Low Level Laser Therapy (LLLT) as an Effective Therapeutic Modality for Delayed Wound Healing

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Low Level Laser Therapy (LLLT) as an Effective Therapeutic Modality for Delayed Wound Healing

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ABSTRACT: Low level laser therapy (LLLT) is a form of phototherapy that involves the application of low power monochromatic and coherent light to injuries and lesions. It has been used successfully to induce wound healing in nonhealing defects. Other wounds treated with lasers include burns, amputation injuries, skin grafts, infected wounds, and trapping injuries. The unique properties of lasers create an enormous potential for specific therapy of skin diseases. As with any new device, the most efficacious and appropriate use requires an understanding of the mechanisms of light interaction with tissue as well as the properties of the laser itself.

KEYWORDS: low level laser therapy (LLLT); wound healing; diabetes; stimulation

INTRODUCTION

Low level laser therapy (LLLT) or more simply known as soft laser therapy, is a dramatic therapy that has become progressively more popular in the management of a wide variety of medical conditions, such as soft tissue injuries (including sports injuries), low back pain, arthritis, and skin traumas. Unlike the higher powered lasers employed in medicine, these low level lasers do not deliver enough power to damage tissue, but they do deliver enough energy to stimulate a response from the body tissues to initiate healing. Laser radiation has a wavelength-dependent capability to alter cellular behavior in the absence of significant heating. Light radiation must be absorbed to provide a biological response. The visible red and infrared portions of the spectrum have been shown to have highly absorbent and unique therapeutic effects in living tissues.

BASIC PRINCIPLES OF LLLT

Low level laser therapy applications include: acceleration of wound healing, enhanced remodeling and repair of bone, restoration of normal neural function

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following injury, pain attenuation, and modulation of the immune system. Laser therapy increases both the rate and the quality of healing, and studies show that as the healing rate increases, bacterial cultures decrease, suggesting a bioinhibitory effect upon wound infection. Nussbaum et al. analyzed the interactions between wavelength and bacterial growth of *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus* and reported that irradiation with 1–20 J/cm² at a wavelength of 630 nm appeared to be commonly associated with bacterial growth inhibition, which is of considerable importance for wound healing. Reports of LLLT applied to soft tissues *in vitro* and *in vivo* suggest stimulation of specific metabolic processes in healing wounds. Whereas low doses of LLLT are stimulatory, high doses of laser radiation are suppressive.

Low level laser therapy irradiation includes wavelengths of between 500 and 1100 nm and typically involves the delivery of 1–4 J/cm² to treatment sites with lasers having output powers between 10 and 90 mW. Low-intensity radiation can inhibit as well as stimulate cellular activity as light irradiation appears to upregulate cellular metabolism and proliferation. Visible red light has long been known to promote healing in the body’s cells and tissues. Irradiating mitochondria with red light causes them to produce cytochromes, which increases their efficiency, and research has shown that fibroblasts and muscle cells grow five times faster when treated with red light. By decreasing the healing time of open wounds, laser therapy significantly reduces the risk of infection and other complications. It also produces a stronger repair with less unattractive scar tissue.

The effects of LLLT are photochemical, not thermal. To produce an effect, the photons must be absorbed, and different substances absorb light of different wavelengths like the cells of injured skin are more sensitive than those of intact tissue. Once the target cells have absorbed the photons, a cascade of biochemical events occurs whose ultimate result is accelerated wound healing. Laser therapy is thought to work through a variety of mechanisms:

1. Photons from a laser probe are absorbed into the mitochondria and cell membranes of the target cells.
2. After a cell absorbs photons the energy is incorporated into the molecule to increase chemical energy, activate or deactivate enzymes, or alter physical or chemical properties of main macromolecules. Photonic energy is converted to chemical energy within the cell, in the form of denosine triphosphate (ATP), which leads to normalization of cell function, pain relief, and healing.
3. Single oxygen molecules build up, which influences the formation of ATP, which in turn leads to replication of DNA.
4. Increased DNA leads to increased neurotransmission.
5. A cascade of metabolic effects results in various physiological changes, which results in improved tissue repair, faster resolution of the inflammatory response, and reduction in pain.

