A Biostimulation Therapy in Periodontics: An Evidence-Based Review

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Abstract

Low-level laser therapy (LLLT) is a light source treatment that generates light of a single wavelength. Low-level lasers do not cause temperature elevation within tissue, but rather produce their effects through photobiostimulation. Low-level lasers (LLL) do not cut or ablate tissue. Low-level laser therapy devices include gallium-aluminum-arsenide (Ga-Al-As) infrared semiconductors and helium-neon (He-Ne) lasers. The output powers range from 50 to 500 mW with wavelengths in the red and near infrared of the electromagnetic spectrum, from 630 to 980 nm, with pulsed or continuous-wave emission. The application of LLLT has become popular in a variety of clinical applications in periodontics including the promotion of wound healing and the reduction of pain following non-surgical and surgical procedures. There is good evidence that the enhanced cell metabolic functions seen after LLLT are the result of the activation of photo-receptors within the electron transport chain of mitochondria. The articles included in this review were searched from PubMed, TRIP, Google Scholar, and Cochrane databases. The purpose of this review was to critically analyze the effectiveness of LLLT on soft and hard tissue in order for dentists and specialists to have a clear understanding of the clinical applications of LLLT in periodontal disease.

Keywords: Lasers; low-level laser therapy; periodontal disease; therapeutic lasers

Introduction

The use of lasers for treatment has become a common phenomenon in the medical field. The term laser is an acronym for "light amplification by the stimulated emission of radiation." Laser light is a beam that is monochromatic, coherent, and collimated. The first laser device was made by Maiman in 1960, based on theories derived by Einstein in the early 1900s.[1] Dr. Leon Goldman used a ruby laser on the tooth of his dentist brother, and the result was painless surface crazing of enamel.[2] The first application of laser in maxillofacial surgery was introduced by Lenz et al. in 1977.[3]

The laser beam is essentially a beam of light comprised of excited photons. A laser device converts electrical or chemical energy into light energy. In contrast to ordinary light that is emitted spontaneously by excited atoms or molecules, the light emitted by the laser occurs when an atom or molecule retains excess energy until it is stimulated to emit it. The radiation emitted by lasers including both visible and invisible light is more generally termed electromagnetic radiation. Albert Einstein first proposed the concept of stimulated emission of light in 1917. He described three processes including absorption, spontaneous emission, and stimulated emission.[3] According to Posten et al, the properties of a low-level laser (LLL) are a power output of 0.001-0.1 watts, a wavelength in the range of 300-10,600 nm, a pulse rate from 0 continuing to 5,000 hertz (cycles per second), an intensity of 0.01-10 W/cm2, and a dose of 0.01-100 J/cm^2.[4] The most common methods of administration of LLLs include ruby (694 nm), argon (Ar) (488 and 514 nm), helium-neon (He-Ne) (632.8 nm), krypton (Kr) (521, 530, 568, and 647 nm), gallium-aluminum-arsenide (Ga-Al-As) (805 or 650 nm), and gallium-arsenide (Ga-As) (904 nm).[4]

Low-level laser therapy (LLLT) was first introduced by Mester and his colleagues and is also called soft laser therapy.[5] An LLL is a red light or infrared light with its absorption parameter in sub-cellular photo receptors, with an electron transfer in the respiratory chain of mitochondria membranes capable of penetrating into tissues to a depth of 3-15

mm.[6] In vivo and in vitro experiments have shown that LLLs are capable of speeding up repair processes.[7,8] They are also capable of reducing post-operative pain, stabilizing nerve cell membranes, and increasing adenosine triphosphate (ATP) production. Low-level laser therapy has been investigated and used clinically for over 30 years, justifying the increasing interest in the effects of lasers and the significant number of scientific publications in the literature.

