

Introduction to Low Level Laser / Light Therapy (LLLT) for Veterinarians

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Introduction

Low Level Light / Laser Therapy (LLLT) is the application of light (usually a low power laser or LED) to promote tissue repair, reduce inflammation or induce analgesia. Unlike other medical laser treatments LLLT is not a cutting or heating therapy, it is more akin to photosynthesis in plants.

Over 300 human clinical trials have published on LLLT and many systematic reviews performed for a range of musculoskeletal pathologies with favorable conclusions and published by The Lancet [1], British Medical Journal (BMJ) [2], International Association for the Study of Pain (IASP) [3] the World Health Organization (WHO) [4] and the the Multinational Association of Supportive Care in Cancer (MASCC) [5].

One companion pet, controlled clinical trial has been published [6]. It was a prospective study to determine if LLLT and surgery for intervertebral disk herniation encouraged ambulation faster than surgery alone. Thirty-six dogs with acute paraparesis/paraplegia due to acute intervertebral disk herniation were evaluated and given a modified Frankel score.

Modified Frankel scores	
5	Pain only
4	Paresis, ambulatory
3	Paresis, non-ambulatory
2	Plegic, nociception positive
1	Plegic, superficial nociception negative, deep nociception positive
0	Plegic, deep nociception negative < 48 hours > 48 hours

Dogs with scores 0 to 3 were included in the study. Dogs were randomized to the control or THOR LLLT treatment group. LLLT group were treated daily for five days. The time to achieve a modified Frankel score of 4 was significantly lower ($P=0.0016$) in the LLLT group (median 3-5 days) than the control group (median 14 days).

LLLT devices are typically laser or LED and in the red and near infrared spectrum (600nm - 1,000nm), with power density range 5mW - 5W/cm² produced by devices as little as 1mW and even up to 10 Watts. Sometimes pulsed and sometimes continuous beams are used. Treatment time is typically in the

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range of 30 - 60 seconds per point. As little as one point may be treated but maybe a dozen or more points may be treated in some cases. For acute and post operative pathologies as little as one treatment may be all that is necessary (two or three may be better) but for chronic pain and degenerative conditions sometimes as little as four and sometimes as many as ten treatment sessions may be necessary.

The following is a brief overview of how LLLT works, the clinical benefits and treatment parameters.

History

In 1967, a few years after the first working laser was invented, Dr Endre Mester in Semmelweis University Budapest, Hungary wanted to find out if this new 'ray of light' might cause cancer. He took some mice, shaved the hair from their backs, divided them into two groups and gave a laser treatment with a low powered ruby laser to one group and not the other. The treatment group did not get cancer and, to his surprise, the hair on the treated group grew back more quickly than the untreated group. He described the effect as "laser biostimulation" [7]. Forty-five years later over 400 human clinical trials and thousands of laboratory studies have been published with over 30 papers being published every month on the mechanism of action, the downstream physiological changes, the clinical benefits (RCTs) and pooled effect sizes in several systematic reviews with meta-analyses. [1-4, 8]

To-date more than 400 randomized double blind placebo controlled clinical trials have been published with some professional guidelines suggesting LLLT is used as part of standard care, including :

- World Health Organization (WHO) Task Force on Neck Pain systematic review [4]
- The Lancet Systematic review of LLLT for Neck Pain [1]
- International Association for the Study of Pain (IASP) fact sheets for Myofascial Pain Syndrome , osteoarthritis and neck pain [3]
- British Medical Journal (BMJ) Systematic review and guidelines for treating tennis elbow [2]
- American Physical Therapy Association (APTA) Systematic review and clinical practice guidelines for achilles tendinopathy: [9]
- British Journal of Sports Medicine (BJSM) Systematic review for frozen shoulder [8]
- European Society for Medical Oncology (ESMO) Clinical practice guidelines for oral mucositis [10]
- Multinational Association for Supportive Cancer Care (MASCC) Clinical practice guidelines for oral mucositis [5]

Applications

Most of the clinical evidence for LLLT is human clinical trails but they will translate to pet companions.

<i>Application</i>	<i>LLLT effects</i>	<i>Refs</i>
Back and neck pain	Analgesic and anti-inflammatory Reduced pain Improved function	[1, 75, 76]
Degenerative joint	Analgesic and anti-inflammatory Reduced pain Reduced disability	[38, 73, 74]
Soft tissue injury	Reduced inflammation, edema Reduced pain earlier rehabilitation	[31, 45, 72]
Post operative	Reduced inflammation, edema Reduced pain Earlier ambulation	[6, 60, 62]
Non healing wounds	Faster healing Reduced infection Less pain	[69-71]
Brain Injury	Improved locomotion Improved cognitive scores Improved behavioral activities	[66-68]
Bone healing	Bone consolidation, stiffness, healing Bone formation (LED) Orthopedically expanded suture in rats (LED)	[63-65]
Oral Pathologies	Post extraction pain, swelling and trismus Chronic Periodontitis Herpes Simplex	[85-87]

Mechanism of action

Most of the effects of LLLT can be explained by light absorption in the mitochondria [11-13]. Every cell in the body has abundant mitochondria (hundreds to thousands per cell). Mitochondria make cellular energy (ATP) from oxygen and pyruvate. In stressed or ischemic tissues, mitochondria make their own nitric oxide (mtNO) [14-16] which competes with oxygen. The mtNO binds to Cytochrome c Oxidase (CcO) (the terminal enzyme in the electron transport chain) and displaces oxygen [17]. This displacement of oxygen has two negative effects;

- Reduced ATP synthesis
- Increased oxidative stress (leading to inflammation via the inflammatory “master switch” NF-κB) [14-16, 18-20].

The effect of LLLT on hypoxic / stressed tissues can be described in four stages:

Primary effect of LLLT: Absorption by cytochrome c oxidase

Cytochrome c oxidase (CcO) absorbs red and near infrared light, the transfer of light energy by this enzyme triggers a series of downstream effects [11, 21-23].

Secondary effect: Modulation of ATP, nitric oxide & reactive oxygen species

Changes in ATP, reactive oxygen species and nitric oxide follow light absorption by CcO. These effects are redox state and dose dependent. In hypoxic or otherwise stressed cells it has been shown many times that following LLLT, nitric oxide is released, ATP is increased and oxidative stress is reduced [24-28].

Tertiary effect: Downstream intracellular responses (gene transcription, and cellular signaling)

The downstream effects of LLLT released nitric oxide, increased ATP and reduced oxidative stress are many. They are context and cell type specific. Either directly or indirectly these biochemical intermediates affect components in the cytosol, cell membrane, and nucleus that control gene transcription and subsequently cell proliferation, migration, necrosis and inflammation [24-28].

Quaternary effect: Extracellular, indirect, distant effects

Tissues that have not absorbed photons can also be affected indirectly via secretions from cells that have absorbed light. Cells in blood and lymph can be activated and they travel significant distances from the treatment area to have distant (systemic) effects [29]. These can be autocrine, paracrine, and endocrine effects (sometimes known as a “bystander” effects).

Edema / Lymphatic flow

There is good evidence that LLLT also improves lymphatic flow. A systematic review of eight clinical trials of LLLT for post mastectomy lymphoedema concludes that “There is moderate to strong evidence for the effectiveness of LLLT for the management of breast cancer related lymphedema” [30]. A controlled clinical trial on soccer players with second degree ankle sprains, found a significant reduction in edema volume for the laser group compared with placebo laser (both groups also had rest, ice, compression and elevation) [31]. A laboratory trial on Carrageenan-induced edema in the mouse paw

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found that treating lymph nodes alone was enough to reduce edema in the mouse paw [32]. The mechanism of action is unknown.

Analgesia

Analgesic effects are probably via a different mechanism from the increased ATP / reduced oxidative stress model described above. According to a systematic review of laser analgesia mechanisms by Chow et al [33], higher power density laser light $> 300\text{mW/cm}^2$, when absorbed by nociceptors, have an inhibitory effect on A δ and C pain fibers. This high power density LLLT treatment slows conduction velocity, reduces amplitude of compound action potentials and suppresses neurogenic inflammation. Chow's own laboratory studies show that LLLT blocks anterograde transport of ATP-rich mitochondria in dorsal root ganglion neurons. Varicosities result from this inhibition, this is normally associated with disruption of microtubules. This effect is completely reversible and lasts only 48 hours [34-36]. More work is needed to fully understand the complete mechanism of action.

Myofascial Trigger points

Myofascial trigger points are palpable nodules in taut muscle bands and contraction of muscle fibers that lead to muscle spasms and limited joint movement. They are a component of several pain conditions, including migraine, tension-type headaches, temporomandibular disorder and neck pain. The motor end plate is central to the etiology of trigger points and EMG studies have shown abnormally high electrical activity over trigger points. Electrical activity is reduced after after LLLT and clinical studies have shown that LLLT has immediate and cumulative effects on reducing pain [37-40], however the mechanism of action is not yet fully understood.

