

Diclofenac, dexamethasone or laser phototherapy?

Part I

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_Introduction

In the May 2013 edition of Photomedicine and Laser Surgery, the editorial written by Prof. Tina Karu is titled "Is it time to consider photobiomodulation as a drug equivalent?" Well, is it? Let us have a look and see what the literature has to say about two very popular drugs:

NSAIDs (non-steroidal anti-inflammatory drugs) are the best sold pharmaceuticals ever. The short-term effects on pain and inflammation are obvious and valuable. The long-term effects, however, have been questioned and this is especially valid considering the many side effects of NSAIDs. Millions of patients are on long-term medication with NSAIDs, and even lifelong. Indeed, many persons die from their medication. So an alternative option is required. I believe it is already available: laser phototherapy! First, let us have a look at the strength of the scientific evidence for NSAIDs as such, and long term use of these in particular:

The meta-analysis by Bjordal[1] on the effect of NSAIDs on knee osteoarthritis pain appears to become important for the recognition and future development of LPT. Let us read the abstract: The research group summarises that non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase-2 inhibitors (coxibs), reduce short-term pain associated with knee osteoarthritis only slightly better than placebo, and long-term use of these agents should be avoided. Up for analysis were 23 placebo-controlled trials involving 10,845 patients, 7,767 of whom received NSAID therapy and 3,078 placebo therapy. All in all 21 of the NSAID-studies were funded by the pharmaceutical industry, and the results of 13 of these studies were inflated by patient selection bias as previous NSAID-users were excluded if they had not previously responded favourably to NSAID. Such an exclusion criterion for non-responders has never been seen in any controlled trial of LPT or other non-pharmacological therapies of osteoarthritis. In the remaining ten unbiased NSAID-trials, the difference from placebo was only 5.9 mm on a 100 mm pain scale.

This is far less than established data on differences that are considered minimally perceptible (9 mm) or clinically relevant (12 mm) for knee osteoarthritis patients. In addition, none of the trials found any effects beyond 13 weeks. This bleak support for long term use of NSAIDs is an excellent support for non-pharmaceutical methods, such as LPT. Diclofenac is one of the best-selling NSAIDs. Several investigators have compared the effect of LPT and diclofenac.



Ramos[3] investigated the effects of LPT (810 nm) in rat-induced skeletal muscle strain. Male rats were anaesthetised with halothane prior to the induction of muscle strain. Previous studies have determined that a force equal to 130 % of the body weight corresponds to approximately 80 % of the ultimate rupture force of the muscle tendon unit. In all animals, the right leg received a controlled strain injury while the left leg served as control. A small weight corresponding to 150 % of the total body weight was attached to the right leg in an appropriate apparatus and left to induce muscle strain twice for 20 minutes with three-minute intervals. Walking index, C-reactive protein, creatine kinase, vascular extravasation and histological analysis of the tibial muscle were performed after six, twelve and 24 hours of lesion induction. LPT in an energy-dependent manner markedly or even completely reduced the Walking Index, leading to a better quality of movement. C-reactive protein production



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The aim of a study by Marcos[2] was to evaluate the short-term effects of LPT or sodium diclofenac treatments on biochemical markers and biomechanical properties of inflamed Achilles tendons. Wistar rats Achilles tendons (n = 6/group) were injected with saline (control) or collagenase at peritendinous area of Achilles tendons. After one hour animals were treated with two different doses of LPT (810 nm, 1 and 3 J) at the sites of the injections, or with intramuscular sodium diclofenac. Regarding biochemical analyses, LPT significantly decreased COX-2, TNF-alpha, MMP-3, MMP-9, and MMP-13 gene expression, as well as PGE2 production when compared to collagenase group. Interestingly, diclofenac treatment only decreased PGE2 levels. Biomechanical properties were preserved in the laser-treated groups when compared to collagenase and diclofenac groups.

was completely inhibited by laser treatment, even more than observed with Sodium diclofenac inhibition (positive control). Creative Kinase activity was also significantly reduced by laser irradiations. In conclusion, LPT operating in 810 nm markedly reduced inflammation and muscle damage after experimental muscle strain, leading to a highly significant enhancement of walking activity.