Mechanism of Action of LLLs

The biostimulatory and inhibitory effects of LLLT are governed by the Arndt-Schulz law. According to this law, low doses increase physiologic processes, and strong stimuli will inhibit physiological activity. The output powers for LLLT range from 50 to 500 mW with wavelengths from 630 to 980 nm in the red and near infrared of the electromagnetic spectrum with pulsed or continuous-wave emission. Low-level lasers do not cause temperature elevation within the tissue, but rather produce their effects through photobiostimulation. Low-level lasers do not cut or ablate the tissue and LLLT has been referred to as biostimulation and biomodulation.[9] The biostimulatory effect of laser irradiation represents a set of structural, biochemical, and functional changes in living microorganisms. It acts directly by stimulating components of the so-called antenna pigments of the respiratory chain which manifests as an immediate effect cell vitalization by mitochondrial ATP production increase. Laser enhanced biostimulation has been reported to induce intracellular metabolic changes, resulting in faster cell division, proliferation rate, migration of fibroblasts, and matrix production.[10,11]

The Molecular Mechanism by Which LLLs Stimulate Cell Proliferation and Matrix Production

Low-level lasers can stimulate a number of biological processes including cell growth, proliferation, and differentiation. In vitro, the effects on cell proliferation by LLLT have been studied in various cell types including fibroblasts, endothelial cells, skeletal cells, keratinocytes, myoblasts, and other cell types. However, the molecular mechanism associated with the stimulatory effects of LLLT has not been fully clarified. One classic mechanism involved is that the laser energy is absorbed by intracellular chromophores and converted to metabolic energy since cellular ATP levels increase almost two-fold following He-Ne laser irradiation.[12]

Current research about the mechanism of LLLT involves mitochondria. Cytochrome c oxidase is a multicomponent membrane protein that contains a binuclear Cu_A center along with a heme a_3-Cu_B binuclear center, both of which facilitate the transfer of electrons from water soluble cytochrome c oxidase to oxygen. It is a terminal enzyme of the electron transport chain and plays a vital role in the bioenergetics of a cell.[12] It was proposed that cytochrome c oxidase is the primary photo acceptor for the red-NIR range in mammalian cells because absorption spectra obtained for cytochrome c oxidase in different oxidation states was found to be very similar to the action spectra for biological responses to light.[12] The absorption of photons by cytochrome c oxidase leads to electronically excited states, and consequently can lead to the quickening of electron transfer reactions. More electron transport causes increased production of ATP, which acts via multiple P2 nucleotide receptor subtypes to increase intracellular calcium (Ca^{2+}) concentration. Simultaneously, ATP regulates protein synthesis, DNA synthesis, and the expression of immediate-early and delayed-early genes.[13] The light induced increase in ATP synthesis and increased proton gradient lead to increased activity of the Na+/H+ and Ca^{2+}/Na+ antiporters and all the ATP driven carriers for ions, such as Na+/K+ ATPase and Ca^{2+} pumps. ATP is the substrate for adenyl cyclase, and therefore, the ATP level controls the level of cyclic adenosine monophosphate (cAMP). Both Ca^{2+} and cAMP are very important second messengers. Ca^{2+} regulates numerous processes in the human body such as muscle contraction, blood coagulation, signal transfer in nerves, and gene expression. Therefore, the photoactivation of terminal enzymes, such as cytochrome c oxidase, plays a vital role in the activation of the diverse biological cascade observed subsequent to laser irradiation.[14]

The first commercialized biostimulative laser was a He-Ne laser of <1 mW. The use of the He-Ne laser for biostimulation is limited by the need for an optic fiber, the size of the machine, and the still rather low power option, now typically in the range of 5-25 mW. It has generally been replaced by the aluminum-gallium-indium-phosphide (Al-Ga-In-P) laser, a diode producing red laser in the range of 600-700 nm that is able to deliver as much as 500 mW.[15]

The most frequently used laser for LLLT in dentistry is the Ga-Al-As laser. It often operates in the spectrum between 780 and 830 nm. The output is typically between 10 and 500 mW. An advantage of the diode lasers is the small size and the option for battery operation, making them rather handy and portable. These lasers work in continuous mode, but can be mechanically or electronically pulsed. The biostimulatory effect of laser irradiation is determined by the magnitude of the absorbed light energy. Energy depth of penetration depends on factors such as wavelength, optical and temperature characteristics, power, energy values, exposure time, wave shape, and the optical characteristics of tissue-absorption and scattering coefficient.[10]

The mechanisms of LLLT are complex, but essentially rely upon the absorption of particular visible red and near infrared wavelengths by photoreceptors within subcellular components, particularly the electron transport (respiratory) chain within the membranes of mitochondria. Photon absorption causes a shift in the molecular configuration of the photo acceptor associated with an alteration in the molecular signal of the cell. The alterations in photo acceptor function are the primary reactions, with subsequent alterations in cellular signaling and cellular functions being the secondary reactions.[16]

