The anti-inflammatory mechanism of low level laser therapy and its relevance for clinical use in physiotherapy

Jan Magnus Bjordal1,2, Rodrigo Alvaro Brandão Lopes-Martins3, Jon Joensen1,2, Vegard Vereide Iversen4

1Centre for Evidence-Based Practice, Bergen University College, Norway, 2Section of Physiotherapy Science, University of Bergen, Norway, 3Institute of Biomedical Sciences, Pharmacology Department, Universidade São Paulo, Brazil, 4Institute of Education, Bergen University College, Norway

Background: Low level laser therapy (LLLT) is a modality that has been used by physiotherapists for more than two decades. Clinical use has largely relied on empirical data, but new evidence suggests that LLLT can trigger specific photobiological mechanisms.

Objective: To review possible therapeutic windows for LLLT in inflammatory reactions.

Methods: Systematic review of LLLT in studies with cell cultures and animals where inflammation is induced. Skin wound studies were excluded unless they measured the influence of drugs on LLLT effects, or made a direct comparison of LLLT and drugs in inflammation.

Results: We identified 1 review, 34 cell studies, 54 animal studies and 106 skin incision studies potentially eligible for analysis. Eleven cell studies and 27 animals studies met all our inclusion criteria, and another six animal studies met our inclusion criteria for drug comparisons and LLLT interactions. There is strong evidence of an anti-inflammatory effect from LLLT, which is consistent across all 12 tested laboratory models and phases of inflammation and wavelengths between 633 and 904 nm. The magnitude of the anti-inflammatory effect is not significantly different from that of non-steroidal anti-inflammatory drugs (NSAIDs), but it is slightly less than glucocorticoid steroids. There is moderate evidence that concomitant use of glucocorticoid steroid has a negative effect on LLLT mechanisms and should be avoided.

Conclusion: Red and near infrared LLLT administered with mean laser output of 2.5–100 mW, irradiation times of 16–600 s and doses of 0.6–9.6 J reduces inflammation significantly, and is equally effective as NSAIDs in animal laboratory studies. Scattered evidence from human studies have found similar anti-inflammatory effects of LLLT, suggesting that this mechanism may be responsible for many of the significant effects reported in clinical LLLT studies.

Keywords: Odema, Inflammation, Injury, Low level laser therapy, Animal

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a standard treatment for musculoskeletal disorders in treatment guidelines and surveys of clinical practice. NSAIDs are the most frequently recommended or administered therapy for traumatic injury, post-operative pain, and neck and low back disorders. Although inflammation is mostly associated with acute conditions, NSAIDs are still the most common treatment for chronic conditions like osteoarthritis and chronic pain in Europe. Another common anti-inflammatory therapy is glucocorticoid injections, which are recommended for osteoarthritis, subacute and chronic tendinopathies. Although anti-inflammatory drug treatments dominate musculoskeletal pain management, they are also a cause for concern due to their adverse effects.

There are some data suggesting that physiotherapists’ involvement in acute injuries is associated with significantly better outcomes than if physiotherapy is not prescribed by doctors. It is interesting to note that this is the case even if physiotherapists do not have an anti-inflammatory intervention at their disposal. A timely research question is whether any of the physical agents used by physiotherapists can modulate inflammation in the same way as anti-inflammatory drugs.

Since the 1980s, low level laser therapy (LLLT) has been a controversial modality with conflicting results.
Twenty-five years later, early positive results have yet to be translated into consistent significant results in clinical trials. The first animal trial where LLLT showed effects in an experimental inflammation model was published in 1985, and a few more publications followed during the next decade. Still, when basic and clinical LLLT research was reviewed 15 years ago, the conclusion was that LLLT had not made the difficult transition from positive laboratory findings become an established therapeutic tool. Today, the situation is changing and the PEDro database of clinical physiotherapy studies now holds 69 randomized controlled clinical trials with acceptable method scores (60% or more of method criteria met) and the efficacy results are mixed. LLLT involves a complexity of biophysical, photobiological, pathological, and clinical aspects, and treatment success may be compromised by a lack of understanding of the mechanisms and their possible dose-dependency.

Inflammation may be present in both acute and chronic musculoskeletal pain disorders; for instance, episodes with flares of symptom aggravation in degenerative and systemic arthritis are associated with increased synovial inflammatory activity. For tendon disorders, short-lived flares in disease activity seem to be associated with physical overload, although a definite link between pain aggravation and inflammatory activity is still uncertain. On the other hand, anti-inflammatory treatment with NSAIDs and steroids seems to provide short-term pain relief in acute and subacute tendinopathies. For chronic muscle pain, both the capacity of the muscle cells to withstand fatigue and the vasoactive response to muscle contractions seem impaired. Recently, signs of inflammation have also been detected in active myofascial trigger points and one study found significant effects of anti-inflammatory treatment with a topical NSAID patch placed in active myofascial trigger points in neck pain patients. These findings may suggest that anti-inflammatory treatment could find a new role to play in conditions such as neck muscle pain.