The aim of the study by de Almeida[4] was to analyse the effects of sodium diclofenac (topical application), cryotherapy, and LPT on pro-inflammatory cytokine levels after a controlled model of muscle injury. For such, we performed a single trauma in the tibialis anterior muscle of rats. After one hour, animals were treated with sodium diclofenac (11.6 mg/g of solution), cryotherapy (20 min), or LPT (904 nm; superpulsed; 700 Hz; 60 mW mean output power;

1.67 W/cm^2; 1, 3, 6 or 9 J; 17, 50, 100 or 150 s). Assessment of interleukin-1 and interleukin-6 (IL-1 and IL-6) and tumour necrosis factor-alpha levels was performed at six hours after trauma employing enzyme-linked immunosorbent assay method. LPT with 1 J dose significantly decreased IL-1, IL-6, and TNF-alpha levels compared to non-treated injured group as well as diclofenac and cryotherapy groups. On the other hand, treatment with diclofenac and cryotherapy does not decrease pro-inflammatory cytokine levels compared to the non-treated injured group. Therefore, the authors conclude that 904 nm LPT with 1 J dose has better effects than topical application of diclofenac or cryotherapy in acute inflammatory phase after muscle trauma.

The purpose of a study by Albertini[5] was to investigate the effect of LPT on the acute inflammatory process. Male rats were used. Paw oedema was induced by a sub-plantar injection of carrageenan, the paw volume was measured before and one, two, three and four hours after the injection, using a hydroplethysmometer. To investigate the action mechanism of the GaAlAs laser on inflammatory oedema, parallel studies were performed using adrenalectomised rats or rats treated with sodium diclofenac. Different laser irradiation protocols were employed for specific energy densities (EDs), exposure times and repetition rates. The rats were irradiated with laser for 80 s each hour. The EDs that produced an anti-inflammatory effect were 1 and 2.5 J/cm^2, reducing the oedema by 27 % and 45.4 %, respectively. The ED of 2.5 J/cm^2 produced anti-inflammatory effects similar to those produced by the cyclooxigenase inhibitor sodium diclofenac at a dose of 1 mg/kg. In adrenalectomised animals, the laser irradiation failed to inhibit the oedema. These results suggest that LPT possibly exerts its anti-inflammatory effects by stimulating the release of adrenal corticosteroid hormones.

The aim of a work by Meneguzzo[6] was to investigate the effects of infrared 810 nm on the acute inflammatory process by the irradiation of lymph nodes, using the classical model of carrageenan-induced rat paw oedema. Thirty mice were randomly divided into five groups. The inflammatory induction was performed in all groups by a sub-plantar injection of carrageenan (1 mg/paw). The paw volume was measured before and 1, 2, 3, 4 and 6 hours after the injection using a plethysmometer. Myeloperoxidase (MPO) activity was analysed as a specific marker of neutrophil accumulation at the inflammatory site. The control group did not receive any treatment (GC); GD group received sodium diclofenac (1mg/kg) 30 minutes before the carrageenan injection; GP group received laser irradiation directly on the paw (1 Joule, 100 mW, 10 sec) one and two hours after the carrageenan injection; GLY group received laser irradiation (1 Joule, 100 mW, 10 sec) on the inguinal lymph nodes; GP+LY group received laser irradiation on both paw and lymph nodes one and two hours after the carrageenan injection. MPO activity was similar in the sodium diclofenac as well as in the GP and GLY groups, but significantly lower than the GC and GP + LY groups. Paw oedema was significantly inhibited in GP and GD groups when compared to the other groups. Interestingly, the GP+LY groups presented the biggest oedema, even bigger than in the control group. LPT showed an anti-inflammatory effect when the irradiation was performed on the site of lesion or at the correlated lymph nodes, but showed a pro-inflammatory effect when both paw and lymph nodes were irradiated during the acute inflammatory process.

The aim of a study by Barretto[23] was to investigate the analgesic and anti-inflammatory activity of LPT on the nociceptive behavioural as well as histomorphological aspects induced by injection of formalin and carrageenan into the rat temporomandibular joint. The 2.5 % formalin injection (FRG group) induced behavioural responses characterized by rubbing the orofacial region and flinching the head quickly, which were quantified for 45 min. The pretreatment with systemic administration of diclofenac sodium-DFN group (10 mg/kg i.p.) or irradiation with infrared LPT (LST group, 780 nm, 70 mW, 30 s, 2.1 J, 52.5 J/cm^2), significantly reduced the formalin-induced nociceptive responses. The 1 % carrageenan injection (CRG group) induced inflammatory responses over the time-course of the study (24 h, three and seven days) characterised by the presence of intense inflammatory infiltrate rich in neutrophils, scanty areas of liquefactive necrosis and intense interstitial oedema, extensive haemorrhagic areas, and enlargement of the joint space on the region. The DFN and LST groups showed an intensity of inflammatory response that was significantly lower than in CRG group over the time-course of the study, especially in the LST group, which showed exuberant granulation tissue with intense vascularization, and deposition of newly formed collagen fibres (three and seven days).

