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Low-Level Laser Therapy in Acute Pain: A Systematic Review of Possible Mechanisms of Action and Clinical Effects in Randomized Placebo-Controlled Trials

JAN MAGNUS BJORDAL, P.T., Ph.D.,[1] MARK I. JOHNSON, Ph.D.,[2]
VEGARD IVERSEN, Ph.D.[3] FLAVIO AIMBIRE, M.SC.,[4] and
RODRIGO ALVARO BRANDAO LOPES-MARTINS, M.Pharmacol., Ph.D.[5]

ABSTRACT

Objective: **The aim of this study was to review the biological and clinical short-term effects of low-level laser therapy (LLLT) in acute pain from soft-tissue injury.** ***Background Data:*** **It is unclear if and how LLLT can reduce acute pain.** ***Methods:*** **Literature search of (i) controlled laboratory trials investigating potential biological mechanisms for pain relief and (ii) randomized placebo-controlled clinical trials which measure outcomes within the first 7 days after acute soft-tissue injury.** ***Results:*** **There is strong evidence from 19 out of 22 controlled laboratory studies that LLLT can modulate inflammatory pain by reducing levels of biochemical markers (PGE_2, mRNA Cox 2, IL-1 , TNF), neutrophil cell influx, oxidative stress, and formation of edema and hemorrhage in a dose-dependent manner (median dose 7.5 J/cm², range 0.3–19 J/cm²). Four comparisons with non-steroidal anti-inflammatory drugs (NSAIDs) in animal studies found optimal doses of LLLT and NSAIDs to be equally effective. Seven randomized placebo-controlled trials found no significant results after irradiating only a single point on the skin overlying the site of injury, or after using a total energy dose below 5 Joules. Nine randomized placebo-controlled trials (*n* = 609) were of acceptable methodological quality, and irradiated three or more points and/or more than 2.5 cm² at site of injury or surgical incision, with a total energy of 5.0–19.5 Joules. Results in these nine trials were significantly in favor of LLLT groups over placebo groups in 15 out of 18 outcome comparisons. Poor and heterogeneous data presentation hampered statistical pooling of continuous data. Categorical data of subjective improvement were homogeneous (Q-value = 7.1) and could be calculated from four trials (*n* = 379) giving a significant relative risk for improvement of 2.7 (95% confidence interval [CI], 1.8–3.9) in a fixed effects model.** ***Conclusion:*** **LLLT can modulate inflammatory processes in a dose-dependent manner and can be titrated to significantly reduce acute inflammatory pain in clinical settings. Further clinical trials with adequate LLLT doses are needed to precisely estimate the effect size for LLLT in acute pain.**

INTRODUCTION

TREATMENT OF PAINFUL DISORDERS with LLLT is still considered to be experimental by mainstream medicine. Proponents of LLLT have put forward multiple hypotheses about its biological actions, but these have been met with scepticism. Recently, there has been renewed interest in the clinical use of LLLT by mainstream medicine following the publication of articles in prestigious medical journals. For example, a scholarly paper in the *Journal of Rheumatology*[1] suggests that LLLT could be a viable alternative to drug medication in arthritis management. Ten years ago, a review of basic and clinical re-

[1]Section of Physiotherapy Science, University of Bergen, and Institute of Physiotherapy, Bergen University College, Bergen, Norway.
[2]Faculty of Health, Leeds Metropolitan University, Leeds, United Kingdom.
[3]Institute of Biomedical Sciences, Department of Physiology, University of Bergen, Bergen, Norway.
[4]Laboratory of Animal Experiments, IP&D Universidade Vale do Paraiba (UNIVAP), São José dos Campos, SP, Brazil.
[5]Institute of Biomedical Sciences, Pharmacology Department, Universidade Sao Paulo, São Paulo, SP, Brazil.

search concluded that, despite positive laboratory findings, LLLT had not established itself as a therapeutic tool.[2] Since then there have been an additional 79 controlled studies in cell cultures, 77 controlled studies in animals, and 58 randomized controlled clinical trials published in peer-reviewed journals. The bulk of new evidence needs to be systematically reviewed in order to determine the factors that influence LLLT outcome and to determine the optimal characteristics for treatment success.

LLLT is no longer believed to be a mythical alternative therapy with diffuse and hypothetical mechanisms of biological action, as it has distinct biophysical properties[3,4] and a dose-dependent mechanism of action.[5] Nevertheless, well-designed randomized controlled trials continue to use LLLT doses that are well below those expected to achieve biological responses.[6,7] This is likely to bias studies towards showing no effect from LLLT, and this may have contributed to the contradictory findings. This "shoot in the dark" approach to LLLT needs to be replaced by selecting LLLT parameters and titrating LLLT dose according to evidence gathered in a systematic manner.

