

Lasers Med Sci. 2013 Apr 24. [Epub ahead of print]

## **Potential anti-inflammatory effect of low-level laser therapy on the experimental reflux laryngitis: a preliminary study.**

Marinho RR, Matos RM, Santos JS, Ribeiro MA, Ribeiro RA, Lima RC Jr, Albuquerque RL Jr, Thomazzi SM.

### **Source**

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### **Abstract**

The most common cause of laryngitis is the laryngopharyngeal reflux disease. The symptoms of laryngitis can be hoarseness, globus, chronic cough, voice fatigue, throat pain, and dysphagia. Low-level laser therapy (LLLT) is beneficial to reduce the pain and inflammatory response without side effects. Therefore, LLLT may be a useful tool for the treatment of laryngitis. This study proposes to analyze the effect of laser therapy in a model of reflux-induced laryngitis. The animals were randomly put into three groups: control-non-intubated; nasogastric intubation-intubated; and nasogastric intubation with laser therapy-intubated treated with 105-J/cm<sup>2</sup> laser irradiation. For the induction of laryngitis, the animals were anesthetized and a nasogastric tube was inserted through the nasopharynx until it reached the stomach, for 1 week. Thereafter, measurement of myeloperoxidase activity and the histopathological procedures were performed. In conclusion, we observed in this study that 105-J/cm<sup>2</sup> infrared laser reduced the influx of neutrophils in rats, and it improved the reparative collagenization of the laryngeal tissues.

Lasers Med Sci. 2012 Nov 24. [Epub ahead of print]

## **Infrared low-level diode laser on inflammatory process modulation in mice: pro- and anti-inflammatory cytokines.**

Fukuda TY, Tanji MM, Silva SR, Sato MN, Plapler H.

### **Source**

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### **Abstract**

To evaluate the modulation of proinflammatory (interleukin-6, IL-6; tumor necrosis factor- $\alpha$ , TNF- $\alpha$ ; and interferon- $\gamma$ , IFN- $\gamma$ ) and anti-inflammatory cytokines (transforming growth factor-B1, TGF-B1) in the inflammation processes in vivo with low-level laser action, 50 isogenic mice were randomly distributed into three groups: control (no surgical procedure, n=10), sham (surgical procedure with three standard cutaneous incisions, followed by an abdominal muscle incision and suture, n=20), and laser (same procedure followed by laser exposure, n=20). The sham group was divided into three subgroups: sham I (euthanasia and evaluation, 36 h after

surgical procedure), sham II (euthanasia and evaluation, 60 h after surgical procedure), and sham III (euthanasia and evaluation, 84 h after surgical procedure). The laser group was also divided in three subgroups: laser I (a single laser session, 12 h after surgery), laser II (two laser sessions, 12 and 36 h after surgery), and laser III (three laser sessions, 12, 36, and 60 h after surgery). All animals in the laser groups received three points per session of continuous infrared laser (wavelength of 780 nm, power of 20 mW, fluency of 10 J/cm<sup>2</sup>), exposure time of 20 s per point, and energy of 0.4 J). After euthanasia, spleen mononuclear cells were isolated and cultured for 48 h. Concentrations of IL-6, TNF- $\alpha$ , IFN- $\gamma$ , and TGF-B1 were obtained by enzyme-linked immunosorbent assay method. There was a significant difference between the IL-6 and TNF- $\alpha$  concentrations in the 60- and 84-h evaluations when the laser and sham groups were compared to the control group ( $p < 0.05$ ), except for laser II in the TNF- $\alpha$  analysis ( $p > 0.05$ ). The IFN- $\gamma$  concentration analysis showed a significant difference only in sham II when compared to the control group ( $p < 0.05$ ). Thus, there was a modulatory effect of TNF- $\alpha$  and IFN- $\gamma$  in the laser group, particularly in the 60-h postoperative evaluation. There was no significant difference between the laser, sham, and control groups for TGF-B1 analysis ( $p > 0.05$ ). The low-level laser application decreased the TNF- $\alpha$  and IFN- $\gamma$  release in vivo of spleen mononuclear cells in mice, especially after two exposure sessions. However, there was no modulation of the IL-6 and TGF-B1 release.

Lasers Med Sci. 2012 Aug 31. [Epub ahead of print]

## **Low-level laser therapy improves the inflammatory profile of rats with heart failure.**

Hentschke VS, Jaenisch RB, Schmeing LA, Cavinato PR, Xavier LL, Dal Lago P.

### **Source**

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### **Abstract**

Following heart failure (HF), immune activation leads to an imbalance between pro-inflammatory and anti-inflammatory cytokines. Low-level laser therapy (LLLT) has been used as an anti-inflammatory treatment in several disease conditions. However, the effect of LLLT on the skeletal muscle of rats with HF remains unclear. The present report aimed to evaluate the influence of LLLT on the inflammatory profile of rats with HF. The left coronary artery was ligated to induce HF and a sham operation was performed in the control groups. Male Wistar rats ( $n=49$ ) were assigned to one of six groups: placebo sham rats (P-Sham;  $n=8$ ), LLLT at a dose of 3 J/cm<sup>2</sup> sham rats (3 J/cm<sup>2</sup>-Sham;  $n=8$ ), LLLT at a dose of 21 J/cm<sup>2</sup> sham rats (21 J/cm<sup>2</sup>-Sham;  $n=8$ ), placebo HF rats (P-HF;  $n=9$ ), LLLT at a dose of 3 J/cm<sup>2</sup> HF rats (3 J/cm<sup>2</sup>-HF;  $n=8$ ), and LLLT at a dose of 21 J/cm<sup>2</sup> HF rats (21 J/cm<sup>2</sup>-HF;  $n=8$ ). Four weeks after myocardial infarction or sham surgery, rats were subjected to LLLT (InGaAlP 660 nm, spot size 0.035 cm<sup>2</sup>), output power 20 mW, power density 0.571 W/cm<sup>2</sup>, energy density 3 or 21 J/cm<sup>2</sup>, exposure time 5.25 s and 36.75 s) on the right gastrocnemius for 10 consecutive days. LLLT reduced plasma IL-6 levels (61.3 %;  $P < 0.01$ ), TNF- $\alpha$ /IL-10 (61.0 %;  $P < 0.01$ ) and IL-6/IL-10 ratios (77.3 %;  $P < 0.001$ ) and increased IL-10 levels (103 %;  $P < 0.05$ ) in the 21 J/cm<sup>2</sup>-HF group. Moreover, LLLT reduced the TNF- $\alpha$  (20.1 % and 21.3 %; both  $P < 0.05$ ) and IL-6 levels (54.3 % and 37.8 %;  $P < 0.01$  and  $P < 0.05$ , respectively) and the IL-6/IL-10 ratio (59.7 % and 42.2 %;  $P < 0.001$  and  $P < 0.05$ , respectively) and increased

