The current status of low level laser therapy in dentistry. Part 1. Soft tissue applications

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Abstract
Despite more than 30 years of experience with low level laser therapy (LLLT) or 'biostimulation' in dentistry, concerns remain as to its effectiveness as a treatment modality. Controlled clinical studies have demonstrated that while LLLT is effective for some specific applications, it is not a panacea. This paper provides an outline of the biological basis of LLLT and summarizes the findings of controlled clinical studies of the use of LLLT for specific soft tissue applications in dentistry. Areas of controversy where there is a pressing need for further research are identified.

Key words: Low level laser therapy, wound healing, biostimulation, fibroblasts.

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Introduction
The last decade has seen an explosion of research work in the application of laser technology to general dental practice. Despite the many advantages which 'hard' or 'hot' surgical lasers (such as CO₂, Nd:YAG and Er:YAG) offer for both soft tissue surgical and tooth-related procedures, issues such as instrument costs and the potential for thermal injury to dental pulp from thermal changes, have limited the uptake of this technology in general dental practice.1,2

At the opposite end of the equipment spectrum are the semiconductor diode lasers, which are sometimes referred to as 'cold' or 'soft' lasers. Unlike their high-powered 'hard' surgical laser counterparts, diode lasers are compact, low cost devices which have very high electrical and optical efficiencies. In medicine and dentistry, diode lasers have been used predominantly for applications which are broadly termed low level laser therapy (LLLT) or 'biostimulation';3 however, there is controversy surrounding the effectiveness of some of these procedures.4,5

The use of LLLT in dentistry is not new, and LLLT techniques have been in widespread use in Japan6 and in Europe7,8 for more than 10 years. Interest in LLLT in dentistry has been particularly high in the former Eastern block countries. In fact, the Russian literature has reports on LLLT which cover 30 years of experience with the technique,9,10 although this literature has remained largely inaccessible to the Western world. While much of this work has been done with helium-neon (HeNe) gas lasers, an identical laser wavelength (632 nm) can now be produced by diode laser devices.

There have been many claims for the therapeutic effects of LLLT on a broad range of disorders. A short selection from the list of LLLT applications promoted by some users and manufacturers of LLLT devices includes: acceleration of wound healing, enhanced remodelling and repair of bone, restoration of normal neural function following injury, normalization of abnormal hormonal function, pain attenuation, stimulation of endorphin release, and modulation of the immune system.11,12 Published data on efficacy exist for some but not all of these applications, and this presents a dilemma to the clinician faced with decisions as to what constitutes appropriate therapy.

The purpose of this report is to provide an overview of the available literature on the biology of LLLT and its clinical effects in terms of soft tissue pathology. Emphasis will be placed on controlled studies published in refereed journals, rather than on the larger body of anecdotal material and abstracts. The subsequent paper in this two-part series will examine hard tissue applications of LLLT and the related safety issues, and will provide an outline of some important aspects of the technology used in LLLT.

Biological effects of LLLT
Absorption of laser energy in LLLT

The major absorbing structures for the red visible and near infra-red laser wavelengths used in LLLT
are most likely proteins; however, the identity of the photoreceptors responsible for the biological effects of LLLT has not been resolved. Several studies have suggested that either elements in the mitochondrial cytochrome system or endogenous porphyrins in the cell are the energy-absorbing chromophores in LLLT.\textsuperscript{13,14}

Since the tissue penetration of the laser energy used in LLLT can be in the order of 5-10 mm, both superficial and deeper structures can be affected. However, as the energy penetrates the tissues, there is multiple scattering by both erythrocytes and microvessels, and thus both blood rheology and the distribution of microvessels influence markedly the final distribution of laser energy.\textsuperscript{15} It is unclear whether the photobiological effects which occur with LLLT are specific to monochromatic coherent laser energy, or can be elicited by conventional light sources emitting non-coherent energy over a similar range of wavelengths.