We have shown in a previous systematic review that LLLT is effective for chronic joint disorders such as osteoarthritis, if LLLT is administered at the anatomic location of the pathology and the dose is titrated to achieve the desired biological action. For instance, in osteoarthritis of the knee when a minimum of 3 cm^2 of the joint capsule is exposed, the optimal parameters for infrared GaAs 904-nm pulse lasers are an intensity of 12–60 mW/cm^2 and a dose of 1–4 Joule per point. Optimal parameters for infrared GaAlAs 820–30-nm lasers are an intensity of 30–210 mW/cm^2 and a dose 6–24 Joule per session.[8] Similarly, this approach to developing optimal parameters and dosage has been adopted by the World Association of Laser Therapy (WALT) in their recommendations for treating musculoskeletal disorders with LLLT (www.walt.nu).

LLLT has been used in pain management for over two decades. Pain is a subjective experience, and acute pain is a warning signal which expresses that body tissue is about to be injured. If injury actually occurs, then a cascade of pathophysiological events will take place in a well-mapped simultaneous and chronological order.[9] Pain intensity is usually most prevalent in the inflammatory phase during the first hours and days after injury, and in most cases, pain decreases as the tissue repair processes get under way. In chronic pain, the experience of pain may be different, and pain may be present in the absence of known pathology or tissue damage. This may be due to a state of persistent central sensitization within the central nervous system despite the healing of the original injury. In peripheral nerve injury, pain may occur from persisting mechanical pressure, neurogenic inflammation, or damage to the nerve structure. Inflammation may also be present in some chronic musculoskeletal pain disorders. Particularly in episodes with flares of symptom aggravation in degenerative and systemic arthritis, increased synovial inflammatory activity may be similar to what is seen in acute injuries.[10,11] For tendon disorders, short-lived flares in disease activity seem to be associated physical overload, although a definite link between pain aggravation and inflammatory activity is still uncertain.[12] On the other hand, NSAIDs have been shown to reduce pain in both acute and subacute tendinopathies.[13] Reducing oxidative stress with anti-oxidants has also been shown to preserve tendon structure *in vitro*,[14] and LLLT has been found to reduce oxidative stress[15] and improve healing[16] in acute tendon injuries. For chronic muscle pain, both the capacity of the muscle cells to withstand fatigue and subsequently cell damage, and the vasoactive response to muscle contractions, seems impaired.[17,18] In this plethora of pathophysiological processes, LLLT has been suggested to modulate several of the processes involved. One hypothesis has been that LLLT can modulate inflammatory processes,[19] and a second hypothesis is that LLLT acts by altering excitation and nerve conduction in peripheral nerves.[20] A third hypothesis has been that LLLT stimulates the release of endogenous endorphins.[21]

In order to test the evidence behind the most common hypotheses for acute pain modulation by LLLT, first, we decided to search and critically appraise the evidence from laboratory trials which assess possible pain-relieving effects within the first 72 h of the inflammatory phase. Secondly, we wanted to assess the effect of LLLT in randomized controlled clinical trials within 1 week after an acute musculoskeletal injury. And thirdly, we wanted to subgroup the clinical trials by the adequacy of the doses used and the recommended doses that can be extrapolated from controlled dose-finding laboratory trials.

METHODS

A review protocol was specified prior to conducting the review.

Review protocol specification for laboratory studies

1. To search published literature for controlled LLLT trials performed in cell cultures, or acute injuries in animals and healthy humans with outcomes measured within 7 days after induction of injury.
2. To extract power density and dose of LLLT used in positive outcome studies in order to reveal putative mechanisms of pain relief and potential dose-response patterns.

Review protocol specification for randomized controlled clinical trials

1. To search published literature for randomized controlled trials that applied LLLT to acute injuries or post-surgery, and outcomes were recorded during the first 7 days.
2. To evaluate the methodological quality of each study using the Jadad scale.[22]
3. To estimate the size of effect at 4, 6, 8, 12, 24, 48, 72, or 168 h after injury.
4. To conduct a subgroup analysis to compare the effect size of adequate versus inadequate LLLT dose and treatment procedure, as determined by the findings from the review of laboratory studies.

Literature search

A search of published literature was performed using Medline, Embase, The Cochrane Library, CINAHL, and the Physiotherapy Evidence database (PEDro). The search string used

for laboratory trials was as follows: acute OR injury OR soft-tissue OR pain OR inflammation OR edema OR neutrophil influx AND low laser therapy AND controlled. The search string used for clinical trials was as follows: acute OR injury OR soft-tissue OR surgery AND pain AND low laser therapy AND randomized OR randomized. In addition, hand searches of national Scandinavian physiotherapy journals, conference abstracts, and reference lists of systematic reviews were performed, and experts in the field were consulted. No language restrictions were applied.