IL-10 levels (81.0 % and 85.1 %; both  $P < 0.05$ ) and the IL-10/TNF- ratio (171.5 % and 119.8 %;  $P < 0.001$  and  $P < 0.05$ , respectively) in the gastrocnemius in the 3 J/cm<sup>2</sup>-HF and 21 J/cm<sup>2</sup>-HF groups. LLLT showed systemic and skeletal muscle anti-inflammatory effects in rats with HF.

Lasers Med Sci. 2012 Aug 23. [Epub ahead of print]

## **Prevention and treatment of mice paw edema by near-infrared low-level laser therapy on lymph nodes.**

Meneguzzo DT, Lopes LA, Pallota R, Soares-Ferreira L, Lopes-Martins RA, Ribeiro MS.

### **Source**

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Abstract Low-level laser therapy (LLLT) has been demonstrated to modulate inflammatory processes and immunological responses. The aim of this work was to investigate the hypothesis that near infrared LLLT (830 nm) over lymph nodes may reduce paw edema and contribute to the modulation of inflammation. The edema was induced by carrageenan inoculation (CGN) into the plantar surface of 100 male mice left hind paw. Animals were divided into five groups: CGN (control), no treatment; Diclo, sodium diclofenac; Paw, LLLT on the paw; Ly, LLLT on the inguinal lymph nodes; and Paw+Ly, LLLT in both paw and lymph nodes, and subdivided according to moment of irradiation: A-1 h and 2 h before CGN, B-1 h and immediately before CGN, C-1 and 2 h after CGN, and D-3.5 and 4.5 h after CGN. The parameters used were: energy=1 J, fluence=35 J/cm<sup>2</sup>, power=100 mW during 10 s. Paw volume was measured before and 1 to 6 h after CGN, and myeloperoxidase (MPO) activity was analyzed. Edema prevention was obtained by the irradiation of Paw+Ly at moment A and at Ly at moment B, inhibition of edema formation was achieved by either Paw or Ly at moment C, and edema treatment was obtained by Paw or Ly at moment D ( $p < 0.05$ ). MPO activity was significantly reduced on Paw at moment A, Paw and Ly on C, and in all irradiated groups on B and D. Our results suggest that LLLT was able to produce both anti-inflammatory and pro-inflammatory effects depending on to the site and moment of irradiation.

Lasers Med Sci. 2012 May;27(3):585-91. Epub 2011 Sep 27.

## **Antiinflammatory effect of low-level laser therapy on Staphylococcus epidermidis endophthalmitis in rabbits.**

Ma WJ, Li XR, Li YX, Xue ZX, Yin HJ, Ma H.

### **Source**

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### **Abstract**

A rabbit model of endophthalmitis was established to evaluate the antiinflammatory effect of low-level laser therapy (LLLT) 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 l), group B received 0.5 mg vancomycin + 0.2 mg dexamethasone (100 l), and group C received 0.5 mg vancomycin (100 l) and continuous wave semiconductor 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-) in aqueous fluid were measured at 0 h, and 1, 2, 3, 7 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- in aqueous fluid than group A at 2, 3 and 7 days ( $P < 0.05$ ). There was no significant difference between groups B and C ( $P > 0.05$ ). There was no significant difference between groups A, B and C at 15 days ( $P > 0.05$ ). As an adjunct to vancomycin therapy to treat S. epidermidis endophthalmitis, LLLT has an antiinflammatory effect similar to that of dexamethasone.

Lasers Med Sci. 2012 May;27(3):621-7. Epub 2011 Oct 16.

## **Low-level diode laser therapy reduces lipopolysaccharide (LPS)-induced bone cell inflammation.**

Huang TH, Lu YC, Kao CT.

### **Source**

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### **Abstract**

In this study, the aim is to investigate the cytologic effects of inflammatory bone cells after in vitro low-level laser therapy (LLLT). A human osteosarcoma cell line (MG63) was cultured, infected with lipopolysaccharide (LPS) and exposed to low-level laser treatment at 5 or 10 J/cm<sup>2</sup> using a 920 nm diode laser. MG63 cell attachment was observed under a microscope, and cell viability was quantified by mitochondrial colorimetric assay (MTT). LPS-treated MG63 cells were irradiated with LLLT, and the inflammatory markers iNOS, TNF- and IL-1, were analyzed by reverse transcription polymerase chain reaction (RT-PCR) and Western blot. The data were collected and analyzed by one-way analysis of variance (ANOVA);  $p < 0.05$  indicated a statistically significant difference. Low-level laser treatment on MG63 cells increased their ability to attach and survive. After irradiation, the expression levels of iNOS, TNF- and IL-1 in LPS-infected MG63 cells decreased over time ( $p < 0.05$ ). Conclusions: low-level diode laser treatment increased the MG63 cell proliferative ability and decreased the expression of inflammatory mediators in MG63 cells.

