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REVIEW ARTICLE

Low-level Laser Therapy: A Literature Review

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ABSTRACT

LASER is an acronym for "Light Amplification by Stimulated Emission of Radiation." The arena of lasers has expanded to include light-emitting diodes and other sources of light. Various wavelengths used are in the range of red and near infrared spectrum. Each wavelength has a unique interaction with the respective target tissues. High doses of laser have certain drawbacks and, in order to overcome these issues, widespread research is going on low-level laser therapy (LLLT). Low-level laser therapy results in direct biostimulation action on various cells of the body. It is reported that LLLT could enhance the process of wound healing and also has stimulating effects on bone cells and can hasten the repair process of the bone. In spite of many reports of affirmative findings from experiments conducted *in vitro*, in animal models, and in randomized controlled clinical trials, the effects of LLLT remain debatable. On the contrary, additional research still needs to be done in order to check the efficacy for periodontal treatment. This article focuses on the effects of LLLT on various tissues, its dosage, mechanisms of action, and applications in the field of dentistry.

Keywords: Biostimulation, Low-level laser therapy, Wound healing.

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INTRODUCTION

LASER is an acronym for "Light Amplification by Stimulated Emission of Radiation" and has been widely used in dentistry for more than 30 years. The light produced by laser is powerful as it has three distinctive properties, namely, the light is monochromatic, coherent, and collimated. The first LASER or "Microwave amplification by stimulated emission of radiation (MASER)" was developed by Theodore H. Maiman in the year 1960. Lasers are classified as hard and soft tissue lasers based on the type of laser–tissue interaction and not on the type of tissue exposed. Low-level laser therapy (LLLT) is a form of laser medicine used in physical therapy, which uses low-level lasers or light-emitting diode to alter cellular functions. Low-level laser therapy has various other names like low-power laser, soft tissue lasers, cold lasers, biostimulation laser, therapeutic laser, and laser acupuncture. The average power of laser ranges from 1 to 500 mW and the wavelength ranges from red to near infrared, i.e., 600 to 1000 nm. Whereas high-power lasers ablate tissue, low-power lasers stimulate various tissues and encourage the cells to function. Low-level laser therapy is a noninvasive and painless process that uses photonic energy to provide biological therapeutic advantages, including analgesic effects. It is used in the management of indolent or infected wounds, tissue necrosis, nerve injury, and osteoarthritis or other chronic pain syndromes, such as myofacial pain, fracture healing, tendinous or ligamentous injury, and postsurgical incision care. In dentistry, LLLT is used in the treatment of recurrent aphthous stomatitis (RAS), herpes simplex infections, oral lichen planus, xerostomia, mucositis, paraesthesia, periodontitis, dentinal hypersensitivity, temporomandibular joint disorders (TMD), and pain during orthodontic tooth movement.

MECHANISM OF ACTION

The working of LLLT is vague, but it is shown that it may reduce pain associated with inflammation by lowering the levels of prostaglandin E2 (PGE_2), interleukin-1 beta (IL-1 beta), tumor necrosis factor-alpha (TNF-alpha), cellular influx of neutrophils and granulocytes, oxidative stress, edema, and bleeding in a dose-dependent manner.[1] The dosage of LLLT ranges from 0.3 to 19 J/cm^2. Low-level laser therapy has a stimulatory effect on cells at low dosage and a suppressive effect at high dosage. Another mechanism proposed is by stimulating the mitochondrion to increase adenosine triphosphate (ATP) production in order to increase the reactive oxygen species (ROS), which in turn, influences redox signaling, affecting intercellular homeostasis of the proliferation of cells.[2] Low-level laser therapy also has an effect on the microcirculation, which reduces edema by changing the capillary hydrostatic pressure.[3] The ideal dose of LLLT leads to the formation of new endothelium and blood

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vessels that will help in granulation tissue formation and accelerated healing. Low-level laser therapy leads to relaxation of smooth muscles of various systems, which reduces pain and spasm on the affected muscles.