Procedure

Inclusion criteria. Laboratory studies were included for review if they used (1) a no-treatment or sham treatment control group; and (2) a quantitive measure of acute injury such as neutrophil cell influx, presence of inflammatory markers, cytokine presence, edema, withdrawal latency, physical function, nerve latency time, nerve conduction velocity, hemorrhagia, microcirculation, or pain. Clinical trials were included for review if they used (1) a method of randomisation to allocate patients to groups; (2) a placebo laser control group; (3) outcome measures for either pain, and/or edema and/or function; and (4) assessors who were blinded to treatment group.

Exclusion criteria. Clinical trials were excluded if there was concomitant use of steroid therapy during the trial period or steroid therapy had ended within 4 weeks preceding the start of the trial.

Statistical analysis

For continuous data, mean differences of change for intervention groups and placebo groups, and their respective standard deviations (SD), were included in a statistical pooling. If variance data were not reported as SDs, they were calculated from the trial data of sample size and other variance data such as *p*-value, *t*-value, standard error of the mean, or 95% confidence interval (CI). Results were presented as weighted mean difference (WMD) between test drug and placebo with 95% CI in mm on VAS (i.e., as a pooled estimate of the mean difference in change between the treatment and the placebo groups, weighted by the inverse of the variance for each study).[23] For heterogeneous trial samples, a random effects model was used for calculation, and for confirmed absence of heterogeneity ($p < 0.05$), a fixed effects model was applied.

For categorical data, improvement was calculated by the relative risk ratio and the number-needed-to-treat (NNT) values.[24] NNT can be expressed as the reciprocal of the absolute risk reduction. The 95% CI for the NNT is constructed by inverting and exchanging the limits of a 95% CI for the absolute risk reduction.

RESULTS

The literature search revealed 131 laboratory trials and 102 randomized controlled clinical trials with LLLT. Of these trials, 33 laboratory trials and 15 randomized placebo-controlled satisfied our inclusion criteria for treating acute injury or postoperative pain, and provided outcomes measured within 7 days after trauma (Table 1).

Laboratory studies

A variety of biological mechanisms were identified as potential contributors of pain-relieving responses associated with LLLT (Fig. 1).

Neurophysiological effects. Seven studies found none, or only minor, changes in neurophysiological processes or nerve conduction velocities in intact peripheral nerves after LLLT.[20,25–30] One study in healthy subjects found LLLT reduced nerve conduction velocity and increased negative peak latency with energy dose of 1 Joule per stimulation point, but there were no effects from energy doses at 0.5 or 1.5 Joules when applied over the sural nerve.[31] There was no convincing evidence that LLLT could act by substantial rapid modulation of neurophysiological processes in intact peripheral nerves in the absence of inflammation. Although a possible narrow therapeutic window cannot be ruled out, available evidence suggests that the effect of LLLT on neurophysiological processing was of limited practical use.

Release of endogenous opioids. One study found increased levels of endorphins,[21] although local injection of the opioid antagonist naloxone produced only minor reductions of LLLT-induced pain relief in two studies.[32,33] There was limited evidence that the pain-relieving effects of LLLT are due to an increase in the levels of endorphins.

Local effects on delayed onset muscle soreness. Two studies by the same investigators found that LLLT did not affect delayed onset muscle soreness (DOMS) in healthy humans undergoing eccentric exercises. These investigators used a cluster probe combining a single 820-nm laser with five different wavelengths (range 660–950 nm) of superluminous LED therapy and high doses.[34,35]

Local microcirculatory and angiogenetic effects. There was strong evidence that LLLT improves angiogenesis, through increased growth factor secretion and formation of collateral vessels in the injured region in cell and animal studies during the first 7 days after injury.[36–39] This effect is dose-dependent, with therapeutic windows ranging from 0.5 to 6 J/cm^2, and it has been demonstrated for laser with wavelengths 632, 820, and 904 nm.

Local anti-inflammatory effects. There was strong evidence that LLLT modulates biochemical inflammatory markers and produces local anti-inflammatory effects in cells and soft tissue (Fig. 1).

Effects on biochemical markers. Five studies found that LLLT inhibited the release of PGE_2 when compared to a placebo control.[40–44] One study found that LLLT did not affect levels of tumor necrose factor (TNF), blood monocytes, and vein endothelial cells.[45] However, these findings were contradicted by two other studies.[46,47] This may indicate a narrow therapeutic range for LLLT inhibition of TNF release. Three studies found that LLLT increased plasma fibrinogen levels,[46,48,49] and three studies found that LLLT reduced levels of interleukin-1 .[40,50,51] One study on periodontal inflammation in humans found that LLLT did not alter interleukin-1 but did