Lasers Med Sci. 2012 Jun 26. [Epub ahead of print]

## **Effect of the intravascular low energy laser illumination during percutaneous coronary intervention on the inflammatory process in vascular wall.**

Derkacz A, Protasiewicz M, Por?ba R, Doroszko A, Andrzejak R.

## Source

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## Abstract

The angioplasty procedure is associated with a release of numerous factors triggering the local inflammatory reaction in vascular wall and leading thus to the restenosis. In this study, we hypothesize that the low-energy laser irradiation may exert beneficial effect by limiting this process. A group of 101 subjects (75 men and 26 women, mean age:  $59.1 \pm 10.3$ ) treated with percutaneous coronary intervention (PCI), were recruited to this study. While 52 patients (40 men and 12 women) were subjected to the intravascular low-energy laser irradiation (808 nm) of dilated lesion during the PCI, the remaining patients (35 men and 14 women) constituted the control group. The levels of interleukin 1 $\beta$ , 6 and 10 (IL 1, IL 6 and IL 10) were measured immediately before the procedure, and then at the 6th, 12th hour as well as after 1 month following the PCI. Significantly lower levels of IL 1 and IL 6 in the irradiated group during each analysis after the procedure were observed. Moreover, significantly lower IL 10 level in irradiated group within 6 and 12 hours after PCI was observed. Irradiation of the lesion with low-energy laser radiation during the PCI procedure results in a decrease in the levels of pro-inflammatory IL 1 and IL 6 as well as in an increase in the levels of anti-inflammatory IL 10, which may result in decreased risk for restenosis.

Rev Bras Fisioter. 2011 Mar 18. pii: S1413-35552011005000005. [Epub ahead of print]

## **Inhibition of carrageenan-induced expression of tissue and plasma prekallikreins mRNA by low level laser therapy in a rat paw edema model.**

Silva MP, Bortone F, Silva MP, Araújo TR, Costa MS, Silva Júnior JA.

Universidade Nove de Julho, São Paulo, SP, Brazil.

## Abstract

**BACKGROUND:** Low level laser therapy (LLLT) has been used clinically in order to treat inflammation, where tissue and plasma prekallikrein have crucial importance. Plasma prekallikrein (PPK) is synthesized by the hepatocytes and secreted into the bloodstream, where it participates in the surface-dependent activation of blood coagulation, fibrinolysis, kinin generation and inflammation. Tissue prekallikrein is associated with important disease states (including cancer, inflammation, and neurodegeneration) and has been utilized or proposed as clinically important biomarker or therapeutic target of interest.

**OBJECTIVE:** To evaluate if LLLT modulates tissue and plasma prekallikreins mRNA expression in the carrageenan-induced rat paw edema.

**METHODS:** Experimental groups were assigned as followed: A1 (Control-saline), A2 (Carrageenan-only), A3 (laser 660nm only) and A4 (Carrageenan + laser 660nm). Edema was measured by a plethysmometer. Subplantar tissue was collected for the quantification of prekallikreins mRNA by Real time-Polymerase Chain Reaction.

RESULTS: A significantly decrease in the edema was observed after laser irradiation. Expression of prekallikreins increased after carrageenan injection. Tissue and plasma prekallikrein mRNA expression significantly decreased after LLLT's 660nm wavelength.

CONCLUSION: These results suggest that expression of tissue and plasma prekallikreins is modulated by LLLT, which can be used in clinical practice due to its anti-inflammatory effects.

Photomed Laser Surg. 2010 Dec;28(6):763-71.

## **Low-Level Laser Therapy Associated to N-Acetylcysteine Lowers Macrophage Inflammatory Protein-2 (MIP-2) mRNA Expression and Generation of Intracellular Reactive Oxygen Species in Alveolar Macrophages.**

de Lima FM, Villaverde AB, Albertini R, de Oliveira AP, Neto HC, Aimbire F.

1 Institute of Research and Development , IP&D, UNIVAP, São José dos Campos, São Paulo, Brazil .

### **Abstract**

Abstract Objective: The aim of this work was to investigate the low-level laser therapy (LLLT) effect on alveolar macrophages (AM) activated by oxidative stress and lipopolysaccharide (LPS).

Background data: LLLT has been reported to actuate positively relieving the late and early symptoms of airway and lung inflammation. It is not known if the increased MIP-2 mRNA expression and intracellular reactive oxygen species (ROS) generation observed in acute lung inflammation (ALI) can be influenced by LLLT.

Materials and Methods: Rat AM cell line (AMJ2-C11) was cultured with LPS or H<sub>2</sub>O<sub>2</sub> and laser irradiated. MIP-2 mRNA and ROS production in the AM were evaluated by Real Time-PCR and the 2',7'-dichlorofluorescein diacetate (DCFH-DA) respectively. The NF- $\kappa$ B protein in the AM was measured by the enzyme linked immunoassay method. To investigate the antioxidant effect of laser, the AM were prebathed with N-acetylcysteine (NAC) and then irradiated with laser. LLLT was also studied in the presence of an inhibitor of NF- $\kappa$ B (BMS 205820). In addition, the effect of LLLT on NF- $\kappa$ B protein was investigated.