LLLT parameters

For LLLT to be effective, the irradiation parameters (wavelength, power, power density, pulse parameters) need to be within certain ranges.

Irradiation parameters and dose

Only when the correct parameters are used for the required amount of time is the treatment effective. If the power density is too low and / or the time is too short, then there is no significant effect.

Alternatively, if the power density is too high and / or the treatment time is too long, then the benefit is lost and sometimes unwanted inhibitory effects occur [41-43].

It is imperative that researchers understand the relevance of parameters as well as to accurately measure before proceeding with studies.. Many researchers fail to accurately measure or even report some of these parameters. This is due, in part, to a poor appreciation of the relevance of these parameters and also because some of these measurements require expensive instrumentation that need to be operated by trained engineers or physicists [44].

Parameters should be considered in two parts: the 'medicine' and the 'dose'. These are described in the following two tables.

Irradiation Parameters (The Medicine)

Parameter	Unit	
Wavelength	nm	It is the structure of cytochrome c oxidase and its redox state that determines which wavelengths of light will be absorbed [11-13].. The optimum wavelength is not universally agreed, but most common LLLT devices used are typically within the 600nm - 1000nm range. There are many absorption peaks for cytochrome c oxidase in that range, they penetrate tissues well, and many clinical trials have been successful with them.
Power	W	The most common researched LLLT devices are in the range 50 - 200mW, but power density is just as important (if not more so), especially for large beam areas.
Beam Area	cm	Beam area is required for calculating power density, but is difficult to measure and frequently misreported. Diode laser beams are typically not round (more often they are like an ellipse) and the beams are usually brighter in the middle and gradually weaker towards the edge (Gaussian distribution). This has been poorly understood by most researchers and errors are frequently made. The aperture does not define the beam size, which should be measured using a beam profiler using at the 1/e [44, 81].
Power Density	W/cm	Power density is the product of Power (W)/beam area (cm parameter is frequently misreported due to difficulty with measuring beam area [44, 80]. Studies that have taken the trouble to measure beam power density carefully & made measurements at the target tissue report tissue repair & anti-inflammatory effects in the range of 5 - 55mW/cm power densities; a systematic review found power densities > 300 mW/cm ² are necessary to inhibit nerve conduction in C-fibres and A-delta fibres [33]
Pulse structure	Peak Power (W) Pulse freq. (Hz) Pulse Width (s) Duty cycle (%)	If the beam is pulsed, then the reported power should be the “Average Power” and calculated as follows: Peak Power (W) × pulse width (s) × pulse frequency (Hz) = Average Power (W). A review of the effect of pulses [84] concludes that “there was some evidence that pulsed light does have effects that are different from those of continuous wave light. However further work is needed to define these effects for different disease conditions and pulse structures.” A subsequent study on traumatic brain injury in mice [83] showed that 10Hz to be more effective than 100Hz or CW in reducing the neurological severity score.
Coherence		Coherent light produces laser speckle, which has been postulated to play a role in the photobiomodulation interaction with cells and sub-cellular organelles. No definitive trials have been published to-date to confirm or refute this claim but it is clear that coherence is not required to have good clinical effects. [82]

Dose parameters (time / energy / fluence)

Having established suitable irradiation parameters, they must be applied for adequate amount of time to be effective [41, 42, 45, 46].

Energy (Joules) or energy density (fluence) (W/cm^2) is often referred to as “dose”. These are different calculations and, on their own, are both potentially flawed methods of reporting this therapy. Table 2 shows the formulas and discusses the limitations.

TABLE 2. Dose parameters Time / Energy / Fluence (“Dose”)		
Energy (Joules)	J	Calculated as: Power (W) x time (s)= Energy (Joules) Using Joules as an expression of dose is potentially unreliable as it assumes an inverse relationship between power and time and ignores power density. See Table 1.
Energy Density (Fluence)	J/cm	Calculated as: Power (W) x time (s) / beam area = Energy Density (J/cm^2) Using energy density as an expression of dose is also potentially unreliable, as it assumes an inverse relationship between power, time and power density. See Table 1.
Irradiation Time	s	Given the lack of reciprocity described above, the safest way to record and prescribe LLLT is to define the irradiation parameters, then define the irradiation time and not rely on the total energy or fluence applied. Typically treatment times are in the range 30 - 60 seconds per point.
Treatment interval	Hours Days or weeks	One treatment of acute injuries (or immediately post op) has clinically meaningful effects (though follow up treatment the next day may also be welcomed by the patient). For chronic non healing or chronic pain pathologies, LLLT typically requires two or three treatments a week for two or three weeks to achieve clinical significance.

Depth of penetration

Wavelengths in the range 700nm - 850nm penetrate well and may just about achieve 5mW/cm² at 5cm deep when the laser beam power is 1W and surface density is 5W/cm² according to this author's own (yet to be published) fresh cadaver and porcine experiments. Kendric Smith's paper on photobiological fundamentals [47] includes an experiment on light penetration through the human hand. Broad spectrum light projected through the hand and measured with a spectrophotometer shows that most visible light does not pass through the hand but far red and near infrared in the range 670nm - 900nm penetrates particularly well, with two peaks around 725nm and 810nm. Similar studies on rats found a peak at 810nm [48].

Treatment

There are four common clinical targets for LLLT.

1. The site of injury to promote healing, remodeling and reduce inflammation [49-53]
2. Lymph nodes to help reduce edema and inflammation. [30, 32, 54]
3. Nerves to induce analgesia [33, 34, 36, 55]
4. Trigger points to reduce tenderness and relax contracted muscle fibers [37-40].

Treatment times per point are typically in the range 30 seconds to 1 minute. As little as one point may be treated in some cases, but as many as 10 or 15 points may be treated for more complex dysfunction's.

Safety

There is less risk associated with LLLT (particularly the LED systems) than the class IV surgical lasers. The potential hazards are mostly ocular rather than fire as most LLLT devices are class 3B lasers or LED, though some LLLT devices are defocused class IV lasers. In most cases, LLLT devices emit divergent beams (not collimated), so the ocular risk diminishes over distance (in the range of a couple of yards / meters). See manufacturer's manual for the nominal ocular hazard distance (NOHD). ANSI Z136.3 (2011) is the current definitive USA document on laser safety in health care environments and IEC 60825 is the international standard Part 8: is Guidelines for the safe use of laser beams on humans.

Contraindications

The North American Association for Laser Therapy conference 2010 held a consensus meeting on safety and contraindications: The main recommendations included:

- EYES - Do not aim laser beams into the eyes; everyone present to wear appropriate safety spectacles. LED ONLY is used to treat ocular disorders.
- CANCER - Do not treat over the site of any known primary carcinoma or secondary metastasis unless the patient is undergoing chemotherapy; it's use can be considered in terminally ill cancer patients for palliative relief.
- PREGNANCY - Do not treat directly over a developing fetus (consequences unknown)
- EPILEPTICS - Be aware that low frequency pulsed visible light (<30hz) might trigger a seizure in photosensitive epileptic patients. Make sure they cannot see any pulsing beams.

Adverse effects

The Lancet review on neck pain [1] reported that "Half the studies obtained data for side-effects, with tiredness reported in the laser-treated group in three studies,42'46'" which was significant in one study"

A chronic joint disorder systematic review [38] reported: "In terms of side effects, six of the LLLT trials with optimal dose explicitly stated in their report that no adverse effects were observed. One trial reported an incident of transient adverse effects for one patient in each group.

Conclusion

LLLT is a safe effective treatment for faster healing, better tissue remodeling, reduced inflammation and analgesia in a wide range of pathologies. It is drug free and relatively side-effect free and seems to work where pharmaceuticals do not [57-62].

Glossary

Beam profiler	an instrument for measuring the beam intensity distribution
Laser speckle	a random fuzzy looking pattern produced by coherent laser light. Technically speaking they are a random intensity pattern produced by the mutual interference of a set of wavefronts.
LED	Light Emitting Diode. A narrow spectral width (one colour) semiconductor light source.
Off-label	Use for a condition other than that for which it has been officially approved by a regulatory authority (e.g. FDA in USA, CE for Europe, Health Canada, TGA in Australia).
“Per point”	The region of treatment which may be a small area for a single laser beam (<1cm array of incorporating many laser diodes or LEDs.
Systematic review	A review in which research about a topic has been systematically identified, appraised and summarised.
Tissue remodelling	The third phase of tissue repair after inflammation and cell proliferation
1/e ² point	Light beams do not typically have defined edges and the beam distribution is not usually uniform. To calculate power density laser physicists use the mathematical function 1/e ² to define the area. This is the area in which 86.5% of the power is contained.

Abstracts

Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials.