STIMULATION OF ACTIVITY OF MITOCHONDRION

The capacity of infrared light to stimulate more efficient electron transfer in the cytochrome oxidase pathway is relatively well established. This might be due to the underlying mechanism of action for most of the physiologic effects of LLLT. Cytochrome C oxidase, an enzyme i.e., present in the cellular mitochondrial membrane, plays a key role in ATP synthesis.[4] Mitochondrion is the primary energy storage molecule for most vertebrate cells. Cytochrome c oxidase contains two iron centers, namely, heme a and heme a_3 (also denoted as cytochromes a and a_3), and two copper centers, namely, Cu_A and Cu_B. Completely oxidized cytochrome c oxidase contains both iron atoms in the Fe(III) oxidation state and both copper atoms in the Cu(II) oxidation state, while completely reduced cytochrome *c* oxidase has the iron in Fe(II) oxidation state and copper in Cu(I) oxidation state. A part of this enzyme appears to be a chromophore (light-responsive molecule) that absorbs energy from photons moving on wavelengths in the near infrared spectrum, which accelerates electron transfer rate and further increases the capacity of mitochondria to synthesize ATP. Greater ATP production thus results in increased energy available for the cell's metabolic processes.

EFFECT ON ANGIOGENESIS

The infrared light promotes vascular endothelial development and angiogenesis.[5] This property is significant for both the consideration of tissue healing and when applying laser to highly vascularized tissues. Laser is contraindicated in highly vascular tissues, e.g., neoplasms. Dourado et al[5] reported an increased angiogenesis at different wavelengths (633 and 904 nm) with greater response to 633 nm as compared to 904 nm at lower doses while higher doses of 633 wavelengths appeared to be less effective than 904 nm wavelength. Likewise, Cury et al[6] demonstrated benefit from both 660 and 780 nm but the shorter wavelength was effective only at higher doses and longer wavelength was effective at both high and low doses.

MODULATION OF INFLAMMATION

Low-level laser therapy not only increases the macrophage and neutrophil activity, but they also do so in a way that favorably enhances the output of specific inflammatory mediators. This states that under certain circumstances, laser light may not be a purely nonspecific stimulator of cell metabolism. Briefly, laser inhibits inflammatory catabolic mediators that suppress collagen synthesis and cell proliferation. Low-level laser therapy reduces neutrophil influx into chronically inflamed tissues or fluid-filled spaces and may stimulate production of anti-inflammatory metabolites, such as cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). Laser also helps in reducing edema,[3] which is an important factor in patient discomfort, and retards nutrient exchange in inflamed tissues.

INCREASE IN OXYGEN AVAILABILITY

It is suggested that laser promotes dissociation of oxygen from oxyhemoglobin in the tissue capillary beds,[7] thus making more oxygen available for oxidative metabolism and ATP production. Very few studies that exist have produced equivocal or contradictory results on this. Asimova and Thanh[7] found increased oxygen levels in the skin of patients after irradiation with a 633-nm wavelength at a dose of 0.23 J/cm^2. Whereas, Heu et al[8] found no change in the free oxygen levels in human skin when using a 660-nm wavelength at a dose of 5.73 J/cm^2 for 15 minutes.

EFFECT ON VASODILATION

Low-level laser therapy may increase local circulation via smooth muscle relaxation that results in vasodilation. This can be due to an induction of NO_2 in the perivascular tissue. Carrera et al[9] showed that laser therapy increases vasodilation in acute surgical wounds. Study by Heu et al[8] failed to find any change in local circulation in healthy tissues. Interestingly, an older study by Mi et al[10] suggested that laser may increase the deformability of the erythrocyte molecule with implications for both increasing the rate of erythrocyte flow through peripheral capillary beds and availability of the hemoglobin molecule within the red blood cells.