Results: LLLT attenuated the MIP-2 mRNA expression and intracellular ROS generation after LPS or H<sub>2</sub>O<sub>2</sub>. When the AM were pretreated with NAC, the laser effect was potentiated. BMS 205820 suppresses the effect of LLLT on MIP-2 mRNA expression and ROS generation, stimulated by LPS or H<sub>2</sub>O<sub>2</sub>. On NF- $\kappa$ B transcription factor, both the LLLT and NAC reduced this protein in the AM exposed to LPS or H<sub>2</sub>O<sub>2</sub>. The synergistic effect between LLLT and NAC on the reduction the NF- $\kappa$ B was also evidenced.

Conclusion: Results indicate that there is a synergistic action of LLLT with NAC on MIP-2 mRNA expression from LPS- or H<sub>2</sub>O<sub>2</sub>-stimulated AM, and that both ROS intracellular generation and NF- $\kappa$ B signaling seem to be involved.

Lasers Med Sci. 2010 Aug 25. [Epub ahead of print]

# Low-level laser therapy (LLLT; 780 nm) acts differently on mRNA expression of anti- and pro-inflammatory mediators in an experimental model of collagenase-induced tendinitis in rat.

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## Abstract

Low-level laser therapy (LLLT) has been found to produce anti-inflammatory effects in a variety of disorders. Tendinopathies are directly related to unbalance in expression of pro- and anti-inflammatory cytokines which are responsible by degeneration process of tendinocytes. In the current study, we decided to investigate if LLLT could reduce mRNA expression for TNF-alpha, IL-1beta, IL-6, TGF-beta cytokines, and COX-2 enzyme. Forty-two male Wistar rats were divided randomly in seven groups, and tendinitis was induced with a collagenase intratendinea injection. The mRNA expression was evaluated by real-time PCR in 7th and 14th days after tendinitis. LLLT irradiation with wavelength of 780 nm required for 75 s with a dose of 7.7 J/cm(2) was administered in distinct moments: 12 h and 7 days post tendinitis. At the 12 h after tendinitis, the animals were irradiated once in intercalate days until the 7th or 14th day in and then the animals were killed, respectively. In other series, 7 days after tendinitis, the animals were irradiated once in intercalated days until the 14th day and then the animals were killed. LLLT in both acute and chronic phases decreased IL-6, COX-2, and TGF-beta expression after tendinitis, respectively, when compared to tendinitis groups: IL-6, COX-2, and TGF-beta. The LLLT not altered IL-1beta expression in any time, but reduced the TNF-alpha expression; however, only at chronic phase. We conclude that LLLT administered with this protocol reduces one of features of tendinopathies that is mRNA expression for pro-inflammatory mediators.

Physical Therapy Reviews, Volume 15, Number 4, August 2010 , pp. 286-293(8)

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

**Authors:** Bjordal, Jan Magnus<sup>1</sup>; Lopes-Martins, Rodrigo Alvaro Brand<sup>2</sup>; Joensen, Jon<sup>3</sup>; Iversen, Vegard Vereide<sup>4</sup>

**Source:** Physical Therapy Reviews, Volume 15, Number 4

### Abstract:

**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 animal 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.

Lasers Surg Med. 2010 Aug;42(6):553-8.

## **Anti-inflammatory effects of low-level light emitting diode therapy on Achilles tendinitis in rats.**

Xavier M<>, David DR<>, de Souza RA<>, Arrieiro AN<>, Miranda H<>, Santana ET<>, Silva JA Jr<>, Salgado MA<>, Aimbire F<>, Albertini R<>.

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### **Abstract**

**BACKGROUND AND OBJECTIVES:** The present study investigated the effects of low-level light emitting diode (LED) therapy (880 +/- 10 nm) on inflammatory process in a experimental model of Achilles tendinitis induced by collagenase.

**STUDY DESIGN/MATERIALS AND METHODS:** Fifty-six male Wistar were separated into seven groups (n = 8), three groups in the experimental period of 7 days and four groups in the experimental period of 14 days, the control group (CONT), tendinitis group (TEND), LED therapy group (LEDT) for both experimental periods, and LED therapy group 7th to 14th day (LEDT delay) for 14 days experimental period. The LED parameters was 22 mW CW of optical output power, distributed in an irradiation area of 0.5 cm(2), with an irradiation time of 170 seconds, the applied energy density was 7.5 J/cm(2) in contact. The therapy was initiated 12 hours after the tendinitis induction, with a 48-hour interval between the irradiations. The histological analysis and inflammatory mediators were quantified.

**RESULTS:** Our results showed that LED decreases the inflammatory cells influx and mRNA expression to IL-1 beta, IL-6, tumor necrosis factor-alpha (TNF-alpha) in both phase, and cyclooxygenase-2 (COX-2) just in initial phase ( $P < 0.05$ ).

**CONCLUSION:** Our results suggest that the anti-inflammatory therapy with low-power LED (880 nm) enhanced the tissue response in all groups. We can conclude that the LED was able to reduce signs of inflammation in collagenase-induced tendinitis in rats by reducing the number of inflammatory cells and decrease mRNA expression of cytokines.

Lasers Surg Med. 2010 Aug;42(6):577-83.

## **Evaluation of inflammatory biomarkers associated with oxidative stress and histological assessment of low-level laser therapy in experimental myopathy.**

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### **Abstract**

The objective of the present work was to study the effect of helium-neon (He-Ne) and gallium-arsenide (Ga-As) laser upon inflammatory biomarkers associated with oxidative stress: fibrinogen, nitric oxide (NO), L-citrulline, and superoxide dismutase (SOD). These were evaluated through histological assessment, in rats with experimental myopathy.