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BACKGROUND: Neck pain is a common and costly condition for which pharmacological management has limited evidence of efficacy and side-effects. Low-level laser therapy (LLLT) is a relatively uncommon, non-invasive treatment for neck pain, in which non-thermal laser irradiation is applied to sites of pain. We did a systematic review and meta-analysis of randomised controlled trials to assess the efficacy of LLLT in neck pain. **METHODS:** We searched computerised databases comparing efficacy of LLLT using any wavelength with placebo or with active control in acute or chronic neck pain. Effect size for the primary outcome, pain intensity, was defined as a pooled estimate of mean difference in change in mm on 100 mm visual analogue scale. **FINDINGS:** We identified 16 randomised controlled trials including a total of 820 patients. In acute neck pain, results of two trials showed a relative risk (RR) of 1.69 (95% CI 1.22-2.33) for pain improvement of LLLT versus placebo. Five trials of chronic neck pain reporting categorical data showed an RR for pain improvement of 4.05 (2.74-5.98) of LLLT. Patients in 11 trials reporting changes in visual analogue scale had pain intensity reduced by 19.86 mm (10.04-29.68). Seven trials provided follow-up data for 1-22 weeks after completion of treatment, with short-term pain relief persisting in the medium term with a reduction of 22.07 mm (17.42-26.72). Side-effects from LLLT were mild and not different from those of placebo. **INTERPRETATION:** We show that LLLT reduces pain immediately after treatment in acute neck pain and up to 22 weeks after completion of treatment in patients with chronic neck pain. **FUNDING:** None.

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Acute Low Back Pain with Radiculopathy: A Double-Blind, Randomized, Placebo-Controlled Study.

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Abstract Objective: The aim of this study was to investigate the clinical effects of low-level laser therapy (LLLT) in patients with acute low back pain (LBP) with radiculopathy. **Background Data:** Acute LBP with radiculopathy is associated with pain and disability and the important pathogenic role of inflammation. LLLT has shown significant anti-inflammatory effects in many studies. **Materials and Methods:** A randomized, double-blind, placebo-controlled trial was performed on 546 patients. Group A (182 patients) was treated with nimesulide 200 mg/day and additionally with active LLLT; group B (182 patients) was treated only with nimesulide; and group C (182 patients) was treated with nimesulide and placebo LLLT. LLLT was applied behind the involved spine segment using a stationary skin-contact method. Patients were treated 5 times weekly, for a total of 15 treatments, with the following parameters: wavelength 904 nm; frequency 5000 Hz; 100-mW average diode power; power density of 20 mW/cm² and dose of 3 J/cm²; treatment time 150 sec at whole doses of 12 J/cm². The outcomes were pain intensity measured with a visual analog scale (VAS); lumbar movement, with a modified Schober test; pain disability, with Oswestry disability score; and quality of life, with a 12-item short-form health survey questionnaire (SF-12). Subjects were evaluated before and after treatment. Statistical analyses were done with SPSS 11.5. **Results:** Statistically significant differences were found in all outcomes measured ($p < 0.001$), but were larger in group A than in B ($p < 0.0005$) and C ($p < 0.0005$). The results in group C were better than in group B ($p < 0.0005$). **Conclusions:** The results of this study show better improvement in acute LBP treated with LLLT used as additional therapy.

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Clinical and functional evaluation of patients with acute low back pain and radiculopathy treated with different energy doses of low level laser therapy.

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BACKGROUND/AIM: The main clinical phenomena in acute low back pain (LBP) with radiculopathy are pain and neurological disorders. Although some studies show that low level laser therapy (LLLT) has the ability to modulate inflammatory processes and relieve acute pain condition, the laser therapy dose protocol has not been yet completely established. The aim of this study was to investigate the effects of three different energy doses of LLLT in patients with acute LBP and radiculopathy. **METHODS:** The study included 66 patients with acute LBP and radiculopathy who had been randomly divided into three groups (22 patients each) received three different doses of LLLT. The patients were treated 5 times weekly, for a total of 10 treatments, with the following parameters: wave length 904 nm, frequency 3,000 Hz, average diode power 25 mW; energy dose of 0.1 J per point in the first group, 1 J per point in the second and 4 J per point in the third group; daily treatment time and accumulated energy were 16 s and 0.4 J in the first group, 160 s and 4J in the second group and 640 s and 16 J in the third group, respectively. The parameters of assessment before and after the therapy were: lumbar and leg pain measured by visual analogue scale (VAS), local and general functional changes (Schober test, manual muscle test, straight leg raise test and the modified North American Spine Society-Low Back Pain Outcome Instrument-NASS LBP). **RESULTS:** Highly significant improvements ($p < 0.01$) were noted in all the groups after LLLT with respect to all the investigated parameters. The VAS scores were significantly lower in all the groups without a difference between the groups ($p > 0,05$). Functional improvements were better in the third group treated with the dose of 4 J per point than in other two groups ($p < 0.05$). **CONCLUSIONS:** Three different energy doses of LLLT were equally effective in alleviating lumbar and leg pain without side effects, but the dose of 4 J per point seemed to be more effective in improving the activities of daily living and lumbar mobility.

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A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders.

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We investigated if low level laser therapy (LLLT) of the joint capsule can reduce pain in chronic joint disorders. A literature search identified 88 randomised controlled trials, of which 20 trials included patients with chronic joint disorders. Six trials were excluded for not irradiating the joint capsule. Three trials used doses lower than a dose range nominated a priori for reducing inflammation in the joint capsule. These trials found no significant difference between active and placebo treatments. The remaining 11 trials including 565 patients were of acceptable methodological quality with an average PEDro score of 6.9 (range 5-9). In these trials, LLLT within the suggested dose range was administered to the knee, temporomandibular or zygapophyseal joints. The results showed a mean weighted difference in change of pain on VAS of 29.8 mm (95% CI, 18.9 to 40.7) in favour of the active LLLT groups. Global health status improved for more patients in the active LLLT groups (relative risk of 0.52; 95% CI 0.36 to 0.76). Low level laser therapy with the suggested dose range significantly reduces pain and improves health status in chronic joint disorders, but the heterogeneity in patient samples, treatment procedures and trial design calls for cautious interpretation of the results.

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Meta-Analysis of Pain Relief Effects by Laser Irradiation on Joint Areas.

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Abstract Background: Laser therapy has been proposed as a physical therapy for musculoskeletal disorders and has attained popularity because no side effects have been reported after treatment. However, its true effectiveness is still controversial because several clinical trials have reported the ineffectiveness of lasers in treating pain. **Methods:** In this systematic review, we investigate the clinical effectiveness of low-level laser therapy (LLLT) on joint pain. Clinical trials on joint pain satisfying the following conditions are included: the laser is irradiated on the joint area, the PEDro scale score is at least 5, and the effectiveness of the trial is measured using a visual analogue scale (VAS). To estimate the overall effectiveness of all included clinical trials, a mean weighted difference in change of pain on VAS was used. **Results:** MEDLINE is the main source of the literature search. After the literature search, 22 trials related to joint pain were selected. The average methodological quality score of the 22 trials consisting of 1014 patients was 7.96 on the PEDro scale; 11 trials reported positive effects and 11 trials reported negative effects. The mean weighted difference in change of pain on VAS was 13.96 mm (95% CI, 7.24-20.69) in favor of the active LLLT groups. When we only considered the clinical trials in which the energy dose was within the dose range suggested in the review by Bjordal et al. in 2003 and in World Association for Laser Therapy (WALT) dose recommendation, the mean effect sizes were 19.88 and 21.05 mm in favor of the true LLLT groups, respectively. **Conclusions:** The review shows that laser therapy on the joint reduces pain in patients. Moreover, when we restrict the energy doses of the laser therapy into the dose window suggested in the previous study, we can expect more reliable pain relief treatments.

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Improvement of pain and disability in elderly patients with degenerative osteoarthritis of the knee treated with narrow-band light therapy.

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OBJECTIVE: To evaluate the effects of low-power light therapy on pain and disability in elderly patients with degenerative osteoarthritis of the knee. **DESIGN:** Partially double-blinded, fully randomized trial comparing red, infrared, and placebo light emitters. **PATIENTS:** Fifty patients with degenerative osteoarthritis of both knees were randomly assigned to three treatment groups: red (15 patients), infrared (18 patients), and placebo (17 patients). Infrared and placebo emitters were double-blinded. **INTERVENTIONS:** Self-applied treatment to both sides of the knee for 15 minutes twice a day for 10 days. **MAIN OUTCOME MEASURES:** Short-Form McGill Pain Questionnaire, Present Pain Intensity, and Visual Analogue Scale for pain and Disability Index Questionnaire for disability were used. We evaluated pain and disability before and on the tenth day of therapy. The period from the end of the treatment until the patient's request to be retreated was summed up 1 year after the trial. **RESULTS:** Pain and disability before treatment did not show statistically significant differences between the three groups. Pain reduction in the red and infrared groups after the treatment was more than 50% in all scoring methods (P less than 0.05). There was no significant pain improvement in the placebo group. We observed significant functional improvement in red- and infrared-treated groups (p less than 0.05), but not in the placebo group. The period from the end of treatment until the patients required treatment was longer for red and infrared groups than for the placebo group (4.2 +/- 3.0, 6.1 +/- 3.2, and 0.53 +/- 0.62 months, for red, infrared, and placebo, respectively). **CONCLUSIONS:** Low-power light therapy is effective in relieving pain and disability in degenerative osteoarthritis of the knee.

