# Diclofenac, dexamethasone or laser phototherapy?

## Part II

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[PICTURE: ©ROBERT KNESCHKE]

### _Introduction

In part I, the author informed about studies which investigated the effects of diclofenac and LPT. In the second part, they continue their investigation into the vast literature and studies on this topic and give their conclusion.

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. Although the previously-mentioned studies indicate that LPT is as effective, or more effective as diclofenac, a potentiation of the effect of diclofenac by adding LPT is suggested in the following study:

The aim of the study by Markovic[11] was twofold: (1) to evaluate the postoperative analgesic efficacy, comparing long-acting and intermediate-acting local anaesthetics; and (2) to compare the use of laser irradiation and the non-steroid anti-inflammatory drug diclofenac, which are claimed to be among the most successful aids in postoperative pain control. A twofold study of 102 patients of both sexes undergoing surgical extraction of LTM was conducted. In the first part of the study, twelve patients with bilaterally impacted lower molars were treated in a double-blind crossover fashion; local anaesthesia 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 lower molar surgical extraction with local anaesthesia received postoperative laser irradiation (30 patients) and a preoperative single dose of 100 mg diclofenac (30 patients), or only regular postoperative recommendations (30 patients). The results of the first part of the study showed a strikingly better postoperative analgesic effect of bupivacaine than lidocaine/epinephrine (eleven out of twelve; four out of twelve, respectively, patients without postoperative pain). In the second part of the study, LPT irradiation significantly reduced postoperative pain intensity in patients premedicated with diclofenac, compared with the controls. Provided that basic principles of surgical practice have been achieved, the use of long-acting local anaesthetics and LPT irradiation enables the best postoperative analgesic effect and the most comfortable postoperative course after the surgical extraction of lower molars.

Dexamethasone is a corticosteroid, thus not an NSAID, but the issue of replacing pharmaceuticals with long-term negative effects to a treatment with no side effect is urgent here as well.

A rabbit model of endophthalmitis was established by Ma[12] to evaluate the anti-inflammatory effect of LPT as an adjunct to treatment for *Staphylococcus epidermidis endophthalmitis*. Rabbits were randomly divided into three groups to receive intravitreal injections into their left eye: group A received 0.5 mg vancomycin (100 mcl), group B received 0.5 mg vancomycin + 0.2 mg dexamethasone

(100 mcl), and group C received 0.5 mg vancomycin (100 mcl) and laser irradiation (10 mW, 632 nm) focused on the pupil. Slit lamp examination and B-mode ultrasonography were conducted to evaluate the symptoms of endophthalmitis. Polymorphonuclear cells and tumour necrosis factor alpha (TNF-alpha) in aqueous fluid were measured at 0 h, and one, two, three, seven and 15 days. A histology test was conducted at 15 days. B-mode ultrasonography and histology revealed that groups B and C had less inflammation than group A at 15 days. Groups B and C had fewer polymorphonuclear cells and lower levels of TNF-alpha in aqueous fluid than group A at two, three and seven days. There was no significant difference between groups B and C. There was no significant difference between groups A, B and C at 15 days. As an adjunct to vancomycin therapy to treat *S. epidermidis endophthalmitis*, LPT has an anti-inflammatory effect similar to that of dexamethasone.

Castano[13] tested LPT on rats that had zymosan injected into their knee joints to induce inflammatory arthritis. The author compared illumination regimens consisting of a high and low fluence (3 and 30 J/cm$^2$), delivered at high and low irradiance (5 and 50 mW/cm$^2$) using 810 nm daily for five days, with the positive control of conventional corticosteroid (dexamethasone) therapy. Illumination with a 810 nm laser was highly effective (almost as good as dexamethasone) at reducing swelling, and a longer illumination time (10 or 100 minutes compared to 1 minute) was more important in determining effectiveness than either the total fluence delivered or the irradiance. LPT induced reduction of joint swelling correlated with reduction in the inflammatory marker serum prostaglandin E2 (PGE2).