Primary Reactions After Light Absorption

Several mechanisms of action for LLLT were proposed. The first mechanism, proposed in 1981, was the singlet oxygen hypothesis.[15] Certain photoabsorbing molecules, such as porphyrins, absorb laser light leading to the generation of singlet oxygen, which is needed for stimulation of RNA and DNA synthesis. The next mechanism, proposed in 1988, was the redox properties alteration hypothesis. According to this hypothesis, photo excitation of certain chromatophores in the cytochrome c oxidase molecule, influences the redox state and consequently, the rate of electron flow in the molecule. The latest proposal was the nitric oxide (NO) hypothesis which stated that laser irradiation could reverse this inhibition by photo dissociating NO from its binding sites. Because this coordinate binding is much weaker than a covalent bond, this dissociation is possible by LLLs. The dissociation of NO from cytochrome c oxidase increases the respiration rate. Light can indeed reverse the inhibition caused by NO binding to cytochrome c oxidase, both in isolated mitochondria and in whole cells. LLL can also protect cells against NO induced cell death. The transient local heating hypothesis states that a local transient rise in temperature of absorbing biomolecules may cause structural changes and trigger biochemical activity. In 1993, the superoxide anion hypothesis suggested that activation of the respiratory chain by irradiation would also increase the production of superoxide anions.[16]

Secondary Reactions After Light Absorption (Cellular Signaling)

The secondary reactions that occur after light absorption are through cellular signaling pathways and mitochondrial retrograde signaling. Mitochondrial retrograde signaling is the communication in cells from mitochondria to the nucleus that influences many cellular activities, under both normal and pathophysiological conditions. The low-intensity red and near-infrared light acts on cells through cytochrome c oxidase, which is the primary photo acceptor and the terminal enzyme of the mitochondrial electron transport chain. Absorption of light by cytochrome c oxidase can increase the mitochondrial membrane potential, thereby releasing ATP and reactive oxygen species, which leads to increased energy availability and signal transduction. The overall redox state of a cell represents the net balance between stable and unstable reducing and oxidizing equivalents.[17] Recent studies have revealed

that many cellular signaling pathways are regulated by the intercellular redox state.[18] Oxidants stimulate cell signaling systems, and reductants suppress the upstream signaling cascades, resulting in suppression of transcription factors. Redox based gene expression is a fundamental mechanism in cell biology. In phagocytic cells, irradiation initiates a non-mitochondrial respiratory burst (production of reactive oxygen species, especially superoxide anion) through activation of nicotinamide adenine dinucleotide phosphate-oxidase located in the plasma membrane of these cells. The irradiation effects on phagocytic cells depend on the physiological status of the host organism as well as on radiation parameters.[17,18]

Clinical Applications of LLLT

The application of low-level lasers in medicine was introduced in the 1970s and 1980s. Since then, considerable scientific work including the use of cell cultures, animal models, and clinical studies have been undertaken to evaluate its potentially beneficial effects. The application of LLLT has become popular in a variety of clinical applications, including the promotion of wound healing and reduction of pain. Low level laser applications in dentistry include the promotion of wound healing in a range of sites, including surgical wounds, extraction sites, and recurrent aphthous ulcerations.[19] The main advantage of using LLLT in dental and periodontal treatment is that it has the ability to speed up the healing process. It is also used for pain management in the treatment of gingivectomies. Fibroblast keratinocyte motility, collagen synthesis, angiogenesis, and growth factor release all were facilitated by low level laser.[20]

There are several mechanisms by which LLLT may stimulate the proliferation of fibroblasts. Low-level laser therapy has been shown to stimulate the production of basic fibroblast growth factor (bFGF), a multifunctional polypeptide which supports fibroblast proliferation and differentiation. Fibroblasts that undergo low dose LLLT show both increased cell proliferation and enhanced production of bFGF, while high dose LLLT suppresses both parameters. A further effect of LLLT on fibroblasts that can influence the wound healing process is the transformation of fibroblasts into myofibroblasts, which are responsible for wound contraction.[21]