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Low Level Laser Treatment of Tendinopathy: A Systematic Review with Meta-analysis.

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Abstract Objectives: To assess the clinical effectiveness of Low Level Laser Therapy (LLLT) in the treatment of tendinopathy. Secondary objectives were to determine the relevance of irradiation parameters to outcomes, and the validity of current dosage recommendations for the treatment of tendinopathy. **Background:** LLLT is proposed as a possible treatment for tendon injuries. However, the clinical effectiveness of this modality remains controversial, with limited agreement on the most efficacious dosage and parameter choices. **Method:** The following databases were searched from inception to 1(st) August 2008: MEDLINE, PubMed, CINAHL, AMED, EMBASE, All EBM reviews, PEDro (Physiotherapy Evidence Database), SCOPUS. Controlled clinical trials evaluating LLLT as a primary intervention for any tendinopathy were included in the review. Methodological quality was classified as: high (≥ 6 out of 10 on the PEDro scale) or low (< 6) to grade the strength of evidence. Accuracy and clinical appropriateness of treatment parameters were assessed using established recommendations and guidelines. **Results:** Twenty-five controlled clinical trials met the inclusion criteria. There were conflicting findings from multiple trials: 12 showed positive effects and 13 were inconclusive or showed no effect. Dosages used in the 12 positive studies would support the existence of an effective dosage window that closely resembled current recommended guidelines. In two instances where pooling of data was possible, LLLT showed a positive effect size; in studies of lateral epicondylitis that scored ≥ 6 on the PEDro scale, participants' grip strength was 9.59 kg higher than that of the control group; for participants with Achilles tendinopathy, the effect was 13.6 mm less pain on a 100 mm visual analogue scale. **Conclusion:** LLLT can potentially be effective in treating tendinopathy when recommended dosages are used. The 12 positive studies provide strong evidence that positive outcomes are associated with the use of current dosage recommendations for the treatment of tendinopathy.

Photomed Laser Surg 2009 Aug 26

A randomised, placebo controlled trial of low level laser therapy for activated Achilles tendinitis with microdialysis measurement of peritendinous prostaglandin E2 concentrations.

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BACKGROUND: Low level laser therapy (LLLT) has gained increasing popularity in the management of tendinopathy and arthritis. Results from in vitro and in vivo studies have suggested that inflammatory modulation is one of several possible biological mechanisms of LLLT action. **OBJECTIVE:** To investigate in situ if LLLT has an anti-inflammatory effect on activated tendinitis of the human Achilles tendon. **SUBJECTS:** Seven patients with bilateral Achilles tendinitis (14 tendons) who had aggravated symptoms produced by pain inducing activity immediately before the study. **METHOD:** Infrared (904 nm wavelength) LLLT (5.4 J per point, power density 20 mW/cm²) and placebo LLLT (0 J) were administered to both Achilles tendons in random blinded order. **RESULTS:** Ultrasonography Doppler measurements at baseline showed minor inflammation through increased intratendinous blood flow in all 14 tendons and measurable resistive index in eight tendons of 0.91 (95% confidence interval 0.87 to 0.95). Prostaglandin E2 concentrations were significantly reduced 75, 90, and 105 minutes after active LLLT compared with concentrations before treatment ($p = 0.026$) and after placebo LLLT ($p = 0.009$). Pressure pain threshold had increased significantly ($p = 0.012$) after active LLLT compared with placebo LLLT: the mean difference in the change between the groups was 0.40 kg/cm² (95% confidence interval 0.10 to 0.70). **CONCLUSION:** LLLT at a dose of 5.4 J per point can reduce inflammation and pain in activated Achilles tendinitis. LLLT may therefore have potential in the management of diseases with an inflammatory component.

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Low-level laser treatment can reduce edema in second degree ankle sprains.

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OBJECTIVE: Low-level laser therapy (LLLT) has been used for the last few years to treat sports injuries. The purpose of this study was to compare three therapeutic protocols in treating edema in second degree ankle sprains that did not require immobilization with a splint, under placebo-controlled conditions. **MATERIALS AND METHODS:** Forty-seven soccer players with second degree ankle sprains, selected at random, were divided into the following groups: The first group (n = 16) was treated with the conventional initial treatment (RICE, rest, ice, compression, elevation), the second group (n = 16) was treated with the RICE method plus placebo laser, and the third group (n = 15) was treated with the RICE method plus an 820-nm GaAlAs diode laser with a radiant power output of 40 mW at 16 Hz. Before the treatment, and 24, 48, and 72 h later, the volume of the edema was measured. **RESULTS:** A three by three repeated measures ANOVA with a follow up post hoc test revealed that the group treated with the RICE and an 820-nm GaAlAs diode laser presented a statistically significant reduction in the volume of the edema after 24 h (40.3 +/- 2.4 mL, p < 0.01), 48 h (56.4 +/- 3.1 mL, p < 0.002), and 72 h (65.1 +/- 4.4 mL, p < 0.001). **CONCLUSIONS:** LLLT combined with RICE can reduce edema in second-degree ankle sprains.

J Clin Laser Med Surg 2004 Apr 22(2) 125-8

Low-level laser therapy reduces time to ambulation in dogs after hemilaminectomy: a preliminary study.

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OBJECTIVES: A prospective study to determine if low-level laser therapy and surgery for intervertebral disk herniation encourage ambulation faster than surgery alone. **METHODS:** Thirty-six dogs with acute paraparesis/paraplegia due to acute intervertebral disk herniation were evaluated and given a modified Frankel score. Dogs with scores 0 to 3 were included in the study. Dogs were assigned to the control group (1) or the laser treatment group (2) based on alternating order of presentation. All dogs underwent surgery for their herniated disk. Dogs in group 2 were treated postoperatively with low-level laser therapy daily for five days, or until they achieved a modified Frankel score of 4. A 5x200-mW 810-nm cluster array was used to deliver 25 W/cm² to the skin. All dogs were scored daily by the investigators using the modified Frankel scoring system. **RESULTS:** The time to achieve a modified Frankel score of 4 was significantly lower ($P=0.0016$) in the low-level laser therapy group (median 3.5 days) than the control group (median 14 days). **CLINICAL SIGNIFICANCE:** Low-level laser therapy in combination with surgery decreases the time to ambulation in dogs with T3-L3 myelopathy secondary to intervertebral disk herniation.

J Small Anim Pract 2012 Aug 53(8) 465-9

The Effect of Infrared Laser Irradiation (LLLI) on the Duration and Severity of Postoperative Pain: A Double Blind Trial

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This trial was designed to test the hypothesis that LLLT reduces the extent and duration of postoperative pain. Twenty consecutive patients for elective cholecystectomy were randomly allocated for either LLLT or as controls. The trial was double blind. Patients for LLLT received 6- 8-min treatment (GaAlAs: 830 nm: 60 mW CW: CM) to the wound area immediately following skin closure prior to emergence from GA. All patients were prescribed on demand postoperative analgesia (IM or oral according to pain severity). Recordings of pain scores (0-10) and analgesic requirements were noted by an independent assessor. There was a significant difference in the number of doses of narcotic analgesic (IM) required between the two groups. Controls n = 5.5: LLLT n = 2.5. No patient in the LLLT group required IM analgesia after 24 h. Similarly the requirement for oral analgesia was reduced in the LLLT group. Controls n = 9: LLLT n = 4. Control patients assessed their overall pain as moderate to severe compared with mild to moderate in the LLLT group. The results justify further evaluation on a larger trial population

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Postoperative analgesia after lower third molar surgery: contribution of the use of long-acting local anesthetics, low-power laser, and diclofenac.

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OBJECTIVES: Postoperative pain is a common phenomenon after surgical extraction of lower third molars (LTM), and its successful control is an essential part of routine oral surgery. The aims of the study were twofold: (1) to evaluate the postoperative analgesic efficacy, comparing long-acting and intermediate-acting local anesthetics; and (2) to compare the use of low-power laser irradiation and the nonsteroid anti-inflammatory drug diclofenac, which are claimed to be among the most successful aids in postoperative pain control. **STUDY DESIGN:** A twofold study of 102 patients of both sexes undergoing surgical extraction of LTM was conducted. In the first part of the study, 12 patients with bilaterally impacted LTMs were treated in a double-blind crossover fashion; local anesthesia was achieved with 0.5% bupivacaine plain or 2% lidocaine with 1:80.000 epinephrine. In the second part of the study, 90 patients undergoing LTM surgical extraction with local anesthesia received postoperative low-power laser irradiation (30 patients) and a preoperative single dose of 100 mg diclofenac (30 patients), or only regular postoperative recommendations (30 patients). **RESULTS:** The results of the first part of the study showed a strikingly better postoperative analgesic effect of bupivacaine than lidocaine/epinephrine (11 out of 12; 4 out of 12, respectively, patients without postoperative pain). In the second part of the study, low-power laser irradiation significantly reduced postoperative pain intensity in patients premedicated with diclofenac, compared with the controls. **CONCLUSION:** Provided that basic principles of surgical practice have been achieved, the use of long-acting local anesthetics and low-power laser irradiation enables the best postoperative analgesic effect and the most comfortable postoperative course after surgical extraction of LTMs.

Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006 Nov 102(5) e4-8

Phototherapy promotes healing of chronic diabetic leg ulcers that failed to respond to other therapies.

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OBJECTIVE: We tested the hypothesis that combined 660 and 890 nm LED phototherapy will promote healing of diabetic ulcers that failed to respond to other forms of treatment. **RESEARCH DESIGN AND METHODS:** A double-blind randomized placebo controlled design was used to study 23 diabetic leg ulcers in two groups of 14 patients. Group one ulcers were cleaned, dressed with 1% silver sulfadiazine cream and treated with "placebo" phototherapy ($<1.0 \text{ J cm}^{-2}$) twice per week, using a Dynatron Solaris 705(R) device. Group two ulcers were treated similarly but received 3 J cm^{-2} dose. **RESULTS:** At each of 15, 30, 45, 60, 75, and 90 days of healing, mean ulcer granulation and healing rates were significantly higher for group two than the "placebo" group ($P < 0.02$). While "placebo" treated ulcers worsened during the initial 30 days, group two ulcers healed rapidly; achieving 56% more granulation and 79.2% faster healing by day 30, and maintaining similarly higher rates of granulation and healing over the "placebo" group all through. By day 90, 58.3% of group two ulcers had healed fully and 75% had achieved 90-100% healing. In contrast, only one "placebo" treated ulcer healed fully by day 90; no other ulcer attained $>$ or $=90\%$ healing. **CONCLUSION:** Combined 660 and 890 nm light promotes rapid granulation and healing of diabetic ulcers that failed to respond to other forms of treatment.

Lasers Surg Med 2009 Aug 41(6) 433-41

**Effects of phototherapy on pressure ulcer healing in elderly patients after a falling trauma.
A prospective, randomized, controlled study.**

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BACKGROUND: The effects of infrared and red pulsed monochromatic light, with varied pulsations and wavelengths, on the healing of pressure ulcers were evaluated in this prospective, randomized, controlled study. **METHODS:** Elderly patients (> or =65 years) with Stage 2 or 3 skin ulcers were enrolled and assigned to one of two groups. Both groups were given the same standard ulcer therapy. One group was also given phototherapy with pulsed monochromatic infrared (956 nm) and red (637 nm) light. Treatments lasted 9 min each time using a regimen with pulse repetition frequency varied between 15.6 Hz and 8.58 kHz. Patients were followed for 10 weeks or until the ulcer was healed, whichever occurred first. The ulcer surface area was traced weekly. **RESULTS:** Patients treated with pulsed monochromatic light had a 49% higher ulcer healing rate, and a shorter time to 50% and to 90% ulcer closure compared with controls. Their mean ulcer area was reduced to 10% after 5 weeks compared with 9 weeks for the controls. **CONCLUSION:** The results are encouraging as pulsed monochromatic light increased healing rate and shortened healing time. This will positively affect the quality of life in elderly patients with pressure ulcer.

Photodermatol Photoimmunol Photomed 2001 Feb 17(1) 32-8

The use of low energy photon therapy (LEPT) in venous leg ulcers: a double-blind, placebo-controlled study.

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BACKGROUND: Venous ulcers are estimated to be present in 0.2 to 0.4% of the population. Although new therapies have significant promise, nonhealing ulcers still represent a significant problem.

OBJECTIVE: To evaluate the efficacy of low energy photon therapy (LEPT) in the treatment of venous leg ulcers. **METHODS:** A placebo-controlled, double-blind study using low energy photon therapy was performed in nine patients with 12 venous ulcers. Treatment was given three times a week for 10 weeks, using two monochromatic optical sources. One source provided a wavelength (λ) of 660 nm (red) while the second source delivered a wavelength of 880 nm (infrared). Two optical probes were used, one consisted of an array of 22 monochromatic sources, operating at a wavelength of 660 nm and covering an area 6 x 10 cm². The second probe had seven infrared sources, operating at a wavelength of 880 nm and covering an area of 4 cm². The above configuration of optical probes was selected to cover the majority of the ulcer area being treated. The patients who were randomized to placebo treatment received sham therapy from an identical-appearing light source from the same delivery system.

RESULTS: Nine patients with 12 venous ulcers were randomized to receive LEPT or placebo therapy. At the conclusion of the study, the percentage of the initial ulcer area remaining unhealed in the LEPT and placebo groups was 24.4% and 84.7%, respectively ($P = 0.0008$). The decrease in ulcer area (compared to baseline) observed in the LEPT and placebo groups was 193.0 mm² and 14.7 mm², respectively ($P = 0.0002$). One patient dropped out of the study, complaining of lack of treatment efficacy; he was found to be randomized to the placebo group. There were no adverse effects. **CONCLUSION:** In this placebo-controlled, double-blind study LEPT was an effective modality for the treatment of venous leg ulcers.

Dermatol Surg. 1998 Dec 24(12) 1383-6

Near-Infrared Photobiomodulation in an Animal Model of Traumatic Brain Injury: Improvements at the Behavioral and Biochemical Levels.

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Abstract Objective: The purpose of this was to evaluate the neuroprotective effects of near-infrared (NIR) light using an in-vivo rodent model of traumatic brain injury (TBI), controlled cortical impact (CCI), and to characterize changes at the behavioral and biochemical levels. **Background data:** NIR upregulates mitochondrial function, and decreases oxidative stress. Mitochondrial oxidative stress and apoptosis are important in TBI. NIR enhanced cell viability and mitochondrial function in previous in-vitro TBI models, supporting potential NIR in-vivo benefits. **Methods:** Sprague-Dawley rats were divided into three groups: severe TBI, sham surgery, and anesthetization only (behavioral response only). Cohorts in each group were administered either no NIR or NIR. They received two 670 nm LED treatments (5 min, 50 mW/cm², 15 J/cm²) per day for 72 h (chemical analysis) or 10 days (behavioral). During the recovery period, animals were tested for locomotor and behavioral activities using a TruScan device. Frozen brain tissue was obtained at 72 h and evaluated for apoptotic markers and reduced glutathione (GSH) levels. **Results:** Significant differences were seen in the TBI plus and minus NIR (TBI+/-) and sham plus and minus NIR (S+/-) comparisons for some of the TruScan nose poke parameters. A statistically significant decrease was found in the Bax pro-apoptotic marker attributable to NIR exposure, along with lesser increases in Bcl-2 anti-apoptotic marker and GSH levels. **Conclusions:** These results show statistically significant, preclinical outcomes that support the use of NIR treatment after TBI in effecting changes at the behavioral, cellular, and chemical levels.

Photomed Laser Surg 2012 Jul 13

Transcranial low level laser (light) therapy for traumatic brain injury.

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We review the use of transcranial low-level laser (light) therapy (LLLT) as a possible treatment for traumatic-brain injury (TBI). The basic mechanisms of LLLT at the cellular and molecular level and its effects on the brain are outlined. Many interacting processes may contribute to the beneficial effects in TBI including neuroprotection, reduction of inflammation and stimulation of neurogenesis. Animal studies and clinical trials of transcranial-LLLT for ischemic stroke are summarized. Several laboratories have shown that LLLT is effective in increasing neurological performance and memory and learning in mouse models of TBI. There have been case report papers that show beneficial effects of transcranial-LLLT in a total of three patients with chronic TBI. Our laboratory has conducted three studies on LLLT and TBI in mice. One looked at pulsed-vs-continuous wave laser-irradiation and found 10 Hz to be superior. The second looked at four different laser-wavelengths (660, 730, 810, and 980 nm); only 660 and 810 nm were effective. The last looked at different treatment repetition regimens (1, 3 and 14-daily laser-treatments). ((c) 2012 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim).

J Biophotonics 2012 Jul 17

Low-level laser therapy for closed-head traumatic brain injury in mice: effect of different wavelengths.