TABLE 1. TRIAL CHARACTERISTICS AND DOSAGE IN LABORATORY TRIALS WITH SIGNIFICANT LLLT MODULATION OF INFLAMMATION

First author, year, model	*Inflammatory agent*	*Laser type, mean output power (mW)*	*Power density (mW/cm²)*	*Dose (Joules/cm²)*
Honmura, 1992, rat paw edema	Carrageenan	830 nm, 60 mW	32	9.6
Campana, 1993, arthritis animal	Urate crystals	633 nm, 5 mW	6	0.72
Honmura, 1993, rat paw edema	Carrageenan	830 nm, 60 mW	32	9.6
Shimizu, 1995, ligament cells	Mechanically stretched	830 nm, 30 mW	12	2.3–7.4
Ozawa, 1997, ligament cells	Mechanically stretched	830 nm, 700 mW	6–13	3.9
Sattayut, 1999, myofibroblast cells	Carrageenan	820 nm, 200 mW	22	4–19
Campana, 1999, arthritis aniimal	Urate crystals	633 nm, 30 mW	30	8
Nomura, 2001, fibroblast cells	Lipopoly-saccharide	830 nm, 50 mW	6–13	4–7.9
Sakurai, 2001, fibroblast cells	Lipopoly-saccharide	830 nm, 700 mW	21	1.9–6.3
Shefer, 2001, skeletal muscle cells	Cell starvation	633 nm, 4.5 mW	112	0.34
Campana, 2003, arthritis animal	Pyrophosphate crystals	633 nm, 6.5 mW	200	8.0
Dourado, 2004, mice	Snake venom	904 nm, 50 mW	90	2.8
Albertini, 2004, rat paw edema	Carragenan	660 nm, 2.5 mW	31	7.5
Ferreira, 2004, rat paw edema	Carrageenan PGE_2	633 nm, 12 mW	171	7.5
Pessoa, 2004, rat skin wound	Excised skin flap 0.5 cm²	904 nm, 2.8 mW	5	0.66
Avni, 2005, rat muscle ischemia	Hypoxia	810 nm, 400 mW	42	5.0
Lopes-Martins, 2005, mice pleurisy	Carrageenan	660 nm, 25 mW	31	7.5
Aimbire, 2005, airway hyperreactivity	Lipopoly-saccharide	660 nm, 2..5 mW	31	7.5
Aimbire, 2005, rat lung injury	Bovine serum albumin	660 nm, 2.5 mW	31	7.5
Median results		830 nm (633–904)	31 mW/cm² (5–171)	7.5 J/cm² (0.3–19)

The first column gives the name of first author, year of publication, and the experimental model used. Other columns give inflammatory agent used, laser type, and mean optical output, power density, and dose.

affect other inflammatory outcomes.[52] Two studies found reductions of cyclooxygenase 2 (Cox2) mRNA after LLLT exposure.[44,53] One study found that LLLT reduced levels of plasminogen activator in stretched periodontal ligament cells.[48]

Effects on cells and soft tissue. Laboratory investigations using animal models found that LLLT reduced inflammatory cell infiltration in four studies[47,54–56] and edema volume in four studies.[5,19,57,58] Four studies using cell cultures, rats, and mice found that LLLT reduced the formation of hemorrhagic le-

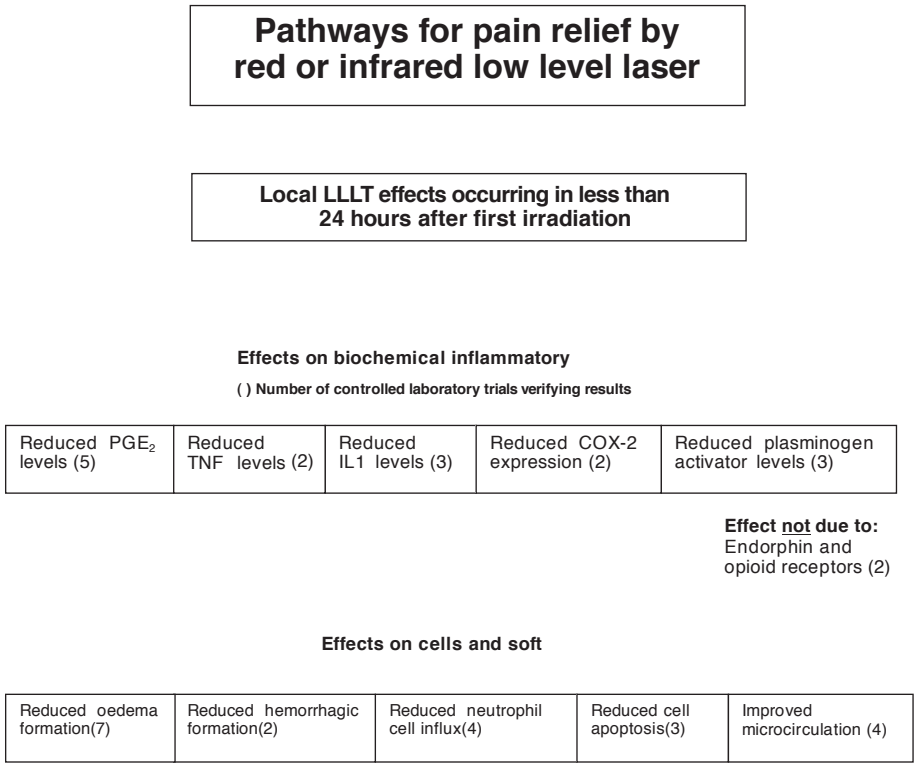

FIG. 1. Flow chart of the evidence behind biological effects of LLLT laboratory trials of acute pain mechanisms. Each identified outcome is listed, as well as the number of laboratory trials supporting or refuting that the specific outcome can be affected by LLLT.

sions,[54] reduced apoptosis,[59] reduced necrosis of muscle cells after ischemia,[60] and increased myotube proliferation[61] when compared to sham-irradiated controls.