**Effects of LLLT on fibroblasts**

The stimulatory effects of LLLT on fibroblast proliferation in vitro are well established. Although it should be noted that most cell culture studies have used dermal fibroblasts, buccal mucosal and gingival fibroblasts have a response profile which is similar to that of dermal fibroblasts. At low doses (e.g., 2 J/cm\(^2\)), LLLT stimulates proliferation, while high doses (e.g., 16 J/cm\(^2\)) are suppressive.\textsuperscript{16,17} The same type of dose response is observed both in vivo and in vitro, and occurs with all common LLLT wavelengths.\textsuperscript{18} Fibroblast maturation and locomotion through the matrix is also influenced by LLLT,\textsuperscript{19} and this in turn may contribute to the higher tensile strengths reported for healed wounds.\textsuperscript{20}

There are several mechanisms by which LLLT may stimulate the proliferation of fibroblasts. LLLT has been shown to stimulate the production of basic fibroblast growth factor (bFGF), a multifunctional polypeptide which supports fibroblast proliferation and differentiation. Fibroblasts irradiated with low dose LLLT show both increased cell proliferation and enhanced production of bFGF, while high dose LLLT suppresses both parameters,\textsuperscript{16,21} indicating a causal relationship between autocrine production of bFGF from fibroblasts and proliferation.

A further effect of LLLT on fibroblasts which can influence the wound healing process is the transformation of fibroblasts into myofibroblasts, which are responsible for wound contraction. LLLT of gingival fibroblasts in culture has been shown to induce transformation into myofibroblasts as early as 24 hours after laser treatment.\textsuperscript{22}

In terms of the effects of LLLT on fibroblasts, it is important to recognize that LLLT may affect immune cells which secrete cytokines and other growth-regulatory factors for fibroblasts. Macrophages, which are a key component of wound healing responses, are themselves prone to the effects of LLLT. Irradiation of macrophage cell lines in vitro using LLLT has been shown to release soluble factors which promote fibroblast proliferation,\textsuperscript{23} although the identity of the factors involved has not been determined.

**Effects of LLLT on immune cells**

While LLLT has been shown to increase both the phagocytic and chemotactic activity of human leukocytes in vitro, there have also been claims that LLLT can act directly and selectively on the immune system.\textsuperscript{24} At the present time, there are no published data which demonstrate that LLLT can either restore or boost the competence of the immune system.

Irradiation of human peripheral blood lymphocytes in vitro at doses which resemble LLLT delivered in vivo induces changes in nuclear chromatin similar to those found after stimulation with the mitogen phytohaemagglutinin (PHA). Moreover, laser irradiation potentiates the proliferative response of peripheral blood lymphocytes to PHA.\textsuperscript{25} In healing wounds, activation of lymphocytes by LLLT may make them more responsive to stimulatory mediators present in injured tissues.

In both in vitro and in vivo systems, LLLT influences macrophage function by promoting the secretion of factors which enhance fibroblast proliferation.\textsuperscript{26} An additional effect of LLLT which has been observed in vivo is an enhancement of the phagocytic activity of macrophages during initial phases of the repair response (6 hours after trauma). This is thought to facilitate debridement of the wound, and thereby establish conditions necessary for the proliferative phase of the healing response to begin.\textsuperscript{26,27}

**Effects of LLLT on epithelial cells**

One possible mechanism by which LLLT may enhance wound healing in vivo is via stimulation of epithelial cells. LLLT increases the motility of human epidermal keratinocytes in vitro,\textsuperscript{28} and this would explain the finding that wound sites treated with LLLT show accelerated closure.\textsuperscript{29} Despite its effects on proliferation, LLLT does not alter normal keratinocyte differentiation or the synthesis of keratins, and thus does not interfere with the formation of a normal, functioning epidermis.\textsuperscript{30} Thus, clinical use of LLLT under conditions which enhance keratinocyte migration should not alter the ultimate integrity or differentiated function of the epidermis that migrates to cover the wounded area.
Effects of LLLT on bone cells

In the laboratory setting, LLLT using a HeNe laser exerts pronounced effects on proliferation, differentiation, and calcification of cultured osteoblastic cells, although there is a specific therapeutic window for these effects. Cell proliferation and DNA synthesis are increased by LLLT only when the cells are in a phase of active growth. LLLT causes increased accumulation of calcium and accelerates calcification in vitro.29 If the in vivo parallel holds true, LLLT of healing sites within bone would be expected to increase bone deposition and promote bone regeneration.

In a study of wound healing after tooth extraction in a rat model, LLLT delivered on a daily basis for one week using a gallium-aluminium-arsenide (GaAlAs) laser, both increased fibroblast proliferation and accelerated formation of bone matrix were found.33 However, studies of the influence of LLLT on bone and connective tissue regeneration in the palate in a canine animal model failed to find an effect.33,34 While at first glance this would suggest major species variations in the response of bone cells to LLLT, in the case in point irradiation levels were low and LLLT treatments were administered every second day rather than daily. Whether LLLT exerts positive results on bone regeneration following tooth extraction in humans remains controversial,35 although there are reports that the formation of granulation tissue during post-extraction healing is accelerated.36

Effects of LLLT on the blood vascular system

Vascular spasm can result in tissue ischaemia, and has been linked to a range of painful conditions. In in vitro systems, LLLT can induce a prompt reduction in isometric tension of vascular smooth muscle, while the same effect can be induced by LLLT in vivo delivered through the skin to the underlying vessels.37 Relaxation of vascular smooth muscle may contribute to analgesic effects of LLLT.

