Sriwijaya Journal of Dentistry

**Sriwijaya Journal of Dentistry (SJD)**
**Volume 3 Issue 1 2022 :23-31**
**https://jurnalkedokteranunsri.id/index.php/SJD/index**

# 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.[1] 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.[2,3]

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.[4,5]

MRONJ is an adverse reaction to several drugs used to control disorder of bone metabolism and malignancy related to bone tissue.[6] Drugs that cause MRONJ are grouped into two categories, such as bisphosphonates (BPs) and non bisphosphonates, including other antiangiogenic or antiresorptive medications.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.[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.[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.[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.[12] Temporary relief by minimizing symptoms and infections may be obtained by conservative approach, but the effectiveness cannot be expected to be successfully resolved.[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.[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.[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.[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.[24,25] This study aimed to review the efficacy of low level laser therapy as adjunctive treatment in medication related osteonecrosis of the jaws.

## 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.

## 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.[26] Bisphosphonates (BPs) are medically used to prevent bone complications in metastatic bone cancer, multiple myeloma, and bone resorption in the treatment of osteoporosis.[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.[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.[29,30]

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.[49] 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.[46]

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.[28,31] 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


1. Mehra P, D'Innocenzo R. Manual of minor oral surgery for the general dentist. John Wiley & Sons; 2015 Aug 3.
2. Hupp JR, Tucker MR, Ellis E. Contemporary oral and maxillofacial surgery. Mosby; 2017.
3. El-Rabbany M, Sgro A, Lam DK, Shah PS, Azarpazhooh A. Effectiveness of treatments for medication-related osteonecrosis of the jaw: A systematic review and meta-analysis. J Am Dent Assoc. 2017;148(8):584-594.e582.
4. Aghaloo T, Hazboun R, Tetradis S. Pathophysiology of osteonecrosis of the jaws. Oral and Maxillofacial Surgery Clinics. 2015;27(4):489-96.
5. Hallmer F, Bjørnland T, Andersson G, Becktor JP, Kristoffersen AK, Enersen M. Bacterial diversity in medication-related osteonecrosis of the jaw. Oral surgery, oral medicine, oral pathology and oral radiology. 2017;123(4):436-44.
6. Minamisako MC, Ribeiro GH, Lisboa ML, Mariela Rodríguez Cordeiro M, Grando LJ. Medication-related osteonecrosis of jaws: a low-level laser therapy and antimicrobial photodynamic therapy case approach. Case reports in dentistry. 2016;2016.
7. Li FL, Wu CB, Sun HJ, Zhou Q. Effectiveness of laser-assisted treatments for medication-related osteonecrosis of the jaw: a systematic review. British Journal of Oral and Maxillofacial Surgery. 2020;58(3):256-67.
8. Hasegawa T, Hayashida S, Kondo E, Takeda Y, Miyamoto H, Kawaoka Y, et al. Medication-related osteonecrosis of the jaw after tooth extraction in cancer patients: a multicenter retrospective study. Osteoporos Int. 2019;30:231-239.
9. Şahin O, Tatar B, Ekmekcioğlu C, Aliyev T, Odabaşı O. Prevention of medication related osteonecrosis of the jaw after dentoalveolar surgery: An institution's experience. Journal of Clinical and Experimental Dentistry. 2020;12(8):e771.
10. Şahin O, Akan E, Tatar B, Ekmekcioğlu C, Ünal N, Odabaşı O. Combined approach to treatment of advanced stages of medication-related osteonecrosis of the jaw patients. Brazilian Journal of Otorhinolaryngology. 2022;88:613-20.
11. Dodson TB. The frequency of medication-related osteonecrosis of the jaw and its associated risk factors. Oral and Maxillofacial Surgery Clinics. 2015;27(4):509-16.
12. Nicolatou-Galitis O, Schiødt M, Mendes RA, Ripamonti C, Hope S, Drudge-Coates L, Niepel D, Van den Wyngaert T. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2019;127(2):117-35.