Infra red laser light at approximately 632 nm appears to be the most effective and stimulatory frequency of laser at a cellular level with a skin penetration depth of 0.5–1 cm. A typical example of a laser used in LLLT is the helium-neon (He-Ne) laser, which can penetrate as deep as 0.5 mm into freshly excised human skin, which is regarded as sufficient for the induction of wound healing because most of the rele-
vant target cells of low level laser irradiation are located within the epidermis and upper dermis.\textsuperscript{5} Studies have found that laser irradiation stimulates fibroblast growth \textit{in vitro} and also facilitates ulcer healing in the clinical situation.\textsuperscript{7}

Karu\textsuperscript{8} found that infrared laser (620 nm) stimulated the bacterial cell growth rate, DNA and RNA synthesis rates, enzyme activity, and cAMP levels. It is postulated that the respiratory chain is stimulated, activating ATP turnover, increasing H\textsuperscript{+}, and ultimately triggering an increase in cell proliferation. The stimulating effects of light appear to occur in “sluggish” cell cultures or during decreased activity such as trophic ulcers and indolent wounds, when low tissue oxygen concentration and pH inhibit cell growth. Conversely, where maximum regeneration is occurring naturally, laser did not appear to enhance the process.\textsuperscript{8}

**LOW LEVEL LASER THERAPY FOR WOUND HEALING**

LLLT, when used appropriately, can stimulate the healing of injured tissues such as those of the dermis.\textsuperscript{9} Investigations into the mechanisms involved have shown that many of the types of cells whose interaction results in dermal repair can be affected in a therapeutically advantageous manner by treatment with LLLT both \textit{in vitro} and \textit{in vivo}. Mast cells and macrophages can be stimulated to release growth factors and other substances, whereas the proliferation of fibroblasts, endothelial cells, and keratinocytes maintained in adverse conditions can also be stimulated. The development of granulation tissue is mainly controlled by growth factors released from macrophages.\textsuperscript{9}

Wound healing involves the following phases:

- **Hemostasis:** platelets, endothelial cells, fibrin, and fibronectin act through growth factors and cytokines.
- **Inflammation:** blood clots form, bacteria are attacked, and there is an orderly recruitment of key cells into the wound site.
- **Proliferation:** cells necessary for wound closure multiply at the wound site to make new tissue and blood vessels.
- **Remodeling:** the wound is healed and the initial scar tissue is restructured.

Any device that can accelerate any of these processes (transition from hematoma to fibroplasias, development of new blood vessels, production of collagen, or even the remodelling process) could accelerate the healing process of wounds.\textsuperscript{9} Early laser studies were confined to \textit{in vitro} studies because little was known about the side effects of laser irradiation.\textsuperscript{10}

Wound healing studies have focused on several types of cells including fibroblasts, lymphocytes, monocytes, macrophages, epithelial cells, and endothelial cells. The wide diversity of experimental protocols and parameters such as cell line, dose, waveform, treatment time, penetration distance, treatment area, and treatment frequency make comparison of these studies difficult. Literature indicates that laser photobioactivation accelerates inflammation, modulates the level of prostaglandin, enhances the action of macrophages, promotes fibroblast proliferation, facilitates collagen synthesis, fosters immunity, and even accelerates the healing process.\textsuperscript{9} Using the He-Ne laser, Van Breugel and Bar\textsuperscript{11} concluded that laser exposure time
and power density determine the effect of the laser. Dependent on exposure time and power density, the laser can either stimulate or inhibit human fibroblasts in vitro.11

In the clinical situation, LLLT is an accepted, efficient, noninvasive, and painless method of treating edema, inflammation, and pain and it is used to increase circulation and promote wound healing.12 Wound healing experiments show acceleration of healing, but these findings are often concentrated in the early phases of the healing process.12 The effects of LLLT on wound healing are often attributed to increased cell proliferation. However, the true effect of LLLT on cell proliferation is still controversial, because of conflicting reports on the effects of visible laser light on cells in culture.