**MATERIALS AND METHODS:** The groups studied were: (A) control, (B) injured, (C) injured and treated with He-Ne laser, (D) injured and treated with Ga-As laser, (E) irradiated with He-Ne; and (F) irradiated with Ga-As laser. Myopathy was induced by injecting 0.05 mg/rat/day of adrenaline in the left posterior limb muscle at the same point on 5 consecutive days, in groups B, C, and D. Low-level laser therapy (LLL) was applied with 9.5 J/cm<sup>2</sup> daily for 7 consecutive days with each laser. The determination of the biomarkers was made by spectrophotometry. The muscles (5/8, single blinded) were stained with Gomori Trichrome and examined by optic microscopy. The quantitative variables were statistically analyzed by the Fisher's test and categorical data by the Axionvision 4.8 program. Pearson's chi-squared test was applied, setting significant difference at  $P < 0.05$  for all cases.

**RESULTS:** In group B, the biomarkers were significantly increased compared to the other groups ( $P < 0.001$ ), except for NO which in group B decreased significantly ( $P < 0.001$ ). In group B, there was a higher inflammatory infiltration level (80.67%) in relation to destroyed fibers.

**CONCLUSIONS:** LLLT caused significant changes in inflammatory biomarkers and oxidative stress: decreased levels of fibrinogen, L-citrulline and SOD as opposed to the increase of NO in rats with experimental myopathies and significant muscle recovery.

Med Pregl. 2010 Mar-Apr;63(3-4):188-93.

# Stimulation of mucoperiosteal slice epithelization by small power laser after the primary plastic of oroantral communication.

[Article in Serbian]

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## Abstract

**INTRODUCTION:** The oroantral communication is a pathologic communication between the oral cavity and maxillary sinus. It originates with extraction of the upper lateral teeth. Primary plastics communication, which is more extensive than 5 mm has been unsuccessful in 16%. Small power lasers have positive reaction on wounds healing. The aim of this work was to determine the lasers effects on slice epithelization after the plastics more extensive than 5 mm.

**MATERIAL AND METHODS:** The experimental research was done on dogs with extraction of the upper second premolars on both sides, and formed oroantral communication having diameter of 10 mm. After the plastics of sinus, the left side slices were exposed to radiation for 7 days, and the opposite slices healed spontaneously. Eight points (8x1J) were treated for 100s by GaAIAs laser, power 10 mW and wavelength 670 nm. Biopses of the slices connections were taken on the 14th day to be laboratory treated and examined microscopially. The study included 36 examinees with communication diameter of 10 mm and performed plastics of sinuses. In half of the examinees wounds were exposed to radiation for 7 days, and in other examinees they healed spontaneously. The results were analyzed on the fourteenth day according to the scale: (1) complete healing, without dehiscention; (2) incomplete healing, with minimal dehiscention; (3) communication did not heal, with partial dehiscention; (4) open communication, with significant dehiscention.

**RESULTS AND DISCUSSION:** The microscopic analysis shows that no wounds exposed to radiation were overcast with mucous membrane which had smooth sub epithelia chronic inflammation and inflammable infiltrate, and strong fibroplasias and granulations. Wounds exposed to radiation had mucous membrane without any signals of inflammation. Laser radiation causes anti-inflammatory reaction, i.e., it provokes reduction of exudation, alteration and proliferation, it blocks cyclo- and lipo-oxygenation by delaying the synthesis of prostaglandin, stimulates neutrophyll, macrophage and lissome activity and it activates the function of immune complex T and B lymphocytes, so this difference could be primary referred to the action of laser. Our clinical study shows that complete healing of oroantral communication was recorded in 88.8% of the examinees who were exposed to radiation in relation to 50%, of those who did not receive radiation therapy which is statistically much higher percentage (chi2 test < 0.05). The surgery was repeated in 5.6% of those who had received radiation therapy and in 16.7% of those who had not been exposed to radiation. Laser radiation stimulates changing of ADP in ATP and it accelerates cells metabolism, it increases microcirculation and accelerates substance exchange of cells, it increases DNK and RNK synthesis and stimulates cells division, which cause quicker regeneration of epithelia, i.e., it accelerates the process of wound healing.

CONCLUSION: It can be concluded that small power laser can be used successfully as additional method of treatment, after closing of oroantral communication surgically.

Photomed Laser Surg. 2010 Feb;28(1):125-9.

## **Helium-neon laser reduces the inflammatory process of arthritis.**

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### **Abstract**

**OBJECTIVE:** A histological study of the anti-inflammatory effect of helium-neon laser in models of arthropathies induced by hydroxyapatite and calcium pyrophosphate in rats.

**BACKGROUND:** Crystal deposition diseases are inflammatory pathologies induced by cellular reaction to the deposit of crystals in the joints.

**METHODS:** Fifty-six Suquia strain rats were distributed in seven groups. Two mg of each crystal diluted in 0.05 ml physiologic solution were injected six times in each back limb joint, during two weeks on alternate days. Eight J/cm<sup>2</sup> were applied daily to the crystal-injected joints on five consecutive days. The joints were cut and put in 10% formaldehyde, stained with hematoxylin-eosin and observed by light microscopy. The percentage of area with inflammatory infiltrates was determined in five optical microscopy photographs (100X) for each group and analyzed using the Axionvision 4.6 program. A Pearson's Chi Squared test was applied, with significance level set at  $p < 0.05$ .

**RESULTS:** Both crystals produced an inflammatory process in the osteoarticular structures, consisting of predominantly mononuclear infiltration, fibrosis, and granulomas of foreign body-type giant cells containing phagocytosed remains of crystals. In the arthritic joints treated with laser, a marked decrease ( $p < 0.0001$ ) was found in the percentage of area with inflammatory infiltrates, although the granulomas remained in a less ostensible form, with adipose tissue cells, fibrosis bands with light residual inflammation, and an absence of or very few crystals. Laser alone or physiologic solution injection did not produce histological changes.

**CONCLUSIONS:** Helium-neon laser reduced the intensity of the inflammatory process in the arthritis model induced by hydroxyapatite and calcium pyrophosphate crystals.