13. Shapiro CL, Yarom N, Peterson DE, Bohlke K, Saunders DP. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO Clinical Practice Guideline Summary. Journal of Oncology Practice. 2019;15(11):603-6.
14. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. Journal of Bone and Mineral Research. 2015;30(1):3-23.
15. Coropciuc RG, Grisar K, Aerden T, Schol M, Schoenaers J, Politis C. Medication-related osteonecrosis of the jaw in oncological patients with skeletal metastases: conservative treatment is effective up to stage 2. British Journal of Oral and Maxillofacial Surgery. 2017;55(8):787-92.
16. Momesso GA, de Souza Batista FR, de Sousa CA, de Lima VN, Polo TO, Hassumi JS, Júnior IR, Faverani LP. Successful use of lower-level laser therapy in the treatment of medication-related osteonecrosis of the jaw. Journal of Lasers in Medical Sciences. 2017;8(4):201.
17. Hamblin MR, Agrawal T, de Sousa M, editors. Handbook of low-level laser therapy. CRC Press; 2016.
18. de Andrade AL, Bossini PS, Parizotto NA. Use of low level laser therapy to control neuropathic pain: a systematic review. Journal of Photochemistry and Photobiology B: Biology. 2016;164:36-42.
19. Chen YJ, Liao CD, Hong JP, Hsu WC, Wu CW, Chen HC. Effects of laser therapy on chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. Clinical Rehabilitation. 2022;36(3):289-302.
20. Clijsen R, Brunner A, Barbero M, Clarys P, Taeymans J. Effects of low-level laser therapy on pain in patients with musculoskeletal disorders: a systematic review and meta-analysis. European Journal of physical and rehabilitation medicine. 2017;53(4):603-10.
21. Deana NF, Zaror C, Sandoval P, Alves N. Effectiveness of low-level laser therapy in reducing orthodontic pain: a systematic review and meta-analysis. Pain Research and Management. 2017;2017.
22. Huisstede BM, Hoogvliet P, Franke TP, Randsdorp MS, Koes BW. Carpal tunnel syndrome: effectiveness of physical therapy and electrophysical modalities. An updated systematic review of randomized controlled trials. Archives of Physical Medicine and Rehabilitation. 2018;99(8):1623-34.
23. Yeh SW, Chien-Hsiung H, Shih MC, Tam KW, Huang YH, Yi-Chun K. Low-level laser therapy for fibromyalgia: a systematic review and meta-analysis. Pain Physician. 2019;22(3):241.
24. Anders JJ, Lanzafame RJ, Arany PR. Low-level light/laser therapy versus photobiomodulation therapy. Photomedicine and Laser Surgery. 2015;33(4):183-4.
25. Hamblin MR. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. AIMS Biophysics. 2017;4(3):337.
26. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. Journal of Oral and Maxillofacial Surgery. 2014;72(10):1938-56.
27. Clézardin P. Mechanisms of action of bisphosphonates in oncology: a scientific concept evolving from antiresorptive to anticancer activities. BoneKEy reports. 2013;2:267.

