The Adjunctive Treatment of Low Level Laser Therapy in Medication related Osteonecrosis of The Jaws

Revina Daniella Dwi March
Dentistry Program, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
*Correspondence author email: Annabellrevina@gmail.com

Abstract

Introduction: Low level laser therapy (LLLT) is the direct application of light to stimulate responses to promote tissue healing, reduce inflammation and pain relief. It is called photobiomodulation due to anti-inflammatory properties and encourage mucosal repair. Medication related osteonecrosis of the jaws (MRONJ) represents an adverse drug reaction, consisting of progressive bone destruction in the mandible or maxilla. The treatment modality of this condition is still challenging. Methods: PubMed and Scopus were searched for published articles that have relevance to medication related osteonecrosis of the jaws and low level laser therapy. In vitro and animal studies were excluded. Eleven articles published between 2014 and 2022 were included in this review. Results: LLLT used as adjunctive therapy for MRONJ produced the improvement of pain, swelling, infection control, faster healing, repair of mucosa, bone regeneration, and prevent patient’s MRONJ stage evolution. Conclusion: The low level laser therapy used as adjunctive treatment in osteonecrosis may be considered as efficient promising option to treat MRONJ in stage II and III.

Keywords: Low level laser therapy; osteonecrosis; pain relief

Introduction

Medication related osteonecrosis of the jaw (MRONJ) is defined as necrotic exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that persists for more than eight weeks in a patient on current or previous anti-resorptive or anti-angiogenic agents in the absence of previous radiation without obvious metastatic disease. This chronic condition is extremely painful, causing halitosis and difficulty while eating and speaking. Clinically, the lesions appeared as oral mucosal ulcerations that expose the underlying bone. MRONJ occurs more commonly in the mandible than in the maxilla, which considered to be a consequence of relatively low mandibular bone’s vascularization in response to the injury. The exposed bone might occur spontaneously and often following an invasive dental procedure.

The pathogenesis of MRONJ is considered to be multifactorial as well as involving a synergistic effect between inflammation and infection. Extraction of teeth with advanced
dental disease and the presence of periapical or periodontal infection associated with the occurrence of inflammation infection. Inability of the alveolar bone to respond the injury and its incapacity to heal after surgical procedures. Furthermore, the exposed bones are susceptible to bacterial colonization and infection, specifically Gram positive actinomycetes.\textsuperscript{4,5}

MRONJ is an adverse reaction to several drugs used to control disorder of bone metabolism and malignancy related to bone tissue.\textsuperscript{6} Drugs that cause MRONJ are grouped into two categories, such as bisphosphonates (BPs) and non bisphosphonates, including other antiangiogenic or antiresorptive medications.\textsuperscript{7} Biphosphonates (BPs) are the most commonly used antiresorptive to prevent skeletal complications in multiple myeloma and metastatic bone cancers as well as to treat bone disorders such as osteoporosis, osteopenia, and Paget’s disease. Bisphosphonates are antiresorptive, antiangiogenic, and synthetic drugs analogous to the inorganic pyrophosphate, an endogenous bone mineralization regulator. These antiresorptive agents inhibit the normal bone resorption activity of osteoclasts. The risk of using injectable biphosphonates in patients with malignant tumors is significantly higher than using oral BPs for patients with osteoporosis.\textsuperscript{8,9} Denosumab is a fully human monoclonal antibody, which has a different mode of action from bisphosphonates. It targets and binds to the RANKL; in doing so it prevents the activations of RANK on the surface of osteoclast precursors. Inhibition of the RANKL-RANK interaction impedes osteoclast formation, function, and survival, thereby decreasing bone resorption.\textsuperscript{10}

The treatment goal for the patients confirmed with MRONJ is to relieve the pain, control infection in soft and hard tissue, and decrease the progress or occurrence of osteonecrosis.\textsuperscript{11} Clinical manifestation, stages, and symptoms of MRONJ affected the treatment option, such as non-surgical management with antibiotic medication, oral bactericidal mouth wash, surgical procedure and debridement of extensive lesions.\textsuperscript{12} Temporary relief by minimizing symptoms and infections may be obtained by conservative approach, but the effectiveness cannot be expected to be successfully resolved.\textsuperscript{13} Therefore, the technique used as adjuvant therapy to surgery, which has improved the results of surgical treatment to reduce period of time for wound healing.\textsuperscript{14}

Low-level laser (light) therapy (LLLT) refers to many types of therapy based on photobiomodulation, a process that cause biological alterations in organisms due to photon interaction with atoms or molecules.\textsuperscript{15} Low-level laser therapy (LLLT) is an emerging, non-
invasive alternative treatment with some efficacy in relieving musculoskeletal or neuropathic pain and improving the quality of life.\textsuperscript{16-23} LLLT (as well as cold laser therapy, therapeutic laser therapy, soft laser therapy) also called as photobiomodulation was categorized as a non-invasive and safe method. The photobiomodulation laser used red light (600-700) nm and infrared light (770-1200) nm in most cases to reduce inflammation, decrease pain level and stimulate the process of healing.\textsuperscript{24,25} This study aimed to review the efficacy of low level laser therapy as adjunctive treatment in medication related osteonecrosis of the jaws.

\textbf{Methods}

This narrative review was conducted using database search on PubMed and Scopus. Articles that were published between 2014 and 2022 included for the preparation of this study. The inclusion criteria comprised case report article and retrospective cohort study that analyzed the treatment outcomes for medication related osteonecrosis of the jaw (MRONJ) utilized low level laser therapy as the adjunctive treatment. The subject or population of the study should be presenting MRONJ symptoms stage II and III based on AAOMS (2014). The terms used for the search were as follows: “osteonecrosis”, “MRONJ (medication related osteonecrosis of the jaw)”, “bisphosphonates”, “photobiomodulation”, “low level laser therapy”, “low level laser treatment”, “cold laser”. In vitro and animal studies were excluded in this study.