Anti-inflammatory effects of LLLT versus non-steroidal anti-inflammatory drugs. Head-to-head comparisons between LLLT and pharmacological substances in four animal studies found that there were no differences in anti-inflammatory effects between LLLT and non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin,[32] meloxicam,[62] celecoxib,[55] and diclofenac[5] when they were administered at doses equivalent to those given in clinical practice (Fig. 2).

Interpretation of evidence on mechanisms for acute pain relief by LLLT

There was strong evidence from 18 out of 19 studies that red and infrared wavelengths of LLLT can act locally and rapidly to modulate the inflammatory processes in injured tissue. These anti-inflammatory effects include changes in biochemical markers, altered distribution of inflammatory cells, and reduced formation of edema, hemorrhage, and necrosis. These anti-inflammatory effects are dose-dependent. LLLT wavelength does not appear to influence outcome by a significant degree providing it lies within the red and infrared range. However, this result does not exclude the possibility that certain wavelengths may be more effective than others in some diseases where specific cell types or specific parts of pathophysiological processes are targeted. There was no convincing evidence that LLLT produces pain relief through any other mechanism during the first hours and days after acute injury.

Transition of laboratory findings into clinical dose recommendations

The median dose at the target location of studies reporting anti-inflammatory effects was 7.5 J/cm^2 (range 0.7–19 J/cm^2) and a power density of 5–171 mW/cm^2 for continuous red lasers with wavelengths of 632–660 nm or infrared lasers with wavelengths of 810–830 nm. For infrared 904-nm lasers, having strong pulses peaking above 1 Watt, efficacy was demonstrated with lower doses at 0.7 and 2.8 Joules. This difference in dose levels coincides with similar findings in meta-analyses of clinical trials.[8,63] In animal studies, the entire inflamed area can be treated by LLLT stimulation at one point by single diode laser. In contrast, the volume of inflamed tissue and edema containing inflammatory cells is larger in the clinical situation and cannot be effectively irradiated with a single diode laser. In clinical practice, LLLT dose is titrated according to the volume of inflamed tissue and edema. If the skin surface is intact, the depth to the target tissue and subsequent energy must also be considered. Lasers without strong pulses and an output of less than 50 mW can effectively irradiate tissue that lies within 10–15 mm of the laser source. Lasers with an output of 100–500 mW can effectively irradiate tissue that lie no more than 30–40 mm from the laser source. However, it should be remembered that excessively high power densities may inhibit cell activity if too near to the laser source.