The magnitude of the laser biostimulation effect depends on the physiological state of the cell at the moment of irradiation. This explains why the effect is not always detectable as well as the variability of the results reported in the literature. In medicine, laser treatment appears to work in cases of severe damage or stress (wounding), whereas the effect of light on normally regenerating wounds may also be insignificant. Karu8 stated that light stimulates cell proliferation if the cells are growing poorly at the time of irradiation. Thus, if a cell is fully functional, there is nothing for laser irradiation to stimulate, and therefore no therapeutic benefit will be observed.8

LLLT may induce positive side effects that are common also after other stimulation therapies (acupuncture). In patients with difficult or longstanding problems, LLLT can be combined very usefully with other forms of therapy (physiotherapy, acupuncture, and manipulation), relaxation therapy (self-hypnosis and meditation), medication (pharmacological, herbal, or homeopathic), and psychiatric or psychological counseling.16 There are no absolute contraindications for LLLT; however, it is always better to be cautious when treating patients in high-risk categories. LLLT should be avoided or given with special caution in the following cases: patients with pacemakers, patients who are pregnant, patients with cancer if there is any doubt of a recurrence of metastases, and patients with labile epilepsy. It is better to avoid LLLT over the thyroid gland, ovaries, and testicles. Although LLLT has not induced cancer in any of the reported studies, the precise reactions of existing tumors to LLLT are unknown.16 Pessoa et al.17 conducted a study to investigate the effect of LLLT on the wound healing process treated with steroid and concluded that LLLT accelerated healing, caused by the steroid, acting as a biostimulative coadjuvant agent, balancing the undesirable effects of cortisone on the tissue healing process.17 Manuskiatti and Fitzpatrick18 conducted a study to compare the clinical response of keloidal and hypertrophic scars after treatment with interlesional corticosteroid alone or combined with 5-fluorouracil (5-FU), 5-FU alone, and the 585-nm pulsed-dye laser (PDL). There was significant improvement in keloidal and hypertrophic scars after treatment in which scar texture and erythema responded better to PDL and the long-term adverse sequelae (hypopigmentation, telangiectasia, and skin atrophy) were demonstrated in corticosteroid therapy but not in PDL.18

LOW LEVEL LASER THERAPY FOR DIABETES

LLLT effectively promotes wound healing without causing burn to adjacent tissue. The operative principle, known as photobiomodulation, is particularly useful
in treating decubitus ulcers, typical of persons with diabetes and frail elderly patients who spend long hours in bed. Some wounds, such as decubitus ulcers, heal slowly or not at all in persons with diabetes or the frail elderly. Diabetes is a chronic metabolic disorder in which utilization of carbohydrate is impaired and that of lipid and protein enhanced. It is caused by an absolute or relative deficiency of insulin. Long-term complications include neuropathy, retinopathy, generalized degenerative changes in large and small blood vessels, and increased susceptibility to infection. The consequences of leaving diabetes untreated are dialysis, heart failure, paralysis, loss of limbs, and early death. Use of a low level laser can start the healing process. Even if a wound such as a leg ulcer will not heal in all cases, pain relief is usually immediate and is the most important benefit. Stimulation of the circulation may be the primary reason that pain relief occurs after the application of LLLT to chronic wounds. Laser treatment increases blood flow and raises local temperature, and no evidence has been found that laser therapy could aggravate diabetic symptoms.