Reis[14] investigated the role of extracellular matrix elements and cells during the wound healing phases following the use of LPT and anti-inflammatory drugs. Thirty-two rats were submitted to a wound inflicted by a 6-mm-diameter punch. The animals were divided into four groups: sham treated, those treated with the LPT (4 J/cm$^2$, 9 mW, 670 nm), those treated with dexamethasone (2 mg/kg), and those treated with both LPT and dexamethasone. After three and five days, the cutaneous wounds were assessed by histopathology using polarised light and ultrastructural assessments by transmission electron microscopy. Changes seen in polymorphonuclear inflammatory cells, oedema, mononuclear cells, and collagen fibre deposition were semi-quantitatively evaluated. The laser-treated group demonstrated increased collagen content and better arrangement of the extracellular matrix. Fibroblasts in these tissues increased in number and were more synthetically active. In the dexamethasone group, the collagen was shown to be non-homogenous and disorganised, with a scarcity of fibroblasts. In the group treated with both types of therapy, fibroblasts were more common and they exhibited vigorous rough endoplasmic reticulum, but they had less collagen production compared to those seen in the laser group. Thus, LPT alone accelerated post-surgical tissue repair and reduced oedema and the polymorphonuclear infiltrate, even in the presence of dexamethasone.

In a study by Jajarm[15] thirty patients with erosive-atrophic OLP were randomly allocated into two groups. The experimental group consisted of patients treated with the 630 nm laser. The control group consisted of patients who used dexamethasone mouth wash. The response rate was defined based on changes in the appearance score and pain score (VAS) of the lesions before and after each treatment. Appearance score, pain score, and lesion severity was reduced in both groups. No significant differences were found between the treatment groups regarding the response rate and relapse. The study demonstrated that LPT was as effective as topical corticosteroid therapy without any adverse effects and it may be considered as an alternative treatment for erosive-atrophic OLP in the future.

The aim of a study by Aimbire[16] was to investigate if LPT can modulate the formation of haemorrhagic lesions induced by immune complex, since there is a lack of information on LPT effects in haemorrhagic injuries of high perfusion organs, and the relative efficacy of LPT compared to anti-inflammatory drugs. A controlled animal study was undertaken with 49 rats, randomly divided into seven groups. Bovine serum albumin i.v. was injected through the trachea to induce an immune complex lung injury. The study compared the effect of irradiation by a 650 nm laser with doses of 2.6 J/cm$^2$ to celecoxib, dexamethasone, and control groups for haemorrhagic index (HI) and myeloperoxide activity (MPO) at 24 h after injury. The HI for the control group was 4.0. Celecoxib, laser, and dexamethasone all induced significantly lower HI than in the control animals at 2.5, 1.8 and 1.5, respectively. Dexamethasone, but not celecoxib, induced a slightly, but significantly lower HI than laser. MPO activity was significantly decreased at 1.6 in groups receiving celecoxib at 0.87, dexamethasone at 0.50, and laser at 0.7 when compared to the control group, but there were no significant differences between any of the active treatments. In conclusion, LPT at a dose of 2.6 J/cm$^2$ induces a reduction of HI levels and MPO activity in haemorrhagic injury, which is not significantly different from that obtained by celecoxib. Dexamethasone is slightly more effective than LPT in reducing HI, but not MPO activity.