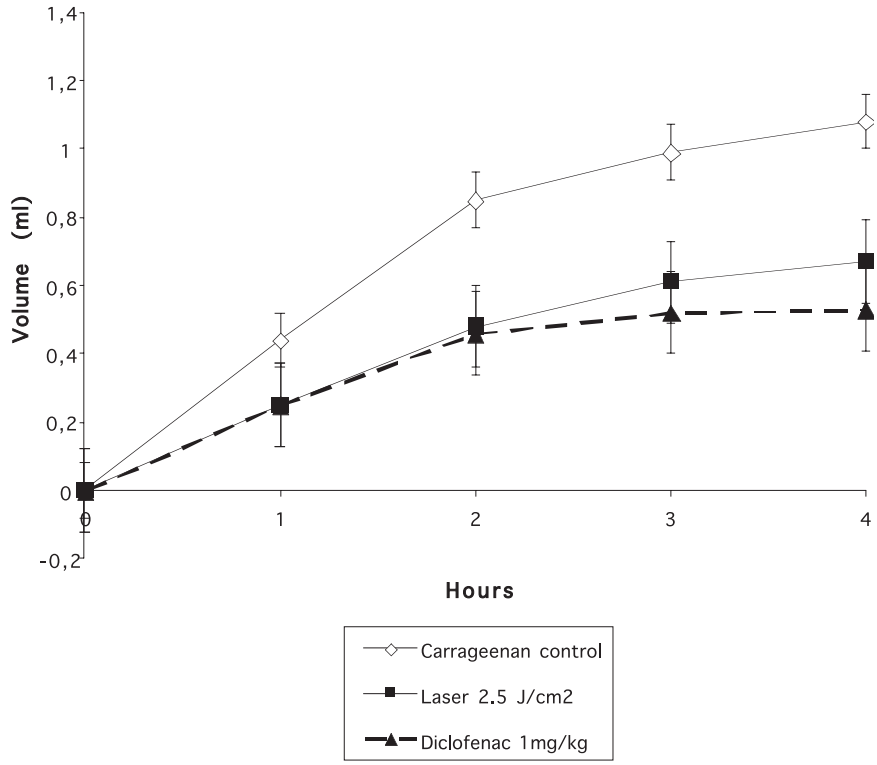

FIG. 2. Development of carrageenan-induced rat paw edema and treatment by LLLT at 2.5 J/cm^2 and a dose of diclofenac potassium at 1 mg/kg, which is 41% higher than the recommended diclofenac dose for humans. For both active treatments, edema development was significantly reduced compared to the control group ($p < 0.05$). (Modified from an experiment from our research group; for full details, see Albertini et al., 2004.)

Clinical trials

Fifteen placebo-controlled trials were included in the review (Table 2). Six of these trials used daily energy doses 5 Joules or less and found no significant effects from LLLT for ankle sprains[64,65] or oral surgery.[41,66] Nine trials ($n = 609$) administered LLLT with daily doses higher than 5 Joules for acute ankle sprains,[67] acute Achilles tendonitis,[68–70] medial tibial shin splint,[71] oral surgery,[56] and cholecystectomy.[72] Eight of these nine trials found that LLLT was significantly better than placebo in at least one of the outcomes measured (Table 3).

The number of cases with subjective improvement on the first day could be calculated from four trials that had administered an adequate dose of LLLT (i.e., 5J/day, $n = 379$). There were 83 patients in the active LLLT group and 27 in the placebo-control group reporting improvement, thus giving a significant Relative Risk for improvement at 2.7 (95% CI, 1.8–3.9) in a fixed effects model (Q = 7.1, not significant for heterogeneity) (Fig. 3). The corresponding value for numbers-needed-to-treat is 2.1 (95% CI, 1.4–2.9).

DISCUSSION

The results of this review demonstrate that an adequate dosage of LLLT produces anti-inflammatory effects and pain relief over that seen with placebo. The effect size in laboratory studies during the first hours after injury equals that of NSAIDs when optimal doses are administered. Inhibition of inflammatory processes after injuries may hinder beneficial processes later in the proliferative and remodelling phases of tissue repair. For example, steroids are very potent therapeutic agents which inhibit inflammatory processes and relieve pain, but they also impair proliferation and delay tissue repair.[16,73,74] Placebo-controlled clinical trials of NSAIDs for ankle injuries also show significant pain relief during the first few days, but this is also associated with impaired edema absorbtion for several weeks.[75] LLLT can be advantageous because its therapeutic window for anti-inflammatory actions overlaps with its ability to improve tissue repair.[2] The ability of LLLT to promote tissue repair in a dose-dependent manner, with optimal doses being 2 J/cm^2 at target tissue, has been extensively studied and was outside the scope of the present review.[76] However, when taken together, the available evidence strongly suggests that, for acute pain, optimal LLLT effects will be achieved if it is administered at high doses, typically 7.5 J/cm^2 at the target tissue, in the first 72 h (to reduce inflammation), followed by lower dosages, typically 2 J/cm^2 at target tissue, in subsequent days (to promote tissue repair).

The speculation about putative biological mechanisms and the difficulty of translating laboratory findings to the clinical situation are likely to have hindered the acceptance of LLLT as an effective therapeutic agent for acute pain.[77] Claims that LLLT irradiation of intact nerves produces meaningful changes in nerve activity and/or endorphin release was not supported by the findings of this review. Evidence for LLLT irradiation of injured

TABLE 2. LLLT THERAPY IN ACUTE PAIN: CHARACTERISTICS FOR TRIALS MEASURING EFFECTS WITHIN 7 DAYS

First author, year, surgical procedure or type of injury	*Laser type, mean output power (mW)*	*Spot size in cm²*	*Number of irradiated points or area (cm²)*	*Total Joules delivered in 24 h*	*Dose above minimum dose limit*	*Method score max 5 (Jadad scale)*
Carillo, 1990, third molar	633 nm 5 mW	0.02	6 point	0.72[a]	No	3
Taube, 1990, third molar	633 nm 4 mW	0.02	1 point	0.48[a]	No	3
Fernando, 1993, third molar	830 nm 30 mW	0.02	1 point	4.0[a]	No	3
Masse, 1993, third molar	633 and 904 nm 5 mW	0.02	1 point	0.37[a]	No	3
Axelsen, 1993, ankle sprain	830 nm 30 mW	0.02	1 point	0.9[a]	No	4
de Bie, 1998, ankle sprain	904 nm 2.5 and 25 mW	0.64	1 point	0.5 and 5[a]	No	5
Røynesdal, 1993, third molar	830 nm 40 mW	0.1	1 point	6	Yes	4
Nekcel, 2001, third molar	809 nm 50 mW	1.0	2.5 cm²	7.5	Yes	3
Kreisler, 2004, endodontic	809 nm 50 mW	1.0	2.5 cm²	7.5	Yes	3
Moore, 1992, cholecystectomy	830 nm 60 mW	0.02	20 points	9.6	Yes	3
Tabau, 1985, ankle sprain	904 nm 6.5 mW	5	5 cm²	19.5	Yes	3
Stergioulas, 2004, ankle sprain	820 nm 40 mW	0.16	10 points	24	Yes	4
Darre, 1994, achilles	830 nm 30 mW	0.2	4 points	16	Yes	4
Bjordal, 2005, achilles	904 nm 10 mW	0.5	3 points	5.4	Yes	5
Nissen, 1994, shin splint	830 nm 40 mW	0.2	2.4 J/cm²	2.4 to ?[a]	?	3