In general terms, in the treatment of a chronic ulcer, a higher dose such as 3–4 J/cm² will be used on points along the periphery of the wound followed by a lower dose of 0.5 J/cm² over the open wound. The open wound needs a lower dosage than the skin-covered periphery as the laser light is not reflected or scattered but rather absorbed by the skin in the unprotected wound because it hits the uncovered cells directly. Laser therapy should be recommended as an additional treatment modality for diabetic foot problems according to Kleinman et al. However, not all results have been positive, and some studies do not support or refute the use of laser therapy as an effective therapeutic modality for diabetic ulcers (TABLE 1).

Diabetic patients have a 22-fold higher risk of nontraumatic foot amputation compared with the nondiabetic population, and according to the World Health Organization, the number of patients with diabetes mellitus will double to 250 million by the year 2050. Attempts have been made to use helium neon, CO₂, and KTP lasers to encourage wound healing in diabetics. Results were inconclusive, so that further research is needed to assess the effectiveness of biostimulation for diabetic wound healing. Stadler et al. reported that low-power laser irradiation at 830 nm significantly enhanced cutaneous wound tensile strength in a murine diabetic model, whereas Schindl et al. reported a beneficial effect on a recalcitrant diabetic neuropathic foot ulcer. Yu et al. used diabetic mice to compare the effect of basic fibroblast growth factor (bFGF), laser irradiation at 660 nm, and a combination of growth factor and laser therapy. Wound closure was significantly enhanced with light therapy alone or most effectively in combination with topical application of bFGF. LLLT is effective in enhancing wound contraction of partial-thickness abrasions. It also facilitates wound contraction of untreated wounds, suggesting an indirect effect on surrounding tissues; however, the exact mechanism by which LLLT facilitates wound healing is largely unknown, and further investigation of the mechanism of LLLT in primary wound healing is warranted.

CONCLUSION

Early laser studies were confined to in vitro studies because little was known about the side effects of laser irradiation. More studies have therefore been performed in the area of wound healing than in any other. The majority of studies have
### TABLE 1. Studies of low level laser therapy (LLLT) on open diabetic wounds

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient characteristics</th>
<th>Therapy</th>
<th>Outcomes</th>
<th>Comments</th>
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</thead>
</table>
| Shuttleworth et al.\textsuperscript{20} $n = 14$; age, 76.3 yr | **Control group:** $n = 8$; 1 diabetic patient  
**Laser group:** $n = 6$; 2 diabetic patients (3 patients received both laser and conventional treatment)  
Leg ulcers caused by a variety of conditions  
Study period: 15 wk/patient | **Control group:** conventional wound care and dressings in accordance with local wound management policy  
**Laser group:** each laser therapy session was a maximum of 4 min using HeNe at 632.8 nm and infrared laser at 904 nm. 4 J/cm²; patients received treatment and dressings twice a week | **Control group:** all patients showed improvement  
**Laser group:** 3 patients improved or healed and 3 deteriorated | Results of this study neither support nor refute the use of LLLT in wound management; further studies should incorporate a larger sample size and actively control or eliminate variables such as size of wounds |
| Landau et al.\textsuperscript{21} | $n = 50$ (patients had chronic diabetic foot ulcers and had not responded to conventional therapy)  
Age: 59 yr (±11 yr)  
Diabetes: Type 1: $n = 14$  
Type 2: $n = 35$  
Ulcer duration: 9 ± 6.6 mo  
Range: 2–70 mo | Hyperbaric oxygen (HBO)  
HBO group: 15 patients  
HBO and laser group: 35 patients  
Unilaser Scan 60, two sources of laser: HeNe at 632.8 nm and infrared laser at 904 nm 4 J/cm²  
Treatment HBO: 2–5 h, laser 20 min, 2–3×/wk  
No of treatments: 25 ± 13  
Range: 7–70  
Duration: 3 ± 1.8 mo  
Range: 1–8 mo | All patients continued medication, and antibiotic treatment was administered according to the sensitivity of the micro-organism  
No significant difference between groups | Topical hyperbaric oxygen alone or combined with a low level energy laser for treatment of patients with chronic diabetic foot ulcers were valuable adjuvants to conventional therapy |
| Gupta et al.\textsuperscript{22} | $n = 9$ (12 venous ulcers)  
**Control group:** Age, 64.7 (±9.4 yr)  
Ulcer duration: 36.0 ± 21.6 wk  
**Intervention group:** Age: 61.0 (±7.8 yr)  
Ulcer duration: 105.8 ± 36.0 wk | **Control group:** placebo treatment received sham therapy from identical appearing light sources, from same delivery system  
**Intervention group:** 2 monochromatic optical sources: 1 (red-light) source 660 nm used over ulcer for 180 s; 1 (infra-red) source 990 nm used on periphery for ulcer for 30 s; treatments were 3/wk for 10 wk | Unhealed ulcers in control group: 87.6%  
Decrease in ulcer area compared to baseline: 14.7 mm²  
Unhealed ulcers in intervention group: 24.4%  
Decrease in ulcer area compared to baseline: 193.0 mm² | Low level laser therapy was effective modality for treatment of venous leg ulcers  
No adverse effects |
shown beneficial effects, and most of the work has been performed using the helium neon (He-Ne) 632.8 nm laser.\textsuperscript{10} Research studies on the effects of low energy laser irradiation on biologic function are growing in number and scope. Although many experiments show alleviation of pain, the quality of the investigations, the number of subjects, and the varied techniques frequently preclude statistical verification. Currently, no universally accepted theory has explained the mechanism of either “laser analgesia” or “laser biostimulation.” Modification of current lasers and innovative advances with biomedical laser instrumentation may eventually allow the physician to match optimally the laser and the treatment procedure with the lesion.\textsuperscript{3} Low level laser therapy is still very controversial, and there are still studies that present conflicting results. However, as knowledge and techniques improve, a scientific explanation may provide an understanding of the cellular and molecular effects of LLLT.\textsuperscript{19}