Soft tissue applications of LLLT

Evaluating the literature describing clinical applications of LLLT is complicated by the wide variations in methodology and dosimetry between different studies. Not only have a range of different wavelengths been examined, but exposure times and the frequency of treatments also vary. The inclusion of sham-irradiated controls in clinical studies is an important element, since placebo effects can be dramatic, particularly in terms of the level of pain experienced following treatment. In the light of these caveats, it is nevertheless informative to look at selected clinical studies of LLLT in medicine and dentistry.

Effects of LLLT on musculoskeletal pathology

Low level laser therapy is currently used in the therapy of rheumatoid arthritis, chronic pain, and muscle strain in both human and veterinary medicine. Physiotherapy has been an area of particularly high utilization of LLLT.38 Although some trials of LLLT in musculoskeletal injuries,39 synovitis, arthritis,40 and chronic low back pain41 have failed to demonstrate the efficacy of this treatment approach, positive results have been obtained in similar trials involving patients with repetitive strain injury, carpal tunnel syndrome, and lateral epicondylitis (‘tennis elbow’).36,43

A comprehensive meta-analysis of the effects of LLLT on musculoskeletal pain has been published.44 Of 23 published trials of LLLT, 17 employed a controlled design and of these ten were double blind. Pooling the pain score data from 13 of these studies revealed only small differences in pain between LLLT and placebo treatments, although it should be recognized that pooling data from studies which used different methodologies and dosimetry is a questionable approach.

Wound healing

Reports of LLLT applied to soft tissues in vitro and in vivo suggest stimulation of specific metabolic processes in healing wounds. While there are variations according to the mode of delivery and the type of tissue studied, a common feature of these studies is that while low doses of LLLT are stimulatory, high doses of laser radiation are suppressive.45,46

In the rat animal model of the healing of skin wounds by secondary intention, daily LLLT during the postoperative period has been shown to stimulate collagen formation and increase the strength of a forming scar. At high laser irradiances (9.3 J/cm²), these reparative processes are slowed and disturbed.47,48 Of interest, studies in which LLLT has been delivered pre-operatively (i.e., prior to wounding) have failed to show significant benefits.49,50 Major changes seen in wounds treated with LLLT include increased granulation tissue, early epithelialization, increased fibroblast proliferation and matrix synthesis, and enhanced neovascularization.51 Of note, daily treatment with LLLT is required to provide the maximal benefit. LLLT delivered every second day provides little benefit.33,52

In humans, anecdotal clinical observations and small case studies have suggested that LLLT (generally using HeNe lasers) stimulates wound healing. However, controlled clinical studies have produced somewhat conflicting results.

In a clinical study of skin wounds in over 125 patients, LLLT increased the strength of the post-operative scar.49 Similarly, in a study of wound
healing involving 152 diabetic patients with purulent injuries of skin and underlying soft tissues. LLLT of wounds resulted in a shortened healing phase. In a third study, LLLT used in 512 patients with corneal wounds, burns, or ulcers resulted in accelerated healing compared with a reference group of patients who received conventional treatment. In all three studies, LLLT comprised daily exposures, which would be expected to give more pronounced effects than either a single treatment or weekly treatments.

Studies of the effects of LLLT on the healing of chronic venous leg ulcers have yielded equivocal results. In one study involving 46 patients, all patients received either active LLLT or placebo LLLT twice weekly for 12 weeks. There were no significant differences in either the proportion of healed ulcers or in the ulcer area in the active LLLT group compared with the placebo group. However, in a parallel study conducted elsewhere at the same time, 12 patients with chronic venous leg ulcers unresponsive to conservative measures showed very positive effects to a course of LLLT over 12 weeks. In the latter study, two ulcers healed completely and there was a 27 per cent reduction in the size of the remaining ulcers. Treatment resulted in a 44 per cent increase in the ulcer floor area occupied by healthy granulation tissue. An additional positive effect of LLLT was a reduction in pain from the lesions following LLLT.