[a]Small dose.

Trials in italics have used doses outside the optimal dose range for LLLT determined from laboratory studies or have failed to cover over one-third of the inflamed tissue volume.

nerves is considerably more mature, with a growing number of laboratory and clinical trials finding positive effects.[78,79]

New hypotheses about LLLT mechanisms, such as systemic effects through nitric oxide synthesis (NOS), cannot be ruled out. But at the moment, targeting modulation of systemic NOS and local TNF levels by LLLT are only experimental possibilities that need to be explored further. Our understanding of how LLLT can be used therapeutically to relieve pain by these two mechanisms is novel, and far from what is required for safe and effective clinical use.

This review demonstrated that a prerequisite for treatment success is that laser energy be distributed across the inflamed tissue using a sufficiently high anti-inflammatory dose (i.e., Joules per day). Clinical trials that fail to do this will bias trial outcome towards negative outcome for LLLT (i.e., no effect). Several trials in this review used doses just above the lower limit of the therapeutic range, and the exact effect size under optimal conditions remains to be estimated. Further weaknesses in published trial data observed in this review were considerable inter-trial variability in baseline pain scores, and inter-trial variability in the selection and reporting of clinical outcomes.

Pharmaceutical companies seeking approval by the U.S. Food and Drug Administration (FDA) for NSAIDs in acute pain tend to use evidence from randomized placebo-controlled trials with impacted third molar surgery.[80] Surprisingly few trials have been performed on more common soft-tissue injuries.

In this review NNT calculations were only possible for measurements taken during the first 24 h after injury or sur-

TABLE 3. OUTCOMES FOR TRIALS WITH ADEQUATE LLLT DOSES AFTER ACUTE SOFT-TISSUE INJURY

First author, year, surgical procedure	*Number of cases*	*Baseline pain VAS*	*Continuous data, pain relief over placebo*	*Rescue drug doses laser/ placebo*	*Improved cases after single dose laser/placebo*	*Other significant outcomes*
Røynesdal, 1993, third molar	50	41	Significant ($p = 0.03$)	n.a.	n.a.	n.a.
Nekcel, 2001, third molar	210	n.a.	n.a.	n.a.	45/22	Pain duration
Kreisl, 2004, endodontic	52	23	Significant ($p = 0.047$)	n.a.	n.a.	n.a.
Moore, 1992, cholecystectomy	20	62	Significant ($p = 0.038$)	39/90	7/1	n.a.
Tabau, 1985, ankle sprain	100	n.a.	n.a.	25/50	25/3	Weight bearing
Stergioulas, 2004, ankle sprain	31	n.a.	n.a.	n.a.	n.a.	Edema
Darre, 1994, achilles	89	71	Not significant	n.a.	Not significant	n.a.
Bjordal, 2005, achilles	14	n.a.	Significant ($p = 0.028$)	n.a.	n.a.	PGE_2—level, single hop test
Nissen, 1994, tibial shin splint	49	n.a.	n.a.	n.a.	6/1 on day 1, not significant on day 7	n.a.
Total	609		4/5	64/140	83/27	

Trials are listed by first number and publication year, number of included patients, baseline pain level on a 100-mm visual analogue scale (VAS), subjective improvement after a single dose, and other reported outcomes.

gery. This contrasts with recently published meta-analyses of postoperative trials, which often use outcomes like TOTPAR, which is the mean summed categorical pain relief, or SPID, which is the summed pain intensity difference. These parameters are becoming standards for post-operative pain research and calculation of NNTs for limited periods such as the first 4–6 h after surgery.[77] Nevertheless, NNTs for LLLT were found to be in the same range as those reported for NSAIDs in postoperative pain.[77] Evidence used to support the FDA-approval of individual NSAIDs for acute pain consisted of placebo-controlled trials enrolling 772–2832 patients for each drug. For instance, celecoxib efficacy was approved by FDA only on the basis of four placebo-controlled third molar extraction trials with significant results ($n = 925$), despite the existence of trials demonstrating no significant effect on orthopedic surgery ($n = 255$). Rofecoxib, which has subsequently been withdrawn, was FDA approved on the findings of three placebo-controlled trials (two of which were dental and one orthopedic surgery) and two trials in dysmenorrhea patients (813 patients in total).