REFERENCES


Low level laser therapy (LLLT) has been suggested as an effective therapeutics in inflammatory processes modulation and tissue repairing. However, there is a lack of studies that analyze the anti-inflammatory effects of the infrared lasers in muscular skeletal injury. The aim of this study was to investigate the effects of low-level laser therapy 904 nm in the repair process of skeletal muscle tissue. The term Laser is the acronym for Light Amplification by Stimulated Emission of Radiation. A laser light is monochromatic, collimated, and coherent. A laser is a device that produces such a light. Low level laser therapy (LLLT) is used by some physiotherapists to treat various musculoskeletal condition. LLLT is a non-invasive light source treatment that generates a single wavelength-dependent capability to alter cellular behavior in the absence of significant thermal effects. To date, LLLT has been used for therapeutic purposes in treating wound healing, musculoskeletal pain and dental. The current experimental study was conducted in compliance with all the ethical guidelines of the Dankook University Institutional Animal Care and Use Committee. 2. Laser irradiation and the measurement of tissue penetration. In rats of two laser groups, a 670-nm diode laser or an 808-nm one (LAS-30A, Daedeok Laser, Daejeon, Korea) were irradiated to the testes at an intensity of 360 J/cm2/day (200 mW ´ 30 min) for five days. Low-level laser therapy. LLLT, also called photobiomodulation, has been investigated as a potential noninvasive technique for the prevention of oral mucositis in patients undergoing head and neck radiotherapy. LLLT involves daily local treatment of the oropharyngeal mucosa with a monochromatic light source. The exact mechanism of action of LLLT is unknown. The principle of using low level laser therapy (LLLT) is to supply direct biostimulative light energy to body cells. Absorbed laser energy causes stimulation of molecules and atoms of cells. Using low-intensity laser radiation on the tissues does not cause rapid and significant increase in tissue temperature.[1] Among various lasers used for periodontal purposes, semiconductor diode lasers are mainly applied in. The mechanisms of low level laser therapy are complex, but essentially rely upon the absorption of particular visible red and near infrared wave lengths in photoreceptors within sub-cellular components, particularly the electron transport chain within the membranes of mitochondria.