ACTION ON WOUND HEALING

It is noted that LLLT has a stimulatory effect on various cells of the body. The cellular responses observed *in vitro* after LLLT are broadly classified as increases in metabolism, migration, and proliferation and increases in synthesis and secretion of various proteins. Low-level laser therapy has also shown to cause vasodilation with increased local blood flow. This vasodilation not only brings in oxygen but also allows for greater traffic of immune cells into the tissue. These two effects contribute to accelerated healing. Although, it appears that most cells respond to

wavelengths between 630 and 980 nm, different cell types may respond to different portions of the spectrum.

Laser light of 632 nm at a dose of 0.43 J/cm^2 stimulates an increase in osteoblast numbers and activity in cell cultures[11]; however, osteoblast cultures respond better to laser light in the 790 to 830 nm range rather than the 660 to 690 nm range at equivalent doses.[12] Similarly, no effect was found with 904-nm light. Though, published data suggest that phototherapy in the 630 to 690 nm range promotes increased adhesion and proliferation of endothelial cells.[13]

Few *in vitro* studies have found that cell cultures respond best to moderate doses of infrared energy and the optimum dose may differ among cell types: Around 15 J/cm^2 in fibroblasts and 3 J/cm^2 in keratinocytes (both at 780 nm). In all the cases, higher doses essentially had a negative effect. A few investigators [Deise et al[14], Kreisler et al[15]] suggested that there can be a cumulative effect to successive laser treatments administered 24 hours apart. The timing of therapy may also play a role. Yu et al[16] studied cultured keratinocytes and fibroblasts that were irradiated at a dose of 0.5 to 1.5 J/cm^2 with a helium–neon (HeNe) laser and found a significant increase in basic fibroblast growth factor (bFGF) release from both keratinocytes and fibroblasts and a significant increase in nerve growth factor release from keratinocytes. Recently, Akgul et al[17] reported that postponing the onset of LLLT after acute inflammatory phase showed better results.

In an animal study by Farouk et al[18], influence of various laser wavelengths (442, 514, 632, 670, 780, 830, and 10600 nm) on the healing of oval full-thickness wounds in Sprague-Dawley rats was evaluated and the accelerated wound closure was from 7.7 to 29% in healing days. A HeNe laser at a wavelength of 632.8 nm gave the best acceleration in the healing days (29%). This study showed wavelength dependency, treatment schedule dependency, and dose dependency of photons in wound healing. Fibroblast absorption and wound healing acceleration is maximal at 632.8 nm, indicating that the acceleration of wound healing is not credited to laser skin transmission. A HeNe laser at 632.8 nm with an incident power density of 10.53 mW/cm^2 gave the optimum wound healing acceleration, indicating the non-dose rate dependency of laser photons in enhancing wound healing.

LOW-LEVEL LASER THERAPY FOR RAS

Recurrent aphthous stomatitis is characterized by recurrent bouts of solitary or multiple shallow, small, round, or ovoid painful ulcers, with circumscribed margins, having yellow or gray floors and are surrounded by erythematous halo. The etiology of RAS is unknown, but the predisposing factors are stress, mechanical injury, hormonal changes, gastrointestinal diseases, and vitamins and trace element deficiencies. Treatment is symptomatic, to relieve pain and enhance the healing process that can be done by the usage of topical agents. A case report by Babu et al[19] concluded that LLLT can decrease the healing time, pain intensity, size, and recurrence of the lesion in RAS and thus can be considered the most appropriate treatment modality with greatest clinical effectiveness.

Agrawal et al[20] proposed that LLLT inhibits conduction of nerve fibers, which was due to a reversible conformational change in the voltage-gated Na–K channels, similar to the action of local anesthetic agents. Studies conducted by De Souza[21] revealed that 75% of the study population reported reduction in pain immediately after a single session of laser treatment. Khademi et al[22] in a double-blind clinical trial treated 12 patients with minor RAS using a diode laser and reported that with the use of LLLT there was a decrease in the healing time and pain intensity in patients with aphthae.