Wu Q, Xuan W, Ando T, Xu T, Huang L, Huang YY, Dai T, Dhital S, Sharma SK, Whalen MJ, Hamblin MR

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BACKGROUND AND OBJECTIVES: Traumatic brain injury (TBI) affects millions worldwide and is without effective treatment. One area that is attracting growing interest is the use of transcranial low-level laser therapy (LLLT) to treat TBI. The fact that near-infrared light can penetrate into the brain would allow non-invasive treatment to be carried out with a low likelihood of treatment-related adverse events. LLLT may treat TBI by increasing respiration in the mitochondria, causing activation of transcription factors, reducing inflammatory mediators and oxidative stress, and inhibiting apoptosis. **STUDY DESIGN/MATERIALS AND METHODS:** We tested LLLT in a mouse model of closed-head TBI produced by a controlled weight drop onto the skull. Mice received a single treatment with continuous-wave 665, 730, 810, or 980 nm lasers (36 J/cm² delivered at 150 mW/cm²) 4-hour post-TBI and were followed up by neurological performance testing for 4 weeks. **RESULTS:** Mice with moderate-to-severe TBI treated with 665 and 810 nm laser (but not with 730 or 980 nm) had a significant improvement in Neurological Severity Score that increased over the course of the follow-up compared to sham-treated controls. Morphometry of brain sections showed a reduction in small deficits in 665 and 810 nm laser treated mouse brains at 28 days. **CONCLUSIONS:** The effectiveness of 810 nm agrees with previous publications, and together with the effectiveness of 660 nm and non-effectiveness of 730 and 980 nm can be explained by the absorption spectrum of cytochrome oxidase, the candidate mitochondrial chromophore in transcranial LLLT. *Lasers Surg. Med.* (c) 2012 Wiley Periodicals, Inc.

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The influence of low-intensity laser therapy on bone healing.

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OBJECTIVE: Low-intensity laser therapy (LILT) is defined to supply direct biostimulative light energy to the cells. While several studies have demonstrated that LILT has stimulating effects on bone cells and can accelerate the repair process of the bone, others reported delayed fracture healing or no effects after LILT. The aim of this article was to review the studies evaluating the biomodulation effects of LILT on bone-derived stem cells. **MATERIALS AND METHODS:** To access relevant articles, searching in three electronic databases including PubMed, Google Scholar and Science Direct was conducted until April 2012. The key words used were low-level laser, low-intensity laser, low-power laser therapy, stem cell, bone marrow stem cell, bone and osteoblast. The articles that met the eligibility criteria were included in this review of literature. **RESULTS:** Twenty-five relevant articles (13 in vitro and 12 animal studies) were included. Eleven in vitro studies showed positive results with regard to acceleration of cell proliferation and differentiation. All animal studies showed improved bone healing in sites irradiated with low-intensity laser. **CONCLUSION:** Based on the results of the reviewed articles, low intensity laser therapy can accelerate bone healing in extraction sites, bone fracture defects and distraction osteogenesis, provided proper parameters were applied.

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Effect of the laser and light-emitting diode (LED) phototherapy on midpalatal suture bone formation after rapid maxilla expansion: a Raman spectroscopy analysis.

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The aim of this study was to analyze the effect of laser or light-emitting diode (LED) phototherapy on the bone formation at the midpalatal suture after rapid maxilla expansion. Twenty young adult male rats were divided into four groups with 8 days of experimental time: group 1, no treatment; group 2, expansion; group 3, expansion and laser irradiation; and group 4, expansion and LED irradiation. In groups 3 and 4, light irradiation was in the first, third, and fifth experimental days. In all groups, the expansion was accomplished with a helicoid 0.020" stainless steel orthodontic spring. A diode laser (λ 780 nm, 70 mW, spot of 0.04 cm², t = 257 s, spatial average energy fluence (SAEF) of 18 J/cm²) or a LED (λ 850 nm, 150 mW +/- 10 mW, spot of 0.5 cm², t = 120 s, SAEF of 18 J/cm²) were used. The samples were analyzed by Raman spectroscopy carried out at midpalatal suture and at the cortical area close to the suture. Two Raman shifts were analyzed: approximately 960 (phosphate hydroxyapatite) and approximately 1,450 cm⁻¹ (lipids and protein). Data was submitted to statistical analysis. Significant statistical difference (p <= 0.05) was found in the hydroxyapatite (CHA) peaks among the expansion group and the expansion and laser or LED groups. The LED group presented higher mean peak values of CHA. No statistical differences were found between the treated groups as for collagen deposition, although LED also presented higher mean peak values. The results of this study using Raman spectral analysis indicate that laser and LED light irradiation improves deposition of CHA in the midpalatal suture after orthopedic expansion.

Lasers Med Sci 2013 Feb 21

Light-emitting diode photobiomodulation: effect on bone formation in orthopedically expanded suture in rats-early bone changes.

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The aim of this experimental study was to evaluate histomorphometrically the effects of light-emitting diode (LED) photobiomodulation therapy (LPT) on bone formation in response to expansion of the interpremaxillary suture in rats. Twenty male, 50- to 60-day-old Wistar rats were divided into two equal groups (control and experimental). Both groups were subjected to expansion for 5 days, and 50 cN of force was applied to the maxillary incisors with helical spring. An OsseoPulse(R) LED device, 618-nm wavelength and 20-mW/cm² output power irradiation, was applied to the interpremaxillary suture for 10 days. Bone formation in the sutural area was histomorphometrically evaluated, including the amount of new bone formation (in square micrometers), number of osteoblasts, number of osteoclasts, and number of vessels. Mann-Whitney U test was used for statistical evaluation at $p < 0.025$ level. Significant differences were found between groups for all investigated histomorphometric parameters. New bone formation area ($p = 0.024$, 1.48-fold), number of osteoblasts ($p < 0.001$, 1.59-fold), number of osteoclasts ($p = 0.004$, 1.43-fold), and number of vessels ($p = 0.007$, 1.67-fold) showed higher values in the experimental group than the control. Bone histomorphometric measurements revealed that bone architecture in the LPT group was improved. The application of LPT can stimulate bone formation in the orthopedically expanded interpremaxillary suture during expansion and the early phase of the retention periods.

Lasers Med Sci 2012 Nov 9

The effect of low level laser therapy on pain reduction after third molar surgery.

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AIM: The aim of this study was to evaluate the effects of low level laser on the postoperative pain of patients who had to undergo third molar surgery. **METHODS:** In a randomized clinical setting, 100 patients were assigned to two groups of 50 in each. Every patient underwent surgical removal of one mandibular third molar (with osteotomy). After suturing the flap, the soft laser was applied to every patient. In group I laser radiation was applied by the dental assistant with output power of 100 mW, in continuous mode with sweeping motion, in group II, the laser hand piece was only brought into position without releasing energy, so that no patient knew which group he belonged to. The patient was given a pain evaluation form where they could determine their individual pain level and duration. **RESULTS:** The statistical tests showed significant difference in pain level between laser and control group ($P < 0.001$) but no significant difference found in pain duration in two groups ($P = 0.019$). **CONCLUSION:** The result of this study verifies the positive effect of the soft-laser therapy in the postoperative complication after third molar extraction.

Minerva Stomatol 2012 Jul-Aug 61(7-8) 319-22

Effect of Adjunctive Low Level Laser Therapy (LLLT) on Nonsurgical Treatment of Chronic Periodontitis.

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Abstract Objective: The aim of this split-mouth, double blinded, short-term, controlled clinical trial was to study the effect of low-level laser therapy (LLLT) as an adjunct to scaling and root planing (SRP) for treatment of chronic periodontitis. Background data: LLLT is reported to improve the outcome of traditional SRP, but the evidence is still weak. Materials and methods: Sixteen patients with a probing pocket depth (PPD) of 4-6 mm involving at least three teeth in each quadrant were recruited for the study. Afterwards, SRP quadrants were randomly assigned for 10 sessions of LLLT. Results: Results showed that when compared to sites treated with SRP alone, those treated with SRP+LLLT (10 sessions, 830 nm, 100 mW, 3 J per point, 3 J/cm²) exhibited greater reductions in PPD at 5 weeks and 3 months but not at 6 months. Further, SRP+LLLT-treated sites had a statistically significant increase in mean radiographic bone density when comparing 6- and 12-month data and overall from baseline to 12 months. There was a trend to reduce interleukin (IL)-1beta but the difference between control and laser sites was not statistically significant. Conclusions: SRP combined with LLLT improved radiographic bone density and short-term PPD reduction in patients with chronic periodontitis, but did not significantly affect either the gingival crevicular fluid of IL-1beta or the gingival or plaque index.

Photomed Laser Surg 2012 Jan 10

The Effect of 670-nm Low Laser Therapy on Herpes Simplex Type 1.

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Abstract Objective: The purpose of this work was to study the effect of low-level laser therapy (LLLT) on the healing and relapse intervals in patients with recurrent labial herpes simplex infections. Background data: Several pharmaceuticals are available to reduce symptoms and improve healing of labial herpes, but only LLLT has been reported to significantly influence the length of the recurrence period. Material and methods: In an initial study, 232 patients with herpes simplex type 1 virus symptoms were consecutively selected for either LLLT or conventional therapy, including acyclovir cream or tablets. One of the dentists was responsible for the diagnosis, a second dentist for the treatment, and a third for the evaluation, to allow for a semi-blinded procedure. Patients in the laser group received 670-nm laser irradiation, 40 mW, 1.6 J, 2.04 J/cm², 51 mW/cm² per blister in the prodromal stage and 4.8 J in the crust and secondarily infected stages, plus 1.2 J at the C2-C3 vertebrae. Patients were monitored daily during the first week to control healing, and monthly for 1 year to check on recurrence. In a consecutive study, 322 patients receiving LLLT were followed during 5 years to observe the period of occurrences. Results: An obvious effect of LLLT was found for both initial healing and for the length of the recurrence periods. Conclusions: LLLT of herpes simplex virus 1 (HSV-1) appears to be an effective treatment modality without any observed side effects.