Physiotherapy management of musculoskeletal disorders has lacked a tool which can effectively reduce inflammation. LLLT may have the potential to fill this gap. This analysis is an attempt to map laboratory evidence for LLLT in various stages of inflammation and tissue types, and outline the treatment potential in physiotherapy management of disorders with an inflammatory component.

**Materials and Methods**

A literature search was performed in the MEDLINE database from 2006 until 1 March 2010. The search words were: laser or low laser therapy or phototherapy, and cell or animal and inflammation. Only trials or reviews with control groups were included, and they were then subjected to mapping in categories. Skin incision studies were excluded unless they presented comparisons of LLLT with pharmacological interventions or compared LLLT effects with and without drugs as co-interventions. Outcomes had to be measured within 7 days after inflicting the experimental injury, and should include some measure of inflammation such as biochemical inflammatory markers, cytokines, oedema, creatine kinase, erythrocyte sedimentation rate, and creatine-reactive protein. Studies measuring aspects of proliferation and tissue repair only, were excluded.

**Results**

In addition to our previous review from 2006, the literature search identified one review of cell studies. The new review focused on molecular and proliferative effects of LLLT, and inflammation was only superficially covered with references to a study from our research group and three studies from other research groups. The new review concluded briefly that the expression and secretion of inflammatory cytokines, prostaglandin E2 (PGE2), tumor-necrosis factor (TNF)-alpha, cyclooxygense-2 (COX-2) and interleukin 1 beta (IL-1β) can be inhibited by LLLT exposure.

In total there were potentially 34 eligible studies in cell cultures and 54 eligible studies in animals. Closer examination revealed that 11 cell culture studies and 27 animal studies met all of our inclusion criteria. We also identified 106 animal studies performed in skin incision wounds, of which six studies were included for investigating head-to-head comparisons between LLLT and anti-inflammatory drugs and negative interactions from drugs.

The results of the laboratory studies were consistently in favor of LLLT across cell culture studies and animal studies. All except one study showed anti-inflammatory effects for at least one of the LLLT dose groups they used. The available cell culture studies and their respective experimental models and treatment parameters are listed in Table 1. For the animal studies, 12 different experimental models of inflammation were used to investigate the anti-inflammatory effect of LLLT (Fig. 1).

The individual animal studies and their characteristics are summarized in Table 2.

**Biochemical markers of inflammation in the initial stage of inflammation**

One cell study found no anti-inflammatory effects from LLLT on blood monocytes and vein endothelial cells and TNF-alpha. The inflammatory marker PGE2 was on the other hand significantly reduced by...
Another three animal studies\(^{28-30}\) also showed significant reductions in PGE\(_2\) levels after LLLT. In addition, two human studies were performed with microdialysis in symptomatic peritendinous Achilles tissue\(^{31}\) and in blood serum in patients with rheumatoid arthritis.\(^{32}\) LLLT inhibition of TNF-alpha release was reported in three animal studies,\(^{21,33,34}\) but only in a narrow dose range. Two cell studies demonstrated significant reduction in COX-2 mRNA levels after LLLT exposure.\(^{24,35}\) COX-2 inhibition was also found in two animal studies,\(^{36,37}\) but not in animals receiving less than 16 seconds of laser irradiation.\(^{37}\) Five cell studies have found that LLLT partially reduced levels of interleukin-1\(\beta\),\(^{27,38-41} \) and four animal studies showed the same effect.\(^{42-45}\) One cell study observed reduced levels of plasminogen activator in stretched periodontal ligament cells.\(^{46}\) The results at the molecular and cellular levels in the early stage of inflammation are summarized in Fig. 2.

