs and it's not a cause of the disease [40]. Literature reports following a tooth extraction 2.9% incidence of MRONJ in cancer patients, 0.15% osteoporosis patients [41,24]. Spontaneous development of MRONJ without any invasive dental treatment have also been reported [18]. Studies have reported increased risk of MRONJ with concurrent management with systemic glucocorticoids, combined therapy of bisphosphonates and anti-angiogenic drugs [24,42-44]. Irrespective of drug holiday there is no evidence of decreased risk for MRONJ in patients on bisphosphonates as the drug persists in skeletal issues for years [37]. Depending upon the medical status and need for dental treatment, the dentist with close liaison to the medical practitioner should decide a drug holiday. Denosumab's effect on bone turnover is eliminated from the body within 9 months of treatment completion [45].

Patient history including past, present and future use of anti-resorptive or anti-angiogenic drugs including their duration.

Low risk patients

Maintaining good oral hygiene & dental care.

Dental prophylaxis, caries control, conservative & restorative therapy.

Atraumatic surgical procedures.

File any sharp edges and remove any unsupported bone fragments.

Following the extraction, gently curette the socket and irrigate with saline.

Try to achieve primary closure if possible.

Prescribe antibiotic therapy (e.g., amoxicillin 500 mg TID or clindamycin 300 mg TID) for at least two weeks following the surgical procedure.

Prescribe 0.12% chlorhexidine mouth rinse BID [46,47].

Re-evaluate the extraction site in approximately two weeks to ensure adequate healing, with additional follow-up scheduled as needed.

If the extraction socket is not healed at 8 weeks, then should be suspected for MRONJ.

Patients with dental implants have a possible risk of developing osteonecrosis, any such noticed consider alternate drugs or a drug holiday [47].

High risk patients

Dental prophylaxis, caries control, conservative & restorative therapy.

Atraumatic surgical procedures.

File any sharp edges and remove any unsupported bone fragments.

Following the extraction, gently curette the socket and irrigate with saline.

Try to achieve primary closure if possible.

Prescribe antibiotic therapy (e.g., amoxicillin 500 mg TID or clindamycin 300 mg TID) for at least two weeks following the surgical procedure.

Prescribe 0.12% chlorhexidine mouth rinse BID [46,47].

Re-evaluate the extraction site in approximately two weeks to ensure adequate healing, with additional follow-up scheduled as needed.

If the extraction socket is not healed at 8 weeks, then should be suspected for MRONJ.

Any elective dentoalveolar surgery procedure should be performed with a drug holiday of 2 months prior to the procedure and 3 months after [47].

Post treatment phase

Patients with an established history should be considered as either low or high risk according to their medicine used and successive dental treatment should be carried.

If a patient has consumed bisphosphonates in their past or denosumab in the past nine months, consider them as if they are still taking the drugs and allocate them as a risk group.

Patients who have previously taken anti-angiogenic drugs in combination with antiresorptive drugs should be allocated to a risk group based on their history of antiresorptive drug use.

Established MRONJ patients

Main treatment objective of these patients includes eliminating pain, control infection of hard and soft tissues and minimize progression or occurrence of necrosis.

Constant source of soft tissue irritation and loose bony sequestra should be removed or recontoured to achieve soft tissue healing and can be performed at any stage of disease.

Presence of symptomatic teeth within the exposed necrotic bone can be extracted with a good antibiotic coverage [48].

CONCLUSION

MRONJ is a serious disorder of maxillofacial region which affects the quality of life to a greater extent. Dentists play a major role in prevention of MRONJ in patients consuming antiresorptives and anti-angiogenic drugs, in early identification of the condition and performing dental treatment for established patients. The dental treatment plan varies for each patient according to their drug, dosage, treatment phase and comorbidities. The clinical practice guidelines only help the clinician to assess and formulate a treatment plan but as each patient is unique the dentist should make a wise decision considering all other factors and treat the patients efficiently.

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AUTHOR CONTRIBUTIONS

Manivasagam Deepigaa has made substantial contributions to the research design, acquisition and analysis of data, and to drafting the paper and revising it critically.

Muthukrishnan Arvind has made substantial contributions to the research design, acquisition and analysis of data, and to drafting the paper

and revising it critically.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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