Photomed Laser Surg 2011 Nov 2

Bibliography

1. Chow, R.T., et al., *Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials*. *Lancet*, 2009. **374**(9705): p. 1897-908.
2. Bisset, L., B. Coombes, and B. Vicenzino, *Tennis elbow*. *Clinical evidence*, 2011. **2011**.
3. IASP, *Global Year Against Musculoskeletal Pain*. <http://tinyurl.com/IASPlaser>, 2010.
4. Haldeman, S., et al., *The Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders: executive summary*. *J Manipulative Physiol Ther*, 2009. **32**(2 Suppl): p. S7-9.
5. Migliorati, C., et al., *Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients*. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*, 2012.
6. Draper, W.E., et al., *Low-level laser therapy reduces time to ambulation in dogs after hemilaminectomy: a preliminary study*. *The Journal of small animal practice*, 2012. **53**(8): p. 465-9.
7. Mester, E., b. Szende, and J.G. Tota, *Effect of laser on hair growth of mice*. *Kiserl Orvostud*, 1967. **19**: p. 628-631.
8. Favejee, M.M., B.M. Huisstede, and B.W. Koes, *Frozen shoulder: the effectiveness of conservative and surgical interventions--systematic review*. *Br J Sports Med*. **45**(1): p. 49-56.
9. Garcia, C.R., et al., *Achilles pain, stiffness, and muscle power deficits: achilles tendinitis*. *The Journal of orthopaedic and sports physical therapy*, 2010. **40**(9): p. A1-26.
10. Peterson, D.E., R.J. Bensadoun, and F. Roila, *Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines*. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*, 2011. **22 Suppl 6**: p. vi78-84.
11. Karu, T.I., *Mitochondrial signaling in mammalian cells activated by red and near-IR radiation*. *Photochem Photobiol*, 2008. **84**(5): p. 1091-9.
12. Eells, J.T., et al., *Mitochondrial signal transduction in accelerated wound and retinal healing by near-infrared light therapy*. *Mitochondrion*, 2004. **4**(5-6): p. 559-67.
13. Karu, T., *Mitochondrial mechanisms of photobiomodulation in context of new data about multiple roles of ATP*. *Photomedicine and Laser Surgery*, 2010. **28**(2): p. 159-60.
14. Palacios-Callender, M., et al., *Endogenous NO regulates superoxide production at low oxygen concentrations by modifying the redox state of cytochrome c oxidase*. *Proceedings of the National Academy of Sciences of the United States of America*, 2004. **101**(20): p. 7630-5.
15. Cleeter, M.W., et al., *Reversible inhibition of cytochrome c oxidase, the terminal enzyme of the mitochondrial respiratory chain, by nitric oxide. Implications for neurodegenerative diseases*. *FEBS letters*, 1994. **345**(1): p. 50-4.
16. Antunes, F., A. Boveris, and E. Cadenas, *On the mechanism and biology of cytochrome oxidase inhibition by nitric oxide*. *Proc. Natl. Acad. Sci. USA*, 2004. **101**: p. 16774-9.
17. Galkin, A., A. Higgs, and S. Moncada, *Nitric oxide and hypoxia*. *Essays in biochemistry*, 2007. **43**: p. 29-42.
18. Lane, N., *Cell biology: power games*. *Nature*, 2006. **443**(7114): p. 901-3.
19. Bolanos, J.P., et al., *Nitric oxide-mediated inhibition of the mitochondrial respiratory chain in cultured astrocytes*. *Journal of neurochemistry*, 1994. **63**(3): p. 910-6.

20. Chen, S., *Natural products triggering biological targets--a review of the anti-inflammatory phytochemicals targeting the arachidonic acid pathway in allergy asthma and rheumatoid arthritis*. Current drug targets, 2011. **12**(3): p. 288-301.
21. Karu, T.I. and S.F. Kolyakov, *Exact action spectra for cellular responses relevant to phototherapy*. Photomed Laser Surg, 2005. **23**(4): p. 355-61.
22. Yu, W., et al., *Photomodulation of oxidative metabolism and electron chain enzymes in rat liver mitochondria*. Photochemistry and photobiology, 1997. **66**(6): p. 866-71.
23. Dyson, M., *Primary, secondary and tertiary effects of phototherapy*. Proc. SPIE 6140, Mechanisms for Low-Light Therapy, 614005, 2006.
24. Zhang, R., et al., *Near infrared light protects cardiomyocytes from hypoxia and reoxygenation injury by a nitric oxide dependent mechanism*. Journal of molecular and cellular cardiology, 2009. **46**(1): p. 4-14.
25. Lim, W., et al., *Modulation of Lipopolysaccharide-Induced NF-kappaB Signaling Pathway by 635 nm Irradiation via Heat Shock Protein 27 in Human Gingival Fibroblast Cells*. Photochemistry and photobiology, 2012.
26. Sharma, S.K., et al., *Dose response effects of 810 nm laser light on mouse primary cortical neurons*. Lasers in surgery and medicine, 2011. **43**(8): p. 851-9.
27. de Lima, F.M., et al., *Low-Level Laser Therapy Restores the Oxidative Stress Balance in Acute Lung Injury Induced by Gut Ischemia and Reperfusion*. Photochemistry and photobiology, 2012.
28. Servetto, N., et al., *Evaluation of inflammatory biomarkers associated with oxidative stress and histological assessment of low-level laser therapy in experimental myopathy*. Lasers in surgery and medicine, 2010. **42**(6): p. 577-83.
29. Hopkins, J.T., et al., *Low-Level Laser Therapy Facilitates Superficial Wound Healing in Humans: A Triple-Blind, Sham-Controlled Study*. J Athl Train, 2004. **39**(3): p. 223-229.
30. Omar, M.T., A.A. Shaheen, and H. Zafar, *A systematic review of the effect of low-level laser therapy in the management of breast cancer-related lymphedema*. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 2012. **20**(11): p. 2977-84.
31. Stergioulas, A., *Low-level laser treatment can reduce edema in second degree ankle sprains*. Journal of clinical laser medicine & surgery, 2004. **22**(2): p. 125-8.
32. Meneguzzo, D.T., et al., *Prevention and treatment of mice paw edema by near-infrared low-level laser therapy on lymph nodes*. Lasers in medical science, 2012.
33. Chow, R., et al., *Inhibitory effects of laser irradiation on peripheral Mammalian nerves and relevance to analgesic effects: a systematic review*. Photomedicine and laser surgery, 2011. **29**(6): p. 365-81.
34. Chow, R.T., M.A. David, and P.J. Armati, *830 nm laser irradiation induces varicosity formation, reduces mitochondrial membrane potential and blocks fast axonal flow in small and medium diameter rat dorsal root ganglion neurons: implications for the analgesic effects of 830 nm laser*. J Peripher Nerv Syst, 2007. **12**(1): p. 28-39.
35. Yan, W., R. Chow, and P.J. Armati, *Inhibitory effects of visible 650-nm and infrared 808-nm laser irradiation on somatosensory and compound muscle action potentials in rat sciatic nerve: implications for laser-induced analgesia*. Journal of the peripheral nervous system : JPNS, 2011. **16**(2): p. 130-5.
36. Artes-Ribas, M., J. Arnabat-Dominguez, and A. Puigdollers, *Analgesic effect of a low-level laser therapy (830 nm) in early orthodontic treatment*. Lasers in medical science, 2012.
37. Carrasco, T.G., et al., *Evaluation of low intensity laser therapy in myofascial pain syndrome*. Cranio : the journal of craniomandibular practice, 2009. **27**(4): p. 243-7.