Positive results have been reported in studies of the effect of LLLT on intraoral wound healing. LLLT has been shown to accelerate the healing of oral mucosal wounds in both mice and rats. Positive effects of LLLT on the healing of lesions of recurrent aphthous stomatitis in humans have also been recorded.

There have been claims that LLLT accelerates healing of dentoalveolar abscesses, periapical granulomas, and gingivitis, but these are based on studies which lack appropriate controls. Studies of LLLT in the treatment of alveolitis, ulcers caused by dentures, herpes simplex labialis, marginal periodontitis and periconodontitis have not revealed any significant benefits. In contrast, there are some positive data which indicate that LLLT promotes healing and dentinogenesis following pulpotomy, and healing of mucositis and oropharyngeal ulcerations in patients undergoing radiotherapy for head and neck cancer.

**LLLT and analgesia**

The ability of LLLT to exert analgesic effects has historically been a major clinical application of the technique. In vivo studies of the analgesic effect of LLLT on nerves supplying the oral cavity have demonstrated that LLLT decreases the firing frequency of nociceptors, with a threshold effect seen in terms of the irradiance required to exert maximal suppression. In vivo, LLLT selectively inhibits a range of nociceptive signals arising from peripheral nerves, including neuronal discharges elicited by pinch, cold, heat stimulation, and chemical irritation. In contrast, neuronal discharges induced by brush stimulation are not affected by LLLT. There is some evidence that laser irradiation may selectively target fibres conducting at slow velocities, particularly afferent axons from nociceptors.

While the target tissues can be irradiated directly to elicit analgesic effects, an alternative approach is to irradiate target skin points used in acupuncture or acupressure. There have been few controlled clinical trials of the effectiveness of this technique. In a large case study of LLLT acupuncture involving 562 cases of surgical exodontia and 48 cases of minor oral surgery, LLLT was able to provide adequate post-operative analgesia in all cases. No sedatives or analgesics were administered before or during any of the procedures. Similar results were obtained in a separate case series in which surgical sites in 3000 patients were irradiated, rather than related acupuncture points. There have been claims that successful analgesia following oral surgery can be achieved with all major LLLT wavelengths from 632 nm to 904 nm.

**LLLT and nerve regeneration**

Low level laser therapy has been shown to both reduce the production of inflammatory mediators of the arachidonic acid family from injured nerves, and to promote neurone maturation and regeneration following injury. In the surgical arena, LLLT has been considered an ideal approach for promoting the regeneration of damaged neural tissue. LLLT has been shown to be effective for promoting axonal growth in injured nerves in animal model systems. The LLLT protocols used typically involve daily irradiation for prolonged periods, e.g., 10 days at 4.5 J per day.

The direct application of this technique to dentistry has yielded positive results in promoting the regeneration of inferior dental nerve (IDN) tissue damaged during surgical procedures. The incidence of IDN damage during removal of third molar teeth has been reported to be as high as 5.5 per cent and up to 100 per cent during sagittal split osteotomy. Sensory aberrations following IDN damage can have a significant impact on quality of life. For this reason, interest has focused on the use of LLLT for treatment of persistent IDN damage (i.e., greater than 6 months post-surgery), which would normally be regarded as a permanent disability. In a recent double-blind clinical trial, the effects of LLLT treatment on touch and temperature sensory perception in 13 patients who suffered from...
long-standing post-surgical IDN injury were assessed. LLLT involved treatment along the distribution of the nerve for a total of 20 treatments. Control subjects received placebo LLLT. The degree of mechanoreceptor impairment and thermal sensitivity disability was comparable in test and control groups before treatment. Following LLLT, the test group showed a significant improvement in mechanoreceptor sensory testing, as well as a subjective improvement in sensory function, indicating that LLLT can improve mechanoreceptor perception in long-standing sensory aberrations in the IDN. However, there was no significant improvement in thermal responses in either group.

**Post-surgical pain**

While there is accumulating evidence to support the analgesic capabilities of LLLT when used postsurgically, the mechanisms of this effect are unclear. The effect has been explained in terms of interference with the mediation of the pain message and/or the stimulation of endorphin production, although direct evidence for these mechanisms has yet to be published.

The effectiveness of LLLT for treating post-surgical pain arising from the oral cavity has been investigated in several studies. There are reports that a single episode of LLLT (irradiance 0.9-2.7 J) is 100 per cent effective for apical periodontitis following root canal treatment and post-extraction pain, however these studies did not include sham-irradiated controls so that placebo effects cannot be excluded.