The results of our review on the effectiveness of LLLT in acute pain compare well to standard NSAID treatment. The better risk-benefit profile of LLLT to NSAIDs suggests that it is time to accept LLLT within mainstream medicine as part of the existing therapeutic armamentarium against acute pain.

Future LLLT trials in acute postoperative pain should make use of validated outcomes such as TOTPAR or SPID, and thereby ease evaluation of LLLT efficacy over placebo, and the relative efficacy between LLLT and other interventions.

CONCLUSION

There is strong evidence that LLLT modulates the inflammatory process and relieves acute pain in the short-term. The evidence for a significant pain-relieving effect from LLLT is fairly consistent, although it is not possible to make robust estimates of the effect size for optimal doses of LLLT due to insufficient evidence. Nevertheless, we found that negative outcome trials used daily doses below 5 Joules, whereas trials reporting positive outcome used daily doses above 5 Joules. For 904-nm lasers, positive effects can be achieved with doses down to 1.8 Joules per point if the total energy dose is above 5 Joules and delivered to a sufficient part of injured tissue. For 810–830-nm lasers, we recommend that LLLT is titrated to target anti-inflammatory mechanisms using doses of minimum 6 Joules for small acute injuries and doses above 10 Joules for larger injuries. Hopefully, these findings will be reflected in future clinical research, so that we can leave behind the publication era of insufficiently dosed LLLT trials.

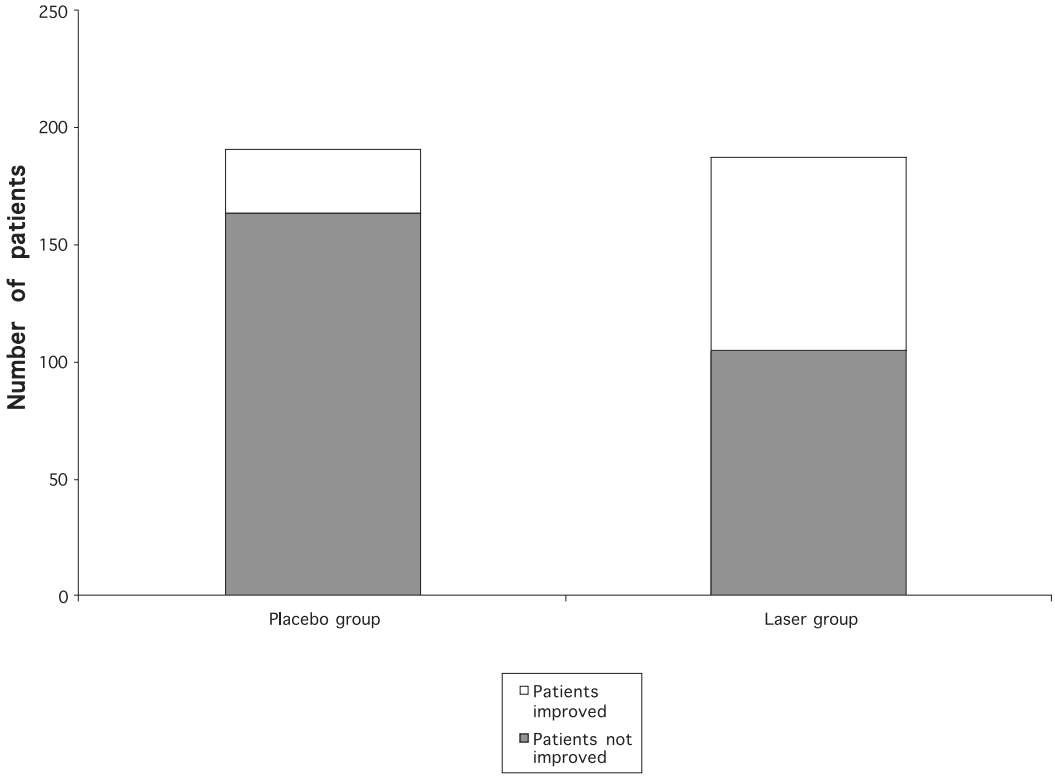

FIG. 3. Categorical data for patients (n = 378) from four trials for subjective improvement after a single-session of LLLT in acute pain. Trials investigated post-operative pain after third molar extraction and cholescystectomy; one trial investigated medial tibial shin splint; and one trial investigated ankle distorsions.

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Address reprint requests to:
Dr. Jan Magnus Bjordal
Section of Physiotherapy Science
University of Bergen
5018 Bergen, Norway Kalfarveien 31

E-mail: jmb@hib.no