Ozawa et al. found that laser therapy significantly inhibits the increase of plasminogen activator induced in human periodontal ligament cells in response to mechanical tension. Plasminogen activator is capable of activating latent collagenase, the enzyme responsible for cleaving collagen fibers. In human gingival fibroblast culture, LLLT significantly inhibited PGE_2 synthesis stimulated by lipopolysaccharide through a reduction of cyclooxygenase-2 gene expression in a dose dependent manner.[22] Mizutani et al. suggested that LLLT inhibits the arachidonic acid cascade in damaged tissue, leading to a decreased production of PGE_2. Later, this phenomenon interferes with the production of bradykinin and many kinds of inflammatory cytokines. In addition, the increase in local blood flow improves acidosis and simultaneously promotes both the release and removal of substances related to pain.[23] A study done by Lui et al. also suggested that the combined course of photodynamic therapy with LLLT could be a beneficial adjunct to nonsurgical treatment of chronic periodontitis on a short-term basis.[24]

To summarize, LLLT has both advantages and disadvantages. Some of the advantages of LLLT include its effectiveness in treating chronic and acute injuries, as well as its ability to reduce pain and inflammation caused by musculoskeletal conditions such as temporomandibular joint disorders. Low-level laser therapy also stimulates the body's own healing process without the risk of burning, and for those sensitive or allergic to harsh medications, LLLT is a wonderful alternative that is safe, natural, and effective.[20] Low-level laser therapy has its disadvantages as well including the fact that patients do not typically get full relief or resolution from their pain symptoms after the first treatment, and they often have to return to the clinician for treatment at least two to four times per week. In addition, old injuries may be aggravated for a few days after treatment, but for most patients this

sensation is short-term and only lasts for a couple of days.[21]

Search Strategy

The articles reviewed were retrieved from PubMed, TRIP, Google Scholar, and Cochrane databases. Relevant studies were identified from January 1987 to July 2021. The Medical Subject Headings (MeSH) terms used were 'lasers, semiconductor' (MeSH Terms) OR ('lasers' [All Fields] AND 'semiconductor' [All Fields]) OR 'semiconductor lasers' (All Fields) OR ('LLLT' [All Fields] AND 'laser' [All Fields]) OR ('LLLT laser' [All Fields]) AND 'periodontal' [All Fields]) AND ('therapy' [Subheading] OR 'therapy' [All Fields] OR 'treatment' [All Fields] OR 'therapeutics' (MeSH Terms) OR 'therapeutics' [All Fields]. Only randomized controlled trials (RCTs), systematic reviews, and meta-analyses were included as evidence in this systematic review. In vitro studies, animal studies, and case reports were excluded (Table 1).

Table 1. Searched papers and their data

Studies With Evidence on Application of LLLs in Periodontics	
Authors, Year	**Type of Study**
Scaling and Root Planing	
Alzoman and Diab, 2016[25]	RCT
Gupta et al., 2016[26]	RCT
Hypersensitivity	
Dilsiz et al., 2010[27]	Case-Control Study
Yilmaz et al., 2011[28]	RCT
Photodynamic Therapy	
Birang et al., 2015[29]	RCT
Teymouri et al., 2016[30]	RCT
Depigmentation	
Suragimath et al., 2016[31]	RCT
Gingivectomy	
Sobouti et al., 2014[32]	RCT
Crown Lengthening	
To et al., 2013[33]	RCT
Ize-Iyamu et al., 2013[34]	RCT
Frenectomy	
Gandhi and Gandhi, 2017[35]	Case-Control Study
Open Flap Surgery	
Lobo and Pol, 2015[36]	RCT
Aena et al., 2015[37]	RCT
Peri-Implantitis	
Papadopoulos et al., 2015[38]	RCT
Arısan V et al., 2015[39]	RCT

RCT: randomized controlled trial

Discussion

Many LLLs have been shown to provide periodontal treatment benefits. To achieve an element of clarity and simplicity on this very complex topic, the following discussions exclusively address the use of LLLT in periodontology.