In a preliminary assessment of the effects of LLLT on post-surgical discomfort, 15 patients who had surgical removal of bilaterally symmetrical mandibular third molars were evaluated, using a split mouth study design. Immediately following third molar surgery, LLLT was applied to one side of each patient’s mouth, while the other side served as the sham-irradiated control. There was a significant reduction in postoperative pain both on the day of surgery and on the first postoperative day.

These results conflict with two more comprehensive studies conducted subsequently. Both studies examined the effect of LLLT on post-extraction pain using a randomized double-blind design. In the first study, 64 patients undergoing the extraction of bilaterally impacted mandibular third molar teeth were assessed. One side was treated with LLLT, while the other side was treated using an apparently identical but non-operating laser. There were no differences in pain and swelling, at either 3 or 7 days after surgery.

In the second study, a similar protocol was followed except that a crossover design was used, and the teeth were removed in two separate operations. Once again, laser treatment was compared with a placebo laser. There were no statistically significant differences in swelling, trismus, and pain between the experimental side and the placebo side.

**Sinusitis**

Available evidence indicates that the effect of LLLT on pain from sinusitis is minimal when the therapy is applied during acute exacerbations of the condition. In one double-blind clinical study, 60 adult patients received 3 treatments with an interval between treatment of 1 to three days. There were no statistically significant differences in pain, well-being or duration of illness observed between patients treated with laser and controls treated by placebo.

In contrast, in a separate study involving 65 children aged 6 to 15 years with sinusitis, LLLT was instituted once acute disease had resolved. It was found that LLLT improved microcirculation, reduced oedema, and reduced the frequency of relapses. One interpretation of these results is that the time at which LLLT is implemented influences the effectiveness of the therapy.

**Post-herpetic neuralgia**

Low level laser therapy with the HeNe laser has shown promising results in the treatment of post-herpetic neuralgia, a condition which presents a significant problem in terms of clinical management. In a study involving 36 patients suffering from this condition, each patient was irradiated at several points around the painful area 2 or 3 times per week. Significant pain relief was found in almost 90 per cent of subjects. In contrast to these positive results, LLLT using a GaAlAs laser (wavelength 904 nm) was shown to be ineffective in the treatment of a variety of chronic oro-facial pain conditions in a double-blind placebo controlled study involving 40 patients.

**Gingivitis**

As inflammation of the gingiva is rarely associated with significant pain, there has been little interest in exploiting possible analgesic effects of LLLT in its management. In a recent study, 10 subjects refrained from all oral hygiene measures for 28 days to induce gingivitis. On days 21 and 24 the marginal gingiva, buccal to one of the lateral mandibular incisors, was subjected to LLLT. The gingiva of the contralateral incisors was exposed to ordinary light as a control. There was no statistical difference between the laser exposed sites and the control sites in terms of either plaque formation, inflammation, or gingival bleeding.
Table 1. Possible mechanisms involved in the acceleration of wound healing by LLLT

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<tr>
<th>Cell Type</th>
<th>Mechanism</th>
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<tr>
<td>Fibroblasts:</td>
<td>Proliferation, M aturation, Locomotion, Transformation into myofibroblasts, Reduced secretion of PGE2 and IL-1, Enhanced secretion of bFGF, M acrophages, Phagocytosis, Secretion of fibroblast growth factors, Fibrin resorption, Lymphocytes: Activation, Enhanced proliferation, Epithelial cells: M otility, Endothelium: Increased granulation tissue, Relaxation of vascular smooth muscle, N eural tissue: Reduced synthesis of inflammatory mediators, M aturation and regeneration, Axonal growth</td>
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Conclusions

It is clear that LLLT can influence the behaviour of many cell types, and that multiple effects can occur simultaneously. The environment of the healing wound is a case in point, in which there are considerable data from cell culture studies and animal models that indicate positive effects of LLLT (Table 1). Nevertheless, much further work is required to determine the mechanisms of action of LLLT at the level of the individual cell. In terms of the clinical applications of LLLT, there is accumulating evidence which supports particular soft tissue applications in dental practice (Table 2), and there is sufficient evidence on which to raise doubts as to the efficacy of others. It is essential that treatment protocols are based on the results of randomized controlled clinical trials. There is an urgent need for more of these studies to be undertaken, and for the results of these to be disseminated widely to clinicians using LLLT. Only then will the aura of controversy and the stigma of anecdote and empiricism be removed from this area of clinical practice.

References


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