Photomed Laser Surg. 2009 Feb;27(1):79-84.

## **Inflammatory and oxidative stress markers in experimental crystallopathy: their modification by photostimulation.**

Rubio CR<>, Simes JC<>, Moya M<>, Soriano F<>, Palma JA<>, Campana V<>.

Cátedra de Física Biomédica, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Córdoba, Argentina.

## **Abstract**

Crystalopathies are inflammatory pathologies caused by cellular reactions to the deposition of crystals in the joints. The anti-inflammatory effect of the helium-neon (He-Ne) laser and that of the nonsteroidal 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. Crystals were injected into the posterior limb joints of the rats. A dose of 8 J/cm<sup>2</sup> of energy from an He-Ne laser was applied for 3 d in some groups and for 5 d in other groups. The levels of some of the biomarkers were determined by spectrophotometry, and that of nitrotyrosine was determined by ELISA. For statistical analysis, Fisher's exact test was used, and  $p \pm 0.05$  was considered significant. In arthritic rats, the fibrinogen, L-citrulline, nitric oxide, and nitrotyrosine levels increased in comparison to controls and to the laser-treated arthritic groups ( $p \pm 0.001$ ), ( $p \pm 0.001$ ), ( $p \pm 0.02$ ), and ( $p \pm 0.01$ ), respectively. When comparing fibrinogen from arthritic rats with disease induced by hydroxyapatite with undiseased and arthritic rats treated with NSAIDs, the He-Ne laser decreased levels to values similar to those seen in controls ( $p \pm 0.01$ ). Inflammatory and oxidative stress markers in experimental crystallopathy are positively modified by photobiostimulation.

Lasers Surg Med. 2009 Jan;41(1):68-74.

## **Low level laser therapy (LLLT): attenuation of cholinergic hyperreactivity, beta(2)-adrenergic hyporesponsiveness and TNF-alpha mRNA expression in rat bronchi segments in E. coli lipopolysaccharide-induced airway inflammation by a NF-kappaB dependent mechanism.**

Mafra de Lima F<>, Costa MS<>, Albertini R<>, Silva JA Jr<>, Aimbire F<>.

Institute of Research and Development (IP&D), São Paulo, Brazil.

**BACKGROUND AND OBJECTIVES:** It is unknown if the decreased ability to relax airways smooth muscles in asthma and other inflammatory disorders, such as acute respiratory distress syndrome (ARDS), can be influenced by low level laser therapy (LLLT) irradiation. In this context, the present work was developed in order to investigate if LLLT could reduce dysfunction in inflamed bronchi smooth muscles (BSM) in rats.

**STUDY DESIGN/MATERIALS AND METHODS:** A controlled ex vivo study was developed where bronchi from Wistar rat were dissected and mounted in an organ bath apparatus with or without a TNF-alpha.

**RESULTS:** LLLT administered perpendicularly to a point in the middle of the dissected bronchi with a wavelength of 655 nm and a dose of 2.6 J/cm<sup>2</sup>, partially decreased BSM

hyperreactivity to cholinergic agonist, restored BSM relaxation to isoproterenol and reduced the TNF-alpha mRNA expression. An NF-kappaB antagonist (BMS205820) blocked the LLLT effect on dysfunction in inflamed BSM.

**CONCLUSION:** The results obtained in this work indicate that the LLLT effect on alterations in responsiveness of airway smooth muscles observed in TNF-alpha-induced experimental acute lung inflammation seems to be dependent of NF-kappaB activation.

Lasers Surg Med. 2008 Sep;40(7):500-8.

## **Anti-Inflammatory effects of low-level laser therapy (660 nm) in the early phase in carrageenan-induced pleurisy in rat.**

Boschi ES, Leite CE, Saciura VC, Caberlon E, Lunardelli A, Bitencourt S, Melo DA, Oliveira JR.

### **Source**

Laboratório de Pesquisa em Biofísica Celular e Inflamação, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Av. Ipiranga 6681 prédio 12C sala 263, CEP 90619-900 Porto Alegre, RS, Brazil.

### **Abstract**

#### **BACKGROUND AND OBJECTIVE:**

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In the classic model of pleurisy there is little evidence about the anti-inflammatory effects of low-level laser therapy (LLLT) as well the dosage characteristics, such as wavelength, total energy, number and pattern of treatment. In this study we investigated the potential effects of LLLT on modulating the pro-inflammatory and anti-inflammatory mediators of acute inflammation in a rat pleurisy model.

#### **STUDY DESIGN/MATERIALS AND METHODS:**

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A sample of 48 female Wistar rats were divided into control and experiential groups. An inflammation was induced by carrageenan (0.2 ml) injected into the pleural cavity. At 1, 2, and 3 hours after induction a continuous wave (20 mW) diode laser of the InGaAlP (660 nm) type was used in the four laser groups with different doses and treatment patterns. One group received a single dose of 2.1 J and the other three groups received a total energy of 0.9, 2.1, and 4.2 J. Four hours later the exudate volume, total and differential leukocytes, protein concentration, NO, IL-6, IL-10, TNF-alpha, and MCP-1 were measured from the aspirated liquid.

#### **RESULTS:**

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All the treatment patterns and quantity of energy studied show significant reduction of the exudate volume ( $P < 0.05$ ). Using energy of 0.9 J only NO, IL-6, MCP-1 and IL-10 are significantly reduced ( $P < 0.05$ ). On the other hand, higher energies (2.1 and 4.2 J) significantly

reduce all variables independently of the treatment pattern. The neutrophil migration has a straight correlation with the TNF-alpha ( $r = 0.551$ ) and NO ( $r = 0.549$ ) concentration.