I. LLLs and Impact on Pain

Pain occurs because of tissue trauma and the release of inflammatory mediators following the removal of local anaesthesia.[40] Low-level

lasers will relieve pain and repair wounds. The mechanism of this pain relief is not yet clear but several studies have offered a mechanism that describes stabilization of the lipid double membrane and increased ATP production.[41] Aparicio et al. reported a study in which LLLT for the treatment of temporomandibular disorders (TMDs) was used. They stated that TMDs have been identified as the most important cause of pain in the facial region. Low-level laser therapy has demonstrated analgesic, anti-inflammatory, and biostimulating effects. Low-level laser therapy is a noninvasive, quick, and safe non-pharmaceutical intervention that may be beneficial for patients with TMDs.[42]

II. LLLs and Gingivectomy

The removal of suprabony pockets or pockets not extending to the mucogingival junction is the purpose of a gingivectomy. Patients may experience pain due to open wound secondary repair following gingivectomy.[43] Amorim et al. conducted a clinical study on gingival healing following gingivectomy and LLLT in a split mouth randomized clinical trial. He studied 20 patients who had two-sided increased gingival volume on a premolar. Gingivectomy was performed in the test group and then an LLL was used for 80 seconds with a wavelength of 685 nm and a power of 50 mW in continuous mode. All surgery dressings were renewed after 24 hours, and postoperatively on the third and seventh days. Following surgeries, photographic images were taken on the third, seventh, fourteenth, twenty-first and forty-fifth days. They were reviewed by three periodontists and clinical condition was noted, which evaluated wound repair, tissue color, and contour. For biometric assessment, reference composite was inserted at the medial section of the buccal plane, then the pocket depth and thickness of keratinized gingiva were measured. Clinical visits showed better wound repair in the laser group patients after the third postoperative day. On the twenty-first and twenty-eighth days, biometric assessment also demonstrated superior improvement in the laser group patients compared to the controls. Finally, Amorim et al. concluded that the application of an LLL along with gingivectomy resulted in improved conditions and faster repair.[44]

In yet another study on wound healing following gingivectomy with low-level irradiation conducted by Ozcelik et al., 20 patients with an increased two-sided gingival volume in at least six teeth participated. In this split mouth randomized controlled clinical trial, LLL was radiated to target points for five minutes per day for a period of one week postoperatively in the test group. A laser with a wavelength of 588 nm and 120 mW of power in continuous mode was used. All operations were performed by the same clinician, no dressing was used, and no pain relievers were prescribed. To check the presence or absence of epithelium, or lack of keratinization, Mira-2-Ton® detector solution was used after each laser application. A comparison was made using image analysis software, and the laser applied group had fewer colored areas after the third, seventh, and fifteenth days ($p<0.001$). Therefore, they found that the application of LLLs results in increased epithelialization and wound healing following gingivectomy and gingivoplasty.[45]

In 2014, Sobouti et al. also found faster and painless wound healing after gingivectomy using a diode LLL in patients with fixed orthodontics for esthetic purposes, compared to those for whom a surgical knife was used.[32]

III. LLLs and Periodontal Flaps

A split mouth study on coronally advanced flaps with adjunctive LLLT on 10 patients with 74 symmetrical Miller's class I and II gingival recessions was conducted by Ozturan et al. Patients affected with at least two adjacent buccal gingival recessions due to traumatic brushing participated. Depth and width of gingival recession, probing depth, and keratinized gingival thickness were recorded prior to surgery and 12 months postoperatively. The laser was radiated to the target area after the coronally advanced flap and before suturing. Parameters included a 588 nm wavelength and a power of 120 mW using continuous mode radiation for five minutes. The laser was also radiated to the target area following suturing and for five minutes per day for a

period of seven days. A dressing was not used. Following the coronally advanced flap surgery a laser was used in the switched off form for blinding in the control group. Significant differences were found in the width and depth of gingival recession, keratinized gingival thickness, and clinical attachment level (P=0.018, P=0.009, P=0.015, P=0.014). Complete root coverage in the test group (n=7.70%) was greater than that of the control group (n=3.30%). These authors suggested that laser application may enhance treatment prognoses following coronally advanced flaps.[46]