28. Miloro M. Peterson's principles of oral and maxillofacial surgery. Ghali GE, Larsen PE, Waite PD, editors. Hamilton: BC Decker; 2022.
29. Kim KM, Rhee Y, Kwon YD, Kwon TG, Lee JK, Kim DY. Medication related osteonecrosis of the jaw: 2015 position statement of the Korean Society for Bone and Mineral Research and the Korean Association of Oral and Maxillofacial Surgeons. Journal of Bone Metabolism. 2015;22(4):151-65.
30. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. Journal of Oral and Maxillofacial Surgery. 2014;72(10):1938-56.
31. Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L, Pompa G. Medication-related osteonecrosis of the jaw: Clinical and practical guidelines. Journal of International Society of Preventive & Community Dentistry. 2016;6(2):97.
32. Kim JW, Kim SJ, Kim MR. Leucocyte-rich and platelet-rich fibrin for the treatment of bisphosphonate-related osteonecrosis of the jaw: a prospective feasibility study. British Journal of Oral and Maxillofacial Surgery. 2014;52(9):854-9.
33. Shapiro CL, Yarom N, Peterson DE, Bohlke K, Saunders DP. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO Clinical Practice Guideline Summary. Journal of Oncology Practice. 2019;15(11):603-6
34. Li FL, Wu CB, Sun HJ, Zhou Q. Effectiveness of laser-assisted treatments for medication-related osteonecrosis of the jaw: a systematic review. Br J Oral Maxillofac Surg. 2020;58:256-67.
35. Momesso GAC, Lemos CAA, Santiago-Júnior JF, Faverani LP, Pel-lizzer EP. Laser surgery in management of medication-relatedosteonecrosis of the jaws: a meta-analysis. Oral Maxillofac Surg.2020;24:133-44.
36. Carroll JD, Milward MR, Cooper PR, Hadis M, Palin WM. Developments in low level light therapy (LLLT) for dentistry. Dental Materials. 2014;30(5):465-75.
37. Vallejo-Rosero KA, Veronese HR, Dias EM. Medication-Related Osteonecrosis of the Jaw (MRONJ) Treatment: An Update.2022
38. Rodríguez-Sánchez MD, Statkievicz C, de Mello-Neto JM, Toro LF, Bassi AP, Garcia VG, Theodoro LH, Ervolino E. The effectiveness of the low-level laser, antibiotic and surgical therapy in the treatment of medication-related osteonecrosis of the jaws: A case report. Journal of Lasers in Medical Sciences. 2020;11(1):98.
39. Şahin O, Akan E, Tatar B, Ekmekcioğlu C, Ünal N, Odabaşı O. Combined approach to treatment of advanced stages of medication-related osteonecrosis of the jaw patients. Brazilian Journal of Otorhinolaryngology. 2022;88:613-20.
40. Torres AA, De Freitas BL, Carneiro PP, de Sousa AL, Ferraz MÂ, de Pinho Mendes J, Costa AL, Pinto AS. Medication-related osteonecrosis of the jaw and low-level laser therapy as adjuvant treatment: A case report. Journal of Lasers in Medical Sciences. 2020;11(4):497.
41. da Silva FD, Dias GF. Medication-Related Osteonecrosis: A Clinical Case Report. Global Journal of Oral Science. 2021;7:41-7.
42. Minamisako MC, Ribeiro GH, Lisboa ML, Mariela Rodríguez Cordeiro M, Grando LJ. Medication-related osteonecrosis of jaws: a low-level laser therapy and antimicrobial photodynamic therapy case approach. Case Reports in Dentistry. 2016;2016.

43. Fornaini C, Cella L, Oppici A, Parlatore A, Clini F, Fontana M, Lagori G, Merigo E. Laser and platelet-rich plasma to treat medication-related osteonecrosis of the jaws (MRONJ): a case report. Laser Therapy. 2017;26(3):223-7.
44. Momesso GA, de Souza Batista FR, de Sousa CA, de Lima VN, Polo TO, Hassumi JS, Júnior IR, Faverani LP. Successful use of lower-level laser therapy in the treatment of medication-related osteonecrosis of the jaw. Journal of Lasers in Medical Sciences. 2017;8(4):201.
45. Altay MA, Tasar F, Tosun E, Kan B. Low-level laser therapy supported surgical treatment of bisphosphonate related osteonecrosis of jaws: a retrospective analysis of 11 cases. Photomedicine and Laser Surgery. 2014;32(8):468-75.
46. Monteiro L, Vasconcelos C, Pacheco JJ, Salazar F. Photobiomodulation laser therapy in a Lenvatinib-related osteonecrosis of the jaw: A case report. Journal of Clinical and Experimental Dentistry. 2021;13(6):e626.
47. da Silva-Souza LG, de Oliveira LD, Nunes GP, dos Santos Cividanes L, Dahan CM, Pereira AK, Kitakawa D, Neder VM, e Silva LF. Effectiveness of the low-level laser therapy in the management of bisphosphonate-induced osteonecrosis of the jaws: A case report. Research, Society and Development. 2021;10(6):e17510615199.
48. Vescovi P, Giovannacci I, Otto S, Manfredi M, Merigo E, Fornaini C, Nammour S, Meleti M. Medication-related osteonecrosis of the jaw: an autofluorescence-guided surgical approach performed with Er: YAG laser. Photomedicine and Laser Surgery. 2015;33(8):437-42.
49. Son HJ, Kim JW, Kim SJ. Pharmacoepidemiology and clinical characteristics of medication-related osteonecrosis of the jaw. Maxillofacial Plastic and Reconstructive Surgery. 2019;41(1):1-7.
50. Vallejo-Rosero KA, Veronese HR, Dias EM. Medication-related osteonecrosis of the jaw (mronj) treatment: an update. Natl J Maxillofac Surg. 2022;13(1):5-10.