Inflammatory cell infiltration and formation of oedema, hemorrhage and necrosis in animal studies

LLLTT in three cell studies.\(^{24,26,27}\) Another three animal studies\(^{28-30}\) also showed significant reductions in PGE\(_2\) levels after LLLT. In addition, two human studies were performed with microdialysis in symptomatic peritendinous Achilles tissue\(^{31}\) and in blood serum in patients with rheumatoid arthritis.\(^{32}\) LLLT inhibition of TNF-alpha release was reported in three animal studies,\(^{21,33,34}\) but only in a narrow dose range. Two cell studies demonstrated significant reduction in COX-2 mRNA levels after LLLT exposure.\(^{24,35}\) COX-2 inhibition was also found in two animal studies,\(^{36,37}\) but not in animals receiving less than 16 seconds of laser irradiation.\(^{37}\) Five cell studies have found that LLLT partially reduced levels of interleukin-1\(\beta\),\(^{27,38-41} \) and four animal studies showed the same effect.\(^{42-45}\) One cell study observed reduced levels of plasminogen activator in stretched periodontal ligament cells.\(^{46}\) The results at the molecular and cellular levels in the early stage of inflammation are summarized in Fig. 2.

**Inflammatory cell infiltration and formation of oedema, hemorrhage and necrosis in animal studies**

Local reduction of inflammatory neutrophil cell infiltration after LLLT was observed in eight animal studies.\(^{34,43,47-52}\) Four studies in rats and dogs have investigated hemorrhagic formation and myocardial infarct size, and all found significant reductions in size after LLLT as compared to sham-irradiated controls.\(^{34,53-55}\) In three trials, the necrotic area after snake venom injection was reduced after LLLT.\(^{48,56,57}\) LLLT showed a significant reduction in oedema volume after soft tissue injury in all five animal studies.\(^{10,30,58-60}\) Differences in histology
between LLLT and control groups in one of our studies in the rat paw oedema model are shown in Fig. 3.

Anti-inflammatory effects of LLLT versus NSAIDs and glucocorticoid steroids in laboratory trials

In four out of five head-to-head comparisons between LLLT and NSAIDs, human equipotent doses of NSAIDs did not exert significantly different effects from LLLT. The anti-inflammatory effect was measured within the first 3 days after experimental injury, and studies included the NSAID indomethacin, meloxicam, celecoxib, and diclofenac. The only study showing significantly less effect of LLLT did not report irradiation time. This may however been as short as 4 seconds if the reported parameters are used for calculation of irradiation time. There is mixed evidence for the comparison between the anti-inflammatory effect of glucocorticoid steroids (dexamethasone) and LLLT. Dexamethasone anti-inflammatory effects were not significantly different from LLLT in