The aim of a study by de Almeida[7] was to analyse the effects of sodium diclofenac (topical application) and LPT on morphological aspects and gene expression of biochemical inflammatory markers. The researchers performed a single trauma in the tibialis anterior muscle of rats. After one hour, animals were treated with sodium diclofenac (11.6 mg/g of solution) or LPT (810 nm; continuous mode; 100 mW; 1, 3 or 9 J; 10, 30 or 90 s). Histological analysis and quantification of gene expression (real-time polymerase chain reaction-RT-PCR) of cyclooxygenase 1 and 2 (COX-1 and COX-2) and tumour necrosis factor-alpha (TNF-alpha) were performed at six, twelve and 24 h after trauma. LPT with all doses improved morphologi-

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cal aspects of muscle tissue, showing better results than injury and diclofenac groups. All LPT doses also decreased COX-2 compared to injury group and to diclofenac group at 24 h after trauma. In addition, LPT decreased TNF-alpha compared both to injury and diclofenac groups. LPT mainly with dose of 9 J is better than topical application of diclofenac in acute inflammation after muscle trauma.

Yet another study by Marcos[8] investigated if a safer treatment such as LPT could reduce tendinitis inflammation, and whether a possible pathway could be through inhibition of either of the two-cyclooxygenase (COX) isoforms in inflammation. Wistar rats (six animals per group) were injected with saline (control) or collagenase in their Achilles tendons. Then they were treated with three different doses of IR LPT (810 nm; 100 mW; 10 s, 30 s and 60 s; 3.57 W/cm^2; 1 J, 3 J, 6 J) at the sites of the injections, or intramuscular diclofenac, a nonselective COX inhibitor/NSAID. It was found that LPT dose of 3 J significantly reduced inflammation through less COX-2-derived gene expression and PGE2 production, and less oedema formation compared to non-irradiated controls. Diclofenac controls exhibited significantly lower PGE2 cytokine levels at 6 h than collagenase control, but COX isoform 1-derived gene expression and cytokine PGE2 levels were not affected by treatments. As LPT seems to act on inflammation through a selective inhibition of the COX-2 isoform in collagenase-induced tendinitis, LPT may have the potential to become a new and safer non-drug alternative to coxibs.

The aim of the study by de Paiva Carvalho[9] was to evaluate the effect of single and combined therapies (LPT, topical application of diclofenac and intramuscular diclofenac) on functional and biochemical aspects in an experimental model of controlled muscle strain in rats. Muscle strain was induced by overloading tibialis anterior muscle of rats. Injured groups received either no treatment, or a single treatment with topical or intramuscular diclofenac (TD and ID), or LPT (3 J, 810 nm, 100 mW) 1 h after injury. Walking track analysis was the functional outcome and biochemical analyses included mRNA expression of COX-1 and COX-2 and blood levels of prostaglandin E2 (PGE2). All treatments significantly decreased COX-1 and COX-2 gene expression compared to the injury group. However, LPT showed better effects than TD and ID regarding PGE2 levels and walking track analysis. The author concludes that LPT has more efficacy than topical and intramuscular diclofenac in treatment of muscle strain injury in acute stage.

Crystalopathies are inflammatory pathologies caused by cellular reactions to the deposition of crystals in the joints. The anti-inflammatory effect of He-Ne laser and that of the non-steroidal anti-inflammatory drugs (NSAIDs) diclofenac, meloxicam, celecoxib, and rofecoxib was studied in acute and chronic arthritis produced by hydroxyapatite and calcium pyrophosphate in rats. The presence of the markers fibrinogen, L-citrulline, nitric oxide, and nitrotyrosine was determined. In the study by Rubio[10], crystals were injected into the posterior limb joints of the rats. A dose of 8 J/cm^2 of energy from a HeNe laser was applied for three days in some groups and for five days in other groups. The levels of some of the biomarkers were determined by spectrophotometry, and that of nitrotyrosine was determined by ELISA. In arthritic rats, the fibrinogen, L-citrulline, nitric oxide, and nitrotyrosine levels increased in comparison to controls and to the laser-treated arthritic groups. When comparing fibrinogen from arthritic rats with disease induced by hydroxyapatite to healthy and arthritic rats treated with NSAIDs, the He-Ne laser decreased levels to values similar to those seen in controls. Inflammatory and oxidative stress markers in experimental crystalopathy are positively modified by photobiostimulation._

Editorial note: To be continued with further studies on the effectiveness of diclofenac and LPT and conclusion in laser 2/2014. An list of references is available from the author.

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