In an effort to clarify the molecular based mechanism of the anti-inflammatory effects of laser irradiation, Abiko[17] used a rheumatoid arthritis (RA) rat model with human rheumatoid synoviocytes (MH-7) challenged with IL-1, treated with laser or dexamethasone (DEX), monitored by gene expressions and analysed by the signal pathway database. RA rats were generated by the immunisation of type-II collagen, after which foot paws and knee joints became significantly swollen. The animals were laser treated and the swelling rates measured. MH-7 was challenged with IL-1β and gene expression levels monitored, using the Affymetrix Gene Chip system, and the signal pathway database analysed using the Ingenuity Pathway Analysis (IPA) tool. LPT significantly reduced swellings in the rats' foot paws and knee joints and made it possible for them to walk on their hind legs. LPT altered many gene expressions of cytokines, chemokines, growth factors and signal transduction factors in IL-β induced MH-7. IPA revealed that LPT as well as DEX kept the MH7A at a normal state to suppress mRNA levels of IL-8, IL-1β, CXC1, NFkB1 and FGF13, which were enhanced by IL-1β treatment. However, certain gene expression of inflammatory factors were reduced by LPT, but were enhanced by DEX. LPT reduced inflammatory factors through altering signal pathways by gene expression levels. Interestingly, LPT altered useful targeted gene expressions, whereas DEX randomly altered many gene expressions, including the unwanted genes for anti-inflammation. Dexomethasone is a steroid known for having a long range of serious side effects. Thus, genome-based gene expression monitored by the Gene Chip system together with a signal pathway based database provide unprecedented access to elucidate the mechanism of the biostimulatory effects of LPT.

It has been suggested that LPT acts on pulmonary inflammation. Thus, Mafra de Lima[18] investigated in a work if LPT (650 nm, 2.5 mW, 31.2 mW/cm$^2$, 1.3 J/cm$^2$, spot size of 0.08 cm$^2$ and irradiation time of 42 s) can attenuate oedema, neutrophil recruitment and inflammatory mediators in acute lung inflammation. Thirty-five male Wistar rats (n = 7 per group) were distributed in the following experimental groups: control, laser, LPS, LPS+laser and dexamethasone+LPS. Airway inflammation was measured 4 h post-LPS challenge. Pulmonary microvascular leakage was used for measuring pulmonary oedema. Bronchoalveolar lavage fluid (BALF) cellularity and myeloperoxidase (MPO) were used for measuring neutrophil recruitment and activation. RT-PCR was performed in lung tissue to assess mRNA expression of tumour necrosis factor-alpha (TNF-alpha), interleukin-1β (IL-1β), interleukin (IL-10), cytokine-induced neutrophil chemoattractant-1 (CINC-1), macrophage inflammatory protein-2 (MIP-2) and intercellular adhesion mole-cule-1 (ICAM-1). Protein levels in both BALF and lung were determined by ELISA. LPT inhibited pulmonary oedema and endothelial cytoskeleton damage, as well as neutrophil influx and activation. Similarly, LPT reduced the TNF-alpha and IL-1β, in lung and BALF. LPT prevented lung ICAM-1 up-regulation. The rise of CINC-1 and MIP-2 protein levels in both lung and BALF, and the lung mRNA expressions for IL-10, were unaffected. Data suggest that the LPT effect is due to the inhibition of ICAM-1 via the inhibition of TNF-alpha and IL-1β.

Steroids are frequently used to treat inflammation. Some studies report a reduced effect of LPT in the presence of steroids, while others have found positive results of LPT even in the presence of steroids. However, steroids are known to delay wound healing through a reduction of leukocyte migration and a suppression of interleukins, while LPT is known to stimulate wound healing. In a study by Pessoa[19], 48 rats were used, and after the execution of a wound on the dorsal region of each animal, they were divided into four groups (n = 12), receiving the following treatments: G1 (control), wounds and animals received no treatment; G2, wounds were treated


[PICTURE: ©NIKOLAY LITOV]

with laser; G3, animals received an intraperitoneal injection of sodium phosphate of dexamethasone, dosage 2 mg/kg of body weight; G4, animals received steroids and wounds were treated with laser. The laser emission device used was a 904 nm unit, in a contact mode, with 2.75 mW gated with 2,900 Hz during 120 sec. After a period of three, seven and 14 days, the animals were sacrificed. The results showed that the wounds treated with steroid had a delay in healing, while laser accelerated the wound healing process. Additionally, wounds treated with laser in the animals, also treated with steroids, presented a differentiated healing process with a larger collagen deposition as well as a decrease in both the inflammatory infiltrated and in the delay on the wound healing process. Laser accelerated healing, delayed by the steroids, acting as a biostimulative coadjutant agent, balancing the undesirable effects of the steroids on the tissue's healing process. The effect of LPT is almost as potent as dexametasone but, again, without side effects.