Table 2 The individual animal studies and study characteristics

<table>
<thead>
<tr>
<th>First author (year), model</th>
<th>Inflammatory agent</th>
<th>Laser wavelength (nm)/mean output power (mW)/irradiation time (seconds)</th>
<th>Power density (mW/cm²)</th>
<th>Dose (J/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagnasco (1985), rat paw edema</td>
<td>Formaldehyde</td>
<td>904/5/100</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td>Honmura (1992), rat paw edema</td>
<td>Carrageenan</td>
<td>830/60/30</td>
<td>32</td>
<td>9.6</td>
</tr>
<tr>
<td>Campana (1993), arthritis animal</td>
<td>Urate crystals</td>
<td>633/5/—</td>
<td>6</td>
<td>0.72</td>
</tr>
<tr>
<td>Honmura (1993), rat paw edema</td>
<td>Carrageenan</td>
<td>830/60/30</td>
<td>32</td>
<td>9.6</td>
</tr>
<tr>
<td>Campana (1998), rat surgical incision</td>
<td>Laparotomy</td>
<td>633/5/40</td>
<td>200</td>
<td>8</td>
</tr>
<tr>
<td>Campana (2003), arthritis animal</td>
<td>Pyrophosphate crystals</td>
<td>633/6.5/40</td>
<td>200</td>
<td>8.0</td>
</tr>
<tr>
<td>Dourado (2004), mice</td>
<td>Snake venom</td>
<td>904/50/92</td>
<td>90</td>
<td>2.8</td>
</tr>
<tr>
<td>Albertini (2004), rat paw edema</td>
<td>Carrageenan</td>
<td>660/2.5/80</td>
<td>31</td>
<td>7.5</td>
</tr>
<tr>
<td>Ferreira (2004), rat paw edema</td>
<td>Carrageenan PGE₂</td>
<td>633/12/80</td>
<td>171</td>
<td>7.5</td>
</tr>
<tr>
<td>Pessoa (2004), rat skin wound</td>
<td>Excised skin flap 0.5 cm²</td>
<td>904/2.8/120</td>
<td>5</td>
<td>0.66</td>
</tr>
<tr>
<td>Avni (2005), rat muscle ischemia</td>
<td>Artery occlusion</td>
<td>810/43/120</td>
<td>1.4–4.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Lopes-Martins (2005), mice pleurisy</td>
<td>Carrageenan</td>
<td>660/2.5/80</td>
<td>31</td>
<td>7.5</td>
</tr>
<tr>
<td>Aimbire (2005), rat airway hyperreactivity</td>
<td>Lipopolysaccharide</td>
<td>660/2.5/80</td>
<td>31</td>
<td>7.5</td>
</tr>
<tr>
<td>Aimbire (2005), rat lung injury</td>
<td>Bovine serum albumin</td>
<td>660/2.5/80</td>
<td>31</td>
<td>7.5</td>
</tr>
<tr>
<td>Laakso (2005), rat paw edema</td>
<td>Carrageenan</td>
<td>780/50/—</td>
<td>50</td>
<td>1.0, 2.5</td>
</tr>
<tr>
<td>Rizzi (2006), rat muscle injury</td>
<td>Blunt trauma</td>
<td>904/45/35</td>
<td>145</td>
<td>5</td>
</tr>
<tr>
<td>Tuby (2006), rat heart infarct</td>
<td>Coronar artery occlusion</td>
<td>804/43/120</td>
<td>8</td>
<td>0.6–2.0</td>
</tr>
<tr>
<td>Albertini (2007), rat paw edema</td>
<td>Carrageenan</td>
<td>660, 684/30/196</td>
<td>23</td>
<td>7.5</td>
</tr>
<tr>
<td>Correa (2007), rat peritonitis</td>
<td>Lipopolysaccharide</td>
<td>904/4/60–150–300</td>
<td>50</td>
<td>3, 7.5, 15.0</td>
</tr>
<tr>
<td>Castana (2007), rat knee arthritis</td>
<td>Zymosan</td>
<td>810/79/60, 600</td>
<td>5, 50</td>
<td>3, 30</td>
</tr>
<tr>
<td>Bosch (2008), rat pleurisy</td>
<td>Carrageenan</td>
<td>660/20/16–74</td>
<td>571</td>
<td>3, 30</td>
</tr>
<tr>
<td>de Lima (2009), rat dissected bronchii</td>
<td>TNF-alpha bath</td>
<td>660/30/62</td>
<td>23</td>
<td>2.6</td>
</tr>
<tr>
<td>Safavi (2008), surgery rat gingiva</td>
<td>Incision</td>
<td>633/17/300</td>
<td>18</td>
<td>7.5</td>
</tr>
<tr>
<td>Moryiama (2009), mice lung</td>
<td>Zymosan injection</td>
<td>655, 905/25/200</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Lopes (2009), hamster mucositis</td>
<td>5-fluorouracil</td>
<td>660/33, 93/16, 6</td>
<td>—</td>
<td>2.8, 11.1</td>
</tr>
<tr>
<td>Silveira (2009), rat muscle injury</td>
<td>Blunt trauma</td>
<td>904/15/40</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>Sussai (2010), rat muscle injury</td>
<td>Forced swimming</td>
<td>660/100/40</td>
<td>3300</td>
<td>133</td>
</tr>
<tr>
<td>Median results</td>
<td></td>
<td>Median 830 (633–904)/25/80</td>
<td>Median 32 (5–3300)</td>
<td>Median 7.5 (0.3–133)</td>
</tr>
</tbody>
</table>
two studies, but slightly superior to LLLT in three other studies in reducing inflammation. The relative effects between LLLT, NSAIDs and glucocorticoid steroids measured as dry weight/wet weight difference in a rat paw oedema model are summarized from studies in our laboratory into Fig. 4.

**Negative drug interactions with anti-inflammatory effects of LLLT**

Four animal studies reported negative interactions and reduced effect from LLLT with concomitant use of glucocorticoid steroids.

**Dose-response patterns for anti-inflammatory effects**

All investigated wavelengths between 632 and 904 nm induced significant anti-inflammatory effects in cell and animal trials. The median value for laser mean optical output was 25 mW. Lower limits for anti-inflammatory effects were found to be 0.6 J/cm² in animal studies, and the lower limit for irradiation time was 16 seconds. Median irradiation time was 80 seconds in animal studies, but one study reported significantly better effects when 3 J/cm² was delivered with low power density (5 mW/cm²) over a longer period of time (600 s), than high power density (50 mW/cm²) over a shorter period of time (60 s). Two studies reported significantly better anti-inflammatory effects when doses were equal, but they were delivered with longer irradiation times in a model of zymosan-induced arthritis. Upper limits for anti-inflammatory effects remain uncertain for power densities above 135 mW/cm² and doses above 15 J/cm². Both infrared and red lasers were significantly better than LED with red wavelength in the same experimental model.