In another split mouth randomized controlled clinical trial by Aena et al., the effect of an 810 nm diode laser radiated following modified Widman flap surgery was studied on thirteen patients. Pain and tissue response was recorded. An aluminum-gallium-zinc-arsenide diode laser with a wavelength of 810 nm and a power of 1 W was continuously radiated for 10 seconds, stopped for 30 seconds, and again radiated at a power of 0.1 W. The switched-off laser was radiated to the target area in the control group after the modified Widman flap. Between the two surgeries the time span was three weeks and the same person performed all surgeries. Patients were prescribed Ibuprofen (200mg) for pain relief every eight hours following the operations. Based on a modified visual analogue scale from 0-10, the patients were asked to note their pain level every night for a period of one week and the number of sedative tablets taken was also noted. Tissue response was also documented based on color and edema as a secondary variable on physical examination. Between the two groups for tissue edema (P<0.041), dose of sedative drug taken (P<0.001), and postoperative pain (P<0.001), significant differences were reported. As for tissue color (P=0.98), no difference was found. Patients reported more pain after the second surgery. Therefore, the author concluded that the application of a diode laser with a wavelength of 810 nm along with a modified Widman flap results in a reduction of pain and postoperative edema.[37]

The findings of Karthikeyan et al. also confirm the results of Aena et al. where LLL-assisted Kirkland flap surgery showed a significant improvement plaque index, bleeding on probing, probing pocket depth, and clinical attachment level at the third and sixth month compared to Kirkland flap surgery alone. Red complex bacteria levels were also significantly reduced in the LLL-assisted group compared to the control group at the third and sixth months. Here, the authors explained that the adjunctive use of the diode laser may aid in the complete removal of remnant epithelium which is not accomplished by the Kirkland flap alone.[47]

IV. LLLs and Free Gingival Grafts

In a split mouth randomized clinical study on the utilization of LLLs during the healing of free gingival grafts conducted by Almeida et al., 10 patients underwent a bilateral gingival graft in the mandible at 30-day intervals performed by the same surgeon. Diode Ga-Al-As lasers with wavelengths of 660 nm (red) for fast repair effect and 780 nm (infrared) for anti-pain effect, were radiated following the graft procedure in the test side. The lasers had a power of 40 mW with an energy dose of 10 j/cm^2. They were continuously emitted onto the test side after surgery and a 48-hour postoperative laser was used twice. A switched off laser was used in the control side following the free gingival graft. At 7, 15, 30, and 60 days postoperatively, photographs were produced and morphology, texture, and shade were examined. Based on a visual analogue scale from 0-10, patients were asked to record their pain level at 3 hours, 24 hours, and 7 days postoperatively. Between the two sides no differences were found and so, it was concluded that LLLT was not useful in the healing of gingival grafts and did not influence pain reduction.[48]

Moslemi et al. also conducted a split mouth randomized clinical trial on 12 patients to evaluate the effect of a 660 nm LLL, with a power of 200 mW, on pain and healing in the palatal donor site. The laser was applied for 32 seconds to the target site after suturing and at one, two, four, and seven days postoperatively in the test group. Switched off lasers were used in the control group in the same way. Photographic images were used to evaluate the amount of epithelialization. During pain assessment any sedative drugs taken were recorded and put into consideration. The laser-applied

group was significantly better healed than the control group with regards to clinical repair and epithelialization at day 14. Epithelialization was also greater in the laser-applied group compared to the control group at day 21. Therefore, the authors concluded that LLLs may improve the healing of palatal graft sites.[49]

By reducing biochemical markers, oxidative stress, and edema in a dose-dependent relation with an active dose range from 0.3 to 19 j/cm² and an average dose of 7.5 j/cm², LLLs may be able to relieve pain as was mentioned by Bjordal et al. in a systematic review article. In the first 72 hours postoperatively, the anti-pain effect of LLLs with a high radiation density was more effective. For faster pain relief, LLL doses have to be continued as was concluded by the authors of previous studies showing that low density lasers relieve pain faster and high doses reduce fibroblast reproduction and growth factor release.[50]

Conclusion

The positive effect of LLLT is due to the unspecific stimulatory action of the laser beam by increasing collagen production, enzyme activity, lymph circulation, and fibroblast proliferation, and by reducing local hypoxia, inflammation, and pain. There is good evidence that the enhanced cell metabolic functions seen after LLLT are the result of the activation of photoreceptors within the electron transport chain of mitochondria. Future trials of new LLLT applications in dentistry should make use of standardized, validated outcomes, and should explore how the effectiveness of the LLLT protocol used may be influenced by wavelength, treatment duration, dosage, and the site of application.

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