38. Bjordal, J.M., et al., *A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders*. Aust J Physiother, 2003. **49**(2): p. 107-16.
39. Chen, K.H., et al., *Electrophysiologic effects of a therapeutic laser on myofascial trigger spots of rabbit skeletal muscles*. American journal of physical medicine & rehabilitation / Association of Academic Physiatrists, 2008. **87**(12): p. 1006-14.
40. Snyder-Mackler, L., et al., *Effects of helium-neon laser irradiation on skin resistance and pain in patients with trigger points in the neck or back*. Physical therapy, 1989. **69**(5): p. 336-41.
41. Huang, Y.Y., et al., *Biphasic dose response in low level light therapy*. Dose Response, 2009. **7**(4): p. 358-83.
42. Huang, Y.Y., et al., *Biphasic dose response in low level light therapy - an update*. Dose-response : a publication of International Hormesis Society, 2011. **9**(4): p. 602-18.
43. Sommer, A.P., et al., *Biostimulatory windows in low-intensity laser activation: lasers, scanners, and NASA's light-emitting diode array system*. J Clin Laser Med Surg, 2001. **19**(1): p. 29-33.
44. Jenkins, P.A. and J.D. Carroll, *How to report low-level laser therapy (LLLT)/photomedicine dose and beam parameters in clinical and laboratory studies*. Photomedicine and Laser Surgery, 2011. **29**(12): p. 785-7.
45. Tumilty, S., et al., *Low level laser treatment of tendinopathy: a systematic review with meta-analysis*. Photomed Laser Surg, 2010. **28**(1): p. 3-16.
46. Bjordal, J.M., et al., *A systematic review with procedural assessments and meta-analysis of Low Level Laser Therapy in lateral elbow tendinopathy (tennis elbow)*. BMC Musculoskeletal Disorders, 2008. **9**: p. 75.
47. Smith, K., *The photobiological basis of low level laser radiation therapy*. Laser Therapy, 1991. **3**: p. 19-24.
48. Byrnes, K.R., et al., *Light promotes regeneration and functional recovery and alters the immune response after spinal cord injury*. Lasers in surgery and medicine, 2005. **36**(3): p. 171-85.
49. Igic, M., et al., *Cytomorphometric and clinical investigation of the gingiva before and after low-level laser therapy of gingivitis in children*. Lasers in medical science, 2012. **27**(4): p. 843-8.
50. Martu, S., et al., *Healing process and laser therapy in the superficial periodontium: a histological study*. Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie, 2012. **53**(1): p. 111-6.
51. Kim, S.J., et al., *Effects of low-intensity laser therapy on periodontal tissue remodeling during relapse and retention of orthodontically moved teeth*. Lasers in medical science, 2012.
52. Aimbire, F., et al., *Low-level laser therapy induces dose-dependent reduction of TNFalpha levels in acute inflammation*. Photomed Laser Surg, 2006. **24**(1): p. 33-7.
53. Pejicic, A., et al., *The effects of low level laser irradiation on gingival inflammation*. Photomedicine and Laser Surgery, 2010. **28**(1): p. 69-74.
54. Lievens, P., *The influence of laser irradiation on the motricity of lymphatical system and on the wound healing process*. Proceedings of the International Congress on Laser in Medicine and Surgery, Bologna, Italy, 1986: p. 4.
55. Esper, M.A., R.A. Nicolau, and E.A. Arisawa, *The effect of two phototherapy protocols on pain control in orthodontic procedure--a preliminary clinical study*. Lasers in medical science, 2011. **26**(5): p. 657-63.
56. Bjordal, J.M., et al., *A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis*. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 2011.

57. Marcos, R.L., et al., *Infrared (810 nm) low-level laser therapy in rat achilles tendinitis: a consistent alternative to drugs*. Photochemistry and photobiology, 2011. **87**(6): p. 1447-52.
58. Bjordal, J.M., et al., *Photoradiation in acute pain: a systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials*. Photomedicine and laser surgery, 2006. **24**(2): p. 158-68.
59. Xiaoting, L., T. Yin, and C. Yangxi, *Interventions for pain during fixed orthodontic appliance therapy. A systematic review*. The Angle orthodontist, 2010. **80**(5): p. 925-32.
60. Markovic, A.B. and L. Todorovic, *Postoperative analgesia after lower third molar surgery: contribution of the use of long-acting local anesthetics, low-power laser, and diclofenac*. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics, 2006. **102**(5): p. e4-8.
61. Aras, M.H. and M. Gungormus, *The effect of low-level laser therapy on trismus and facial swelling following surgical extraction of a lower third molar*. Photomedicine and Laser Surgery, 2009. **27**(1): p. 21-4.
62. Moore, K.C., et al., *The effect of infrared laser irradiation on the duration and severity of postoperative pain a double blind trial*. Laser Therapy, 1992. **Vol 4**: p. 5.
63. Ebrahimi, T., et al., *The influence of low-intensity laser therapy on bone healing*. Journal of dentistry, 2012. **9**(4): p. 238-48.
64. Rosa, C.B., et al., *Effect of the laser and light-emitting diode (LED) phototherapy on midpalatal suture bone formation after rapid maxilla expansion: a Raman spectroscopy analysis*. Lasers in medical science, 2013.
65. Ekizer, A., et al., *Light-emitting diode photobiomodulation: effect on bone formation in orthopedically expanded suture in rats-early bone changes*. Lasers in medical science, 2012.
66. Quirk, B.J., et al., *Near-infrared photobiomodulation in an animal model of traumatic brain injury: improvements at the behavioral and biochemical levels*. Photomedicine and Laser Surgery, 2012. **30**(9): p. 523-9.
67. Huang, Y.Y., et al., *Transcranial low level laser (light) therapy for traumatic brain injury*. Journal of biophotonics, 2012. **5**(11-12): p. 827-37.
68. Wu, Q., et al., *Low-level laser therapy for closed-head traumatic brain injury in mice: effect of different wavelengths*. Lasers in surgery and medicine, 2012. **44**(3): p. 218-26.
69. Minatel, D.G., et al., *Phototherapy promotes healing of chronic diabetic leg ulcers that failed to respond to other therapies*. Lasers in surgery and medicine, 2009. **41**(6): p. 433-41.
70. Schubert, V., *Effects of phototherapy on pressure ulcer healing in elderly patients after a falling trauma. A prospective, randomized, controlled study*. Photodermatology, photoimmunology & photomedicine, 2001. **17**(1): p. 32-8.
71. Gupta, A.K., et al., *The use of low energy photon therapy (LEPT) in venous leg ulcers: a double-blind, placebo-controlled study*. Dermatol Surg, 1998. **24**(12): p. 1383-6.
72. Bjordal, J.M., R.A. Lopes-Martins, and V.V. Iversen, *A randomised, placebo controlled trial of low level laser therapy for activated Achilles tendinitis with microdialysis measurement of peritendinous prostaglandin E2 concentrations*. Br J Sports Med, 2006. **40**(1): p. 76-80; discussion 76-80.
73. Jang, H. and H. Lee, *Meta-analysis of pain relief effects by laser irradiation on joint areas*. Photomedicine and Laser Surgery, 2012. **30**(8): p. 405-17.
74. Stelian, J., et al., *Improvement of pain and disability in elderly patients with degenerative osteoarthritis of the knee treated with narrow-band light therapy*. J Am Geriatr Soc, 1992. **40**(1): p. 23-6.

75. Konstantinovic, L.M., et al., *Acute low back pain with radiculopathy: a double-blind, randomized, placebo-controlled study*. Photomed Laser Surg. **28**(4): p. 553-60.
76. Jovicic, M., et al., *Clinical and functional evaluation of patients with acute low back pain and radiculopathy treated with different energy doses of low level laser therapy*. Vojnosanitetski pregled. Military-medical and pharmaceutical review, 2012. **69**(8): p. 656-62.
77. Oron, U., et al., *Attenuation of infarct size in rats and dogs after myocardial infarction by low-energy laser irradiation*. Lasers in surgery and medicine, 2001. **28**(3): p. 204-11.
78. Lanzafame, R.J., et al., *Reciprocity of exposure time and irradiance on energy density during photoradiation on wound healing in a murine pressure ulcer model*. Lasers in surgery and medicine, 2007. **39**(6): p. 534-42.
79. Castano, A.P., et al., *Low-level laser therapy for zymosan-induced arthritis in rats: Importance of illumination time*. Lasers in surgery and medicine, 2007. **39**(6): p. 543-50.
80. Fred M. Dickey, S.C.H., *Laser Beam Shaping: Theory and Techniques*. 2000.
81. Boreman, G.D., *Basic electro-optics for electrical engineers*. Tutorial texts in optical engineering 1998, Bellingham, Wash.: SPIE Optical Engineering Press. vii, 97 p.
82. Chung, H., et al., *The Nuts and Bolts of Low-level Laser (Light) Therapy*. Annals of biomedical engineering, 2011.
83. Ando, T., et al., *Comparison of therapeutic effects between pulsed and continuous wave 810-nm wavelength laser irradiation for traumatic brain injury in mice*. PLoS ONE, 2011. **6**(10): p. e26212.
84. Hashmi, J.T., et al., *Effect of pulsing in low-level light therapy*. Lasers in surgery and medicine, 2010. **42**(6): p. 450-66.
85. Saber, K., N. Chiniforush, and S. Shahabi, *The effect of low level laser therapy on pain reduction after third molar surgery*. Minerva stomatologica, 2012. **61**(7-8): p. 319-22.
86. Makhlof, M., et al., *Effect of adjunctive low level laser therapy (LLLT) on nonsurgical treatment of chronic periodontitis*. Photomedicine and Laser Surgery, 2012. **30**(3): p. 160-6.
87. Munoz Sanchez, P.J., et al., *The effect of 670-nm low laser therapy on herpes simplex type 1*. Photomedicine and Laser Surgery, 2012. **30**(1): p. 37-40.