LOW-LEVEL LASER THERAPY IN PERIODONTAL THERAPY

Chronic periodontal inflammation results in the destruction of periodontal ligament and leads to the loss of supporting periodontal tissues. Low-level laser therapy is reported to reduce gingival inflammation and expression of metalloproteinase 8 when used after scaling and root planning. Ozawa et al[23] reported that LLLT significantly inhibited increased plasminogen activity induced in human periodontal ligament cells in response to mechanical tensile force. Plasminogen activates latent collagenase, the enzyme, i.e., responsible for cleaving collagen fibers. Low-level laser therapy also has an effect on inhibition of PGE_2 synthesis.[24] Low-level laser therapy brings about modulation of the periodontal inflammatory process, especially through reduction of PGE_2 release. Gokce Aykol et al[25] showed that LLLT used as an adjunctive therapy to nonsurgical periodontal treatment improves periodontal healing.

Amorim et al[26] used LLLT on gingivectomy wounds in 20 patients using a 685-nm laser with a power of 50 mW and energy density of 4 J/cm^2. The authors observed a significant improvement in clinical parameters evaluated in the laser group at 21 and 28 days post surgery compared to the control sites. They postulated that the improvement is likely to be derived from higher collagen production leading to a better remodeling of connective tissue and a reduction of the probing depth, the latter in turn aiding oral hygiene and synergistically contributing to limiting inflammation.

A similar study by Ozcelik et al[27] showed that LLLT could enhance epithelialization and improve wound healing after gingivectomy and gingivoplasty procedures. Using a Mira-2-tone solution to visualize areas of epithelialization, the investigators treated patients with a 588-nm diode laser at 120 mW and 4 J/cm^2 for 7 days post surgery and observed a significant decrease in the non-epithelialized surfaces following LLLT, suggesting that besides stimulating collagen production, LLLT might also facilitate fibroblast and keratinocyte migration, angiogenesis, and growth factor release contributing to decreased inflammation and improved wound healing.

Sanz-Moliner et al[28] studied 13 patients with generalized severe chronic periodontitis in which control sites were randomly selected to receive a Modified Widman Flap (MWF) surgery and the contralateral test sites an MWF surgery in conjunction with an 810-nm diode laser to de-epithelialize the inner part of the periodontal flap and photo-bio-stimulate the surgical area. They concluded that the use of an 810-nm diode laser provided additional benefits to MWF surgery in terms of less edema and postoperative pain.

LOW-LEVEL LASER THERAPY IN MAXILLOFACIAL REGION

Fikácková et al[29] conducted a study to investigate the effects of LLLT for pain caused by TMD in a controlled study comparing applied energy density, subgroups of TMD, and duration of disorders. The study group of 61 patients was treated with 10 or 15 J/cm^2 and the control group of 19 patients was treated with 0.1 J/cm^2. Low-level laser therapy was performed by a Gallium Aluminum Arsenide (GaAlAs) diode laser with an output of 400 mW and emitting radiation wavelength of 830 nm in 10 sessions. Changes in pain were evaluated by self-administered questionnaire. The results suggest that LLLT can be considered as a useful method for the treatment of TMD-related pain, especially long-lasting pain.

In a systematic review by Marcello Melis et al[30] which was performed according to the CONSORT 2010 criteria to evaluate the efficacy of LLLT for the treatment of TMD. A total of 14 articles were included in the review. Studies varied significantly in terms of methodological design, principally regarding the site of application of the laser, the number of applications performed, their duration, the laser beam features (wavelength, frequency, output, and dosage), and outcome measures. The only conclusion drawn was that LLLT is probably more effective for the treatment of TMD and less effective for the treatment of masticatory muscle disorders.