\textbf{Discussions}

Medication-related osteonecrosis of the jaw (MRONJ) is a pathological condition with clinical signs exhibiting bone exposure, intraoral or extraoral fistula as consequence of antiresorptive or antiangogenic drugs.\textsuperscript{26} Bisphosphonates (BPs) are medically used to prevent bone complications in metastatic bone cancer, multiple myeloma, and bone resorption in the treatment of osteoporosis.\textsuperscript{27} Accordingly, it changes the normal bone metabolism. Bone is constantly undergoing remodeling through bone resorption and deposition. These drugs inhibit osteoclast activity and preventing bone breakdown. Osteoblast activity was also interrupted, which in turn secondarily affecting osteoclast activity. Some literatures suggest that bisphosphonates also affect soft tissue wound healing cell which lead to the complex process of this lesion.\textsuperscript{28}
The diagnostic criteria of MRONJ according to The American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014 and the Korean Society for Bone and Mineral Research (KSBMR) and the Korean Association of Oral and Maxillofacial Surgeons (KAOMS) in 2015 as follows: (1) if there is a history of using a bone resorption inhibitor or an angiogenesis inhibitor; (2) if there is no history of radiation therapy to the jaw, exposure of the jaw, or oral or extraoral fistula lasting more than eight weeks; (3) if there is no history of radiation therapy to the jaw or obvious metastatic disease of the jaw. Reports in the current review presented zoledronic acid as commonly used bisphosphonates, followed by ibandronate, alendronate, and risedronate. The administration route of zoledronic acid was intravenous, meanwhile the others were orally. The development risk of MRONJ in bisphosphonates users depends on the type of of bisphosphonates, duration of treatment, and route of administration. The risk of developing MRONJ was described higher in cases with intravenous administration. A rare case reported the association between an antineoplastic therapy, lenvatinib and MRONJ. Lenvatinib is a novel multitarget drug from the family of RTKI, directed mainly to vascular endothelial growth factor receptors, but also fibroblast growth factor receptors (FGF), platelet-derived growth factor receptor-alpha (PDGF), RET and KIT proto-oncogenes, showing antiangiogenic properties and potent anti-tumor activity. The reported patient previously had a follicular thyroid carcinoma with bony metastases and taken the lenvanitib 24 mg orally once a month. Treatment of MRONJ was usually found to be difficult to ensure the complete resolution of this condition. The therapeutic strategy for MRONJ was established regarding to the stage of disease and divided into three stages. Patient was diagnosed with stage 0, if there was no clinical evidence of necrotic bone but have nonspecific clinical and radiographic finding such as pain and change in the bony trabecular pattern of the jaws. It was categorized as stage 1, if the patient have exposed and necrotic bone who are asymptomatic and show no sign of infection. The patients who have exposed and necrotic bone are symptomatic with pain and infection, were diagnosed with stage 2. More advance stage was stage 3, if the patients have exposed and necrotic bone who are symptomatic with pain and infection and one or more following: extraoral fistula, pathologic fracture, exposed and necrotic bone extending beyond the alveolar bone, oro-antral or oro-nasal communication, and osteolysis extending to the inferior border of the mandible or maxillary sinus floor. In this study,
most of the cases were diagnosed MRONJ stage II, followed by stage III. The surgical treatment is achieved through sequestrectomy of necrotic bone with antibiotic medication and antiseptic mouth rinsing, combined with adjunctive treatments. Some studies reported higher success result of adjunctive therapy with low-level laser therapy.\(^{32}\)

According to the Clinical Practice Guidelines of the MASCC/ISOO/ ASCO, for patients with confirmed MRONJ, the treatment goal is to relieve the pain, control infection in soft and hard tissues, and decrease the progress or occurrence of osteonecrosis.\(^{33}\) Low-level laser therapy, known as low dose laser therapy, low-light laser therapy (LLLT) or photobiomodulation has been used to treat patients with various diseases and conditions. The effects of LLLT included improving wound healing, pain relief, increase fibroblast and chondroblast proliferation, collagen synthesis, stimulation of osteogenesis, bone cells differentiation as well as decrease inflammation and faster epithelization. Laser devices have been presented as useful tools for the treatment of MRONJ by providing biomodulation in hard and soft tissue, then the removal of necrotic bone by vaporization.\(^{34-36}\)

Based on the results (Table 1), the LLLT used as adjunctive therapy for MRONJ stage II presented improvement of pain, swelling, infection control, faster healing, repair of mucosa, as well as it prevented the patient’s evolution from stage 2 to stage 3. Based on the articles described the treatment of MRONJ stage III, low level laser therapy presented complete mucosal healing, bone regeneration, immediate relief, and absence of the symptoms. Photobiomodulation (PBM) has been shown to be a promising non-surgical modality for treating the primary stages of MRONJ lesions, 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. Therefore, the healing and repair of the affected bone was improved the patient’s quality of life.\(^{37}\) Therefore, LLLT could be a promising adjuvant treatment for MRONJ due to its ability to modulate the cellular metabolism, improve the wound healing, and relieve pain.\(^{44}\) The combination of two or more approaches that involved non-surgical and surgical procedures showed an increase in the clinical success rates of MRONJ treatment.\(^{50}\)
Conclusion

Various effects of low level laser therapy consisted of pain relief, infection control, faster healing, and bone regeneration. The low level laser therapy used as adjunctive treatment in MRONJ cases based on the scientific results in this review may be considered as efficient and it is a promising option to treat this pathological condition. The combined therapy for MRONJ stage II and III resulted successful treatment.

References

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