## **CONCLUSIONS:**

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LLLT-660 nm induced an anti-inflammatory effect characterized by inhibition of either total or differential leukocyte influx, exudation, total protein, NO, IL-6, MCP-1, IL-10, and TNF-alpha, in a dose-dependent manner. Under these conditions, laser treatment with 2.1 J was more effective than 0.9 and 4.2 J.

Photomed Laser Surg. 2008 Feb;26(1):19-24.

## **Cytokine mRNA expression is decreased in the subplantar muscle of rat paw subjected to carrageenan-induced inflammation after low-level laser therapy.**

Albertini R, Villaverde AB, Aimbire F, Bjordal J, Brugnera A, Mittmann J, Silva JA, Costa M.

Instituto de Pesquisa and Desenvolvimento (IP&D), Universidade do Vale do Paraíba (UNIVAP), São José dos Campos, SP, Brazil.

### **Abstract**

**OBJECTIVE:** The objective of this work was to investigate the anti-inflammatory effects of low-level laser therapy, applied at different wavelengths (660 and 684 nm), on cytokine mRNA expression after carrageenan-induced acute inflammation in rat paw.

**BACKGROUND DATA:** Low-level laser therapy (LLLT) has been observed to reduce pain in inflammatory disorders. However, little is known about the mechanisms behind this effect or whether it is wavelength-specific.

**MATERIALS AND METHODS:** The test sample consisted of 32 rats divided into four groups: A(1) (control-saline), A(2) (carrageenan-only), A(3) (carrageenan + 660 nm laser therapy), and A(4) (carrageenan + 684 nm laser therapy). The animals from groups A(3) and A(4) were irradiated 1 h after induction of inflammation by carrageenan injection. Continuous-wave red lasers with wavelengths of 660 and 684 nm and dose of 7.5 J/cm<sup>2</sup> were used.

**RESULTS:** Both the 660 nm and 684 nm laser groups had 30%-40% lower mRNA expression for cytokines TNF-alpha, IL-1beta, and IL-6 in the paw muscle tissue than the carrageenan-only control group. Cytokine measurements were made 3 h after laser irradiation of the paw muscle, and all cytokine differences between the carrageenan-only control group and the LLLT groups were statistically significant ( $p < 0.001$ ).

**CONCLUSIONS:** LLLT at the 660-nm and 684-nm wavelengths administered to inflamed rat paw tissue at a dose of 7.5 J/cm<sup>2</sup> reduce cytokine mRNA expression levels within 3 h in the laser-irradiated tissue.

Lasers Surg Med. 2008 Jul;40(5):371-8.

# **Irradiation with 780 nm diode laser attenuates inflammatory cytokines but upregulates nitric oxide in lipopolysaccharide-stimulated macrophages: implications for the prevention of aneurysm progression.**

Gavish L<>, Perez LS<>, Reissman P<>, Gertz SD<>.

Department of Anatomy and Cell Biology, The Hebrew University, Hadassah Medical School, Jerusalem 91120, Israel. lilachg@ekmd.huji.ac.il<>

## **Abstract**

**BACKGROUND AND OBJECTIVES:** Low level laser irradiation (LLLI) has been shown to reduce inflammation in a variety of clinical situations. We have shown that LLLI (780 nm) increases aortic smooth muscle cell proliferation and matrix protein secretion and modulates activity and expression of matrix metalloproteinases. Inflammation is a major component of arteriosclerotic diseases including aneurysm. Macrophage recruitment and secretion of pro-inflammatory cytokines and the vasodilator, nitric oxide (NO), are central to most immune responses in the arterial wall. The present study was designed to determine the effect of LLLI on cytokine gene expression and secretion as well as gene expression of inducible nitric oxide synthase (iNOS) and NO production in lipopolysaccharide (LPS)-stimulated macrophages.

**STUDY DESIGN/MATERIALS AND METHODS:** Murine monocyte/macrophages (RAW 264.7) were irradiated with a 780 nm diode laser (2 mW/cm<sup>2</sup>, 2.2 J/cm<sup>2</sup>) during stimulation with LPS (0, 0.1, and 1 microg/ml). Gene expression of chemokines, cytokines, and iNOS were assessed by RT-PCR. Secretion of interleukin (IL)-1beta and monocyte chemotactic protein (MCP)-1 and NO were assessed by ELISA and the Griess reaction, respectively.

**RESULTS:** LLLI reduced gene expression of MCP-1, IL-1alpha, IL-10 (P<0.01), IL-1beta, and IL-6 (P<0.05) when cells were stimulated by 1 microg/ml LPS. LLLI reduced LPS-induced secretion of MCP-1 over non-irradiated cells by 17+/-5% and 13+/-5% at 12 hours (0.1 and 1 microg/ml LPS; P<0.01 and P=0.05, respectively), and reduced IL-1beta by 22+/-5% and 25+/-9% at 24 hours (0.1 and 1 microg/ml LPS, P=0.01 and P=0.06, respectively). However, LLLI increased NO secretion after 12 hours (LLLI vs. Control: without LPS, 1.72+/-0.37 vs. 0.95+/-0.4 microM, P<0.05; 0.1 microg/ml LPS, 7.46+/-1.62 vs. 4.44+/-1.73 microM, P=0.06; 1 microg/ml LPS, 10.91+/-3.53 vs. 6.88+/-1.52 microM, P<0.05).

**CONCLUSIONS:** These properties of LLLI, with its effects on smooth muscle cells reported previously, may be of profound therapeutic relevance for arterial diseases such as aneurysm where inflammatory processes and weakening of the matrix structure of the arterial wall are major pathologic components.

Inflammation. 2008 Jun;31(3):189-97. Epub 2008 Apr 18.