CONCLUSION

Low-level laser therapy offers an attractive, painless, and noninvasive therapeutic way to modulate inflammation in dentistry. Biostimulation is an evolving technology. More is being discovered about the mechanisms of low-level lasers as the day passes. Low-level laser therapy is a useful adjunctive treatment modality in various fields of dentistry. It has positive effects on both hard and soft tissues of the oral cavity and less antagonistic effects. It is clear that LLLT can encourage the behavior of various cell types and that several effects can occur at the same time. The future prospects for LLLT are promising. Usefulness of the LLLT should also be discovered with respect to the wavelength, duration of treatment, and the site of application. Efforts should be focused toward inspecting the accurate dose required for therapeutic effects in order to achieve standardization of treatment protocols.

REFERENCES

1. Gordon SA, Surrey K. Red and far-red light action on oxidative phosphorylation. Radiat Res 1960 Apr;12:325-339.
2. Lubart R, Eichler M, Lavi R, Friedman H, Shainberg A. Low-energy laser irradiation promotes cellular redox activity. Photomed Laser Surg 2005 Feb;23(1):3-9.
3. Yamada EF, Villaverde AGJB, Munin E, Zângaro RA, Pacheco MTT. Effect of low power laser therapy on edema dynamics: sensing by using the electrical capacitance method. Proc SPIE 2004;5319:355-362.
4. Kato K, Shinzawa K, Yoshikawa S. Cytochrome oxidase is a possible photoreceptor in mitochondria. Photobiochem Photobiophys 1981 Jan;2:263-269.
5. Dourado DM, Fávero S, Matias R, de Tarso P, Carvalho C, da Cruz-Hofling MA. Low-level laser therapy promotes vascular endothelial growth factor receptor-1 expression in endothelial and nonendothelial cells of mice gastrocnemius exposed to snake venom. Photochem Photobiol 2011 Mar-Apr;87(2):418-426.
6. Cury V, Moretti AIS, Assis L, Bossini P, Crusca JS, Neto CB, Fangel R, de Souza HP, Hamblin MR, Parizotto NA. Low level laser therapy increases angiogenesis in a model of ischemic skin flap in rats mediated by VEGF, HIF-1a and MMP-2. Photochem Photobiol 2013;125:164-170.
7. Asimova M, Thanh NC. Laser induced photodissociation of oxyhemoglobin: optical method of elimination of hypoxia (oxygen deficiency in biotissue). Opt Spectrosc 2011 Aug;111(2): 224-229.
8. Heu F, Forster C, Namer B, Dragu A, Lang W. Effect of low-level laser therapy on blood flow and oxygen- hemoglobin saturation of the foot skin in healthy subjects: a pilot study. Laser Therapy 2013;22(1):21-30.
9. Carrera M, Pereiraa MC, Bacellar de Pinho C, Medradoa ARP, de Araújo Andradec Z, de Almeida Reis SR. Influence of 670 nm low-level laser therapy on mast cells and vascular response of cutaneous injuries. J Photochem Photobiol B: Biology 2010;98:188-192.
10. Mi XQ, Chen JY, Zhou LW. Effect of low power laser irradiation on disconnecting the membrane-attached haemoglobin from erythrocyte membrane. J Photochem Photobiol B: Biology 2006;83:146-150.