In a study by Lara[20], 44 rats were treated with fluorouracil and, in order to mimic the clinical effect of chronic irritation, the palatal mucosa was irritated by superficial scratching with an 18-gauge needle. When all of the rats presented oral ulcers of mucositis, they were randomly allocated to one of three groups: group I was treated with laser (GaAlAs), group II was treated with topical dexamethasone, and group III was not treated. Excisional biopsies of the palatal mucosa were then performed, and the rats were killed. Tissue sections were stained with haematoxylin and eosin for morphological analyses, and with toluidine blue for mast-cell counts. Group I specimens showed higher prevalence of ulcers, bacterial biofilm, necrosis and vascularisation, while group II specimens showed higher prevalence of granulation tissue formation. There were no significant statistical differences in the numbers of mast cells and epithelial thickness between groups. For the present model of mucositis, rats with palatal mucositis treated with laser showed characteristics compatible with the ulcerative phase of oral mucositis, and rats treated with topical dexamethasone showed characteristics compatible with the healing phase of mucositis. Topical dexamethasone was more efficient in the treatment of rats' oral mucositis than the laser.

It has been suggested that LPT and dexamethasone (DEX) in combination do not bring about any advantages. But the following study suggests that LPT works even in an environment with DEX.

The study by Marchionni[21] aimed to assess the effect of LPT associated with and without dexamethasone on inflammation and wound healing in cutaneous surgical wounds. Limited studies are directed at the possible interference of laser photobiomodulation on the formation of myofibroblasts, associated with an anti-inflammatory drug. Standard skin wounds were performed on 80 Wistar rats, distributed into four groups: no treatment (sham group), laser only (670 nm, 9 mW, 0.031 W/cm$^2$, 4 J/cm$^2$, single dose after surgery), dexamethasone only (2 mg/kg 1 h before surgery), and laser with dexamethasone. Tissue was examined histologically to evaluate oedema, presence of polymorphonuclear, mononuclear cells, and collagen. The analysis of myofibroblasts was assessed by immunohistochemistry and transmission electron microscopy. The intensity was rated semi-quantitatively. The results showed that laser and dexamethasone acted in a similar pattern to reduce acute inflammation. Collagen synthesis and myofibroblasts were more intense in the laser group, whereas animals treated with dexamethasone showed lower results for these variables. In a combination of therapies, the synthesis of collagen and actin as well as desmin-positive cells was less than laser group. Laser was effective in reducing swelling and polymorphonuclear cells and accelerated tissue repair, even in the presence of dexamethasone.

The aim of a study by Garcia[22] was to compare LPT as adjuvant treatment for induced periodontitis with scaling and root planing (SRP) in dexamethasone-treated rats. One-hundred twenty rats were divided into groups: D group (n = 60), treated with dexamethasone; ND group (n = 60) treated with saline solution. In both groups, periodontal disease was induced by ligature at the left first mandibular molar. After seven days, the ligature was removed and all animals were subjected to SRP. They were divided according to the following treatments: SRP, irrigation with saline solution (SS); SRP + LPT, SS and laser irradiation (660 nm; 24 J; 0.428 W/cm$^2$). Ten animals in each treatment were killed after seven days, 15 days and 30 days. The radiographic and histometric values were statistically analysed. In all groups, radiographic and histometric analysis showed less bone loss in animals treated with SRP + LPT in all experimental periods. SRP + LPT was an effective adjuvant conventional treatment for periodontitis in rats treated with dexamethasone.

## _Conclusion

From the above papers it is clear that LPT has an effect similar to that of dexamethasone. It is possibly not as strong as dexamethasone, but without the side effects. Thus, it is a promising alternative, especially for long term use. What still remains is a careful analysis about the optimal dosage windows for LPT._

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