**Discussion**

In the current review, we found surprisingly consistent anti-inflammatory effects of LLLT from 43 out of 44 controlled laboratory trials. One may question the clinical relevance of laboratory studies, but they form the scientific foundation for the development of pharmaceutical agents and are a compulsory hurdle before marketing approval can be given for drugs. Animal studies are useful to determine optimal doses and the time profile of treatment effects on different aspects of the pathophysiology. For pharmacological agents, animal studies have been crucial for determination of
optimal timing of administration with anti-inflammatory drugs. It is encouraging to see that this part of the scientific basis for LLLT mechanisms has improved to a level where LLLT can compare and compete with anti-inflammatory drug treatment. At present there is very limited evidence for anti-inflammatory effects from other electrophysical agents in physiotherapy practice. A few scattered reports have appeared with shortwave diathermy and high voltage electrical stimulation, but the power of this evidence is considerably weaker than the 44 studies with LLLT. The crucial question is if this evidence translates into humans. There are indices of the anti-inflammatory effect of LLLT that can be translated to humans. One study has shown that LLLT significantly reduces the level of inflammatory cytokine PGE$_2$ in the synovial membrane of rheumatoid arthritis patients. Another study in female musculoskeletal pain patients found that decreased PGE$_2$ blood serum levels was significantly associated with treatment success. Our research group has also found that LLLT reduced PGE$_2$ levels measured by microdialysis in activated Achilles tendinitis. We have also found that levels of creatine kinase activity, a cytokine involved in the early phase of muscle damage, and C-reactive protein, a marker of systemic inflammation, could be reduced by LLLT after heavy exercises in animals and in humans. If one looks to approval of drugs for acute pain in the USA, most drugs have been approved on the basis of clinical studies in models of minor oral surgery. In our previous review of human studies, we found that LLLT exhibited a significant dose-dependent anti-inflammatory effect in randomised controlled studies of minor oral surgery. Typically, studies with non-significant effects were under-dosed with doses below 0.5 J.

The available material can tell us something about areas where LLLT has clinical potential. LLLT can be used in combination with active exercises to control possible inflammatory responses to loading from joints and tendons. New knowledge about inflammatory manifestations in active myofascial trigger points offers an additional explanation for why LLLT seems to work so well in neck pain patients and LLLT effects on active trigger points have been demonstrated in one animal study.

The anti-inflammatory effects from monochromatic LLLT seem to occur as a class effect irrespective of laser wavelengths in the red or infrared laser light spectra. The difficult transition into clinical practice has been hampered by a lack of knowledge about LLLT mechanisms and their dose dependency. In short, two major factors seem to cause treatment failure in clinical trials. In studies in small animals, most of the inflamed area can be covered even with a small laser spot size and doses are reported in J/cm$^2$. Extrapolating these results into clinical practice where larger areas need to be irradiated calls for reporting of doses in J. Several studies have based their calculation of clinical doses on tiny spot sizes in J/cm$^2$, leading to insufficient doses in studies of osteoarthritis (0.18 J) and carpal tunnel syndrome (0.9 J). Current guidelines state that clinical doses should use J instead of J/cm$^2$ (www.walt.nu/dosage-recommendations.html). Second, steroids will erase the possible anti-inflammatory effect of LLLT, and several tendinopathy trials have recruited more than 40% of their patients from failures after steroid injection therapy. Perhaps the most important contribution from this analysis, is the finding that the anti-inflammatory effect is occurring locally in the inflamed tissue. Bearing in mind that the tiny laser beam only penetrates with sufficient energy into 1–4 cm$^2$ of human tissue, large pathological tissue volumes need irradiation at several points to make a clinical difference.

More LLLT research with inflammatory experimental models is clearly needed, and it is true that there are several aspects of LLLT mechanisms which have not been investigated yet. LLLT is still considered with scepticism by parts of established medicine and LLLT is hardly recommended in any clinical guidelines. During the past years, much attention has been paid to the side effects of anti-inflammatory drugs and the negative long-term effects of steroid injections in tendon disorders. Toxicity for LLLT is agreed to be lower than that for most drugs, and in view of its superior safety, LLLT should be considered as an alternative to pharmaceutical agents.

Figure 4 Tertiary phase of inflammation – edema volume reduction after LLLT and anti-inflammatory drugs

Conclusion

There is strong evidence that red and infrared LLLT has a dose-dependent anti-inflammatory effect in animals, and scant evidence that the anti-inflammatory effect also occurs after LLLT in humans. The magnitude of the effect is not significantly different from NSAIDs, but the effect can be compromised if LLLT is combined with glucocorticoid steroids. Further research is clearly needed, but clinical use of LLLT should be effective and safe if administered according to WALT guidelines and with location-specific doses.
References