11. Stein A, Benayahu D, Maltz L, Oron U. Low-level laser irradiation promotes proliferation and differentiation of human osteoblasts *in vitro*. Photomed Laser Surg 2005 Apr;23(2):161-166.
12. Barbosa D, de Souza RA, Xavier M, da Silva FF, Arisawa EA, Villaverde AG. Effects of low-level laser therapy (LLLT) on bone repair in rats: optical densitometry analysis. Lasers Med Sci 2013 Feb;28(2):651-656.
13. Bouma MG, Buurman WA, van den Wildenberg FAJM. Low energy laser irradiation fails to modulate the inflammatory function of human monocytes and endothelial cells. Lasers Surg Med 1996;19(2):207-215.
14. Deise AA, Oliveira P, de Oliveira RF, Zangaro RA, Soares CP. Evaluation of Low-Level Laser Therapy of Osteoblastic Cells. Photomed Laser Surg 2008;26(4):401-404.
15. Kreisler M, Christoffers AB, Al Haj H, Willershausen B, d'Hoedt B: Low level 809-nm diode laser-induced in vitro stimulation of the proliferation of human gingival fibroblasts. Lasers Surg Med 2002;30(5):365-369.
16. Yu W, Naim JO, McGowan M, Ippolito K, Lamafame RJ. Photomodulation of Oxidative Metabolism and Electron Chain Enzymes in Rat Liver Mitochondria. Photochem Photobiol 1997;66(6):866-871.
17. Akgul T, Gulsoy M, Gulcur HO. Effects of early and delayed laser application on nerve regeneration. Lasers Med Sci 2014; 29:351-357.
18. Farouk AH, Al-Watban FAH, Zhang XY, Bernard L. Andres. Photomed Laser Surg 2007; 25(2):72-77.
19. Babu B, Uppada UK, Tarakji B, Hussain KA, Azzeghaibi SN, Alzoghaibi I. Versatility of diode lasers in low-level laser therapy for the management of recurrent aphthous stomatitis. J Orofac Sci 2015;7:49-53.
20. Agrawal H, Singh MP, Nahar P, Mathur H, Gv S. Efficacy of lowlevel laser therapy in treatment of recurrent aphthous ulcers: a sham controlled, split mouth follow up study. J Clin Diagn Res 2014;8:218-221.
21. De Souza TO, Martins MA, Bussadori SK, Fernandes KP, Tanji EY, Mesquita-Ferrari RA, et al. Clinical evaluation of low-level laser treatment for recurring aphthous stomatitis. Photomed Laser Surg 2010;28 Suppl 2:S85-88.
22. Khademi H, Shirani AM, Nikegbal F. Evaluation of low level laser therapy in recurrent aphthous stomatitis. Shiraz Univ Dent J 2009;10:160-162.
23. Ozawa Y, Shimizu N, Abiko Y. Low-energy diode laser irradiation reduced plasminogen activator activity in human periodontal ligament cells. Lasers Surg Med. 1997;21(5): 456-463.
24. Shimizu N, Yamaguchi M, Goseki T, Shibata Y, Takiguchi H, Iwasawa T, Abiko Y. Inhibition of prostaglandin E2 and interleukin 1-beta production by low-power laser irradiation in stretched human periodontal ligament cells. J Dent Res 1995 Jul;74(7):1382-1388.
25. Aykol G, Baser U, Maden I, Kazak Z, Onan U, Tanrikulu-Kucuk S, Ademoglu E, Issever H, Yalcin F. The Effect of Low-Level Laser Therapy as an Adjunct to Non-Surgical Periodontal Treatment. J Periodontol 2011;82:481-488.
26. Amorim JC, de Sousa GR, de Barros Silveira L, Prates RA, Pinotti M, Ribeiro MS. Clinical study of the gingiva healing after gingivectomy and low-level laser therapy. Photomed Laser Surg 2006;24:588-594.
27. Ozcelik O, Cenk Haytac M, Kunin A, Seydaoglu G. Improved wound healing by low-level laser irradiation after gingivectomy operations: a controlled clinical pilot study. J Clin Periodontol 2008;35:250-254.
28. Sanz-Moliner JD, Nart J, Cohen RE, Ciancio SG. The effect of an 810-nm diode laser on postoperative pain and tissue response after modified Widman flap surgery: a pilot study in humans. J Periodontol 2013;84:152-158.
29. Fikácková H1, Dostálová T, Navrátil L, Klaschka J. Effectiveness of low-level laser therapy in temporomandibular joint disorders: a placebo-controlled study. Photomed Laser Surg 2007 Aug;25(4):297-303.
30. Melis M, Di Giosia M, Zawawi KH. Low level laser therapy for the treatment of temporomandibular disorders: a systematic review of the literature. Cranio 2012 Oct;30(4): 304-312.