## **Low level laser therapy (LLLT) decreases pulmonary microvascular leakage, neutrophil influx and IL-1beta levels in airway and lung from rat subjected to LPS-induced inflammation.**

Aimbire F<>, Ligeiro de Oliveira AP<>, Albertini R<>, Corrêa JC<>, Ladeira de Campos CB<>, Lyon JP<>, Silva JA Jr<>, Costa MS<>.

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**BACKGROUND AND OBJECTIVE:** Low level laser therapy (LLLT) is a known anti-inflammatory therapy. Herein we studied the effect of LLLT on lung permeability and the IL-1beta level in LPS-induced pulmonary inflammation.

**STUDY DESIGN/METHODOLOGY:** Rats were divided into 12 groups (n = 7 for each group). Lung permeability was measured by quantifying extravasated albumin concentration in lung homogenate, inflammatory cells influx was determined by myeloperoxidase activity, IL-1beta in BAL was determined by ELISA and IL-1beta mRNA expression in trachea was evaluated by RT-PCR. The rats were irradiated on the skin over the upper bronchus at the site of tracheotomy after LPS.

**RESULTS:** LLLT attenuated lung permeability. In addition, there was reduced neutrophil influx, myeloperoxidase activity and both IL-1beta in BAL and IL-1beta mRNA expression in trachea obtained from animals subjected to LPS-induced inflammation.

**CONCLUSION:** LLLT reduced the lung permeability by a mechanism in which the IL-1beta seems to have an important role.

Lasers Surg Med. 2008 Jul;40(5):371-8.

## **Irradiation with 780 nm diode laser attenuates inflammatory cytokines but upregulates nitric oxide in lipopolysaccharide-stimulated macrophages: implications for the prevention of aneurysm progression.**

Gavish L, Perez LS, Reissman P, Gertz SD.

Department of Anatomy and Cell Biology, The Hebrew University, Hadassah Medical School, Jerusalem 91120, Israel. [lilachg@ekmd.huji.ac.il](mailto:lilachg@ekmd.huji.ac.il)

**BACKGROUND AND OBJECTIVES:** Low level laser irradiation (LLLI) has been shown to reduce inflammation in a variety of clinical situations. We have shown that LLLI (780 nm) increases aortic smooth muscle cell proliferation and matrix protein secretion and modulates activity and expression of matrix metalloproteinases. Inflammation is a major component of arteriosclerotic diseases including aneurysm. Macrophage recruitment and secretion of pro-inflammatory cytokines and the vasodilator, nitric oxide (NO), are central to most immune responses in the arterial wall. The present study was designed to determine the effect of LLLI on cytokine gene expression and secretion as well as gene expression of inducible nitric oxide synthase (iNOS) and NO production in lipopolysaccharide (LPS)-stimulated macrophages.

**STUDY DESIGN/MATERIALS AND METHODS:** Murine monocyte/macrophages (RAW 264.7) were irradiated with a 780 nm diode laser (2 mW/cm<sup>2</sup>, 2.2 J/cm<sup>2</sup>) during stimulation with LPS (0, 0.1, and 1 microg/ml). Gene expression of chemokines, cytokines, and iNOS were

assessed by RT-PCR. Secretion of interleukin (IL)-1beta and monocyte chemotactic protein (MCP)-1 and NO were assessed by ELISA and the Griess reaction, respectively.

**RESULTS:** LLLI reduced gene expression of MCP-1, IL-1alpha, IL-10 ( $P < 0.01$ ), IL-1beta, and IL-6 ( $P < 0.05$ ) when cells were stimulated by 1 microg/ml LPS. LLLI reduced LPS-induced secretion of MCP-1 over non-irradiated cells by  $17 \pm 5\%$  and  $13 \pm 5\%$  at 12 hours (0.1 and 1 microg/ml LPS;  $P < 0.01$  and  $P = 0.05$ , respectively), and reduced IL-1beta by  $22 \pm 5\%$  and  $25 \pm 9\%$  at 24 hours (0.1 and 1 microg/ml LPS,  $P = 0.01$  and  $P = 0.06$ , respectively). However, LLLI increased NO secretion after 12 hours (LLLI vs. Control: without LPS,  $1.72 \pm 0.37$  vs.  $0.95 \pm 0.4$  microM,  $P < 0.05$ ; 0.1 microg/ml LPS,  $7.46 \pm 1.62$  vs.  $4.44 \pm 1.73$  microM,  $P = 0.06$ ; 1 microg/ml LPS,  $10.91 \pm 3.53$  vs.  $6.88 \pm 1.52$  microM,  $P < 0.05$ ).

**CONCLUSIONS:** These properties of LLLI, with its effects on smooth muscle cells reported previously, may be of profound therapeutic relevance for arterial diseases such as aneurysm where inflammatory processes and weakening of the matrix structure of the arterial wall are major pathologic components.

Bioelectromagnetics. 2008 Apr;29(3):197-206.

## **Anti-inflammatory effects of low-intensity extremely high-frequency electromagnetic radiation: frequency and power dependence.**

Gapeyev AB<>, Mikhailik EN<>, Chemeris NK<>.

Institute of Cell Biophysics of Russian Academy of Sciences, Pushchino, Moscow Region, Russia. gapeyev@icb.psn.ru

### **Abstract**

Using a model of acute zymosan-induced footpad edema in NMRI mice, the frequency and power dependence of anti-inflammatory effect of low-intensity extremely high-frequency electromagnetic radiation (EHF EMR) was found. Single whole-body exposure of animals to EHF EMR at the intensity of  $0.1 \text{ mW/cm}^2$  for 20 min at 1 h after zymosan injection reduced both the footpad edema and local hyperthermia on average by 20% at the frequencies of 42.2, 51.8, and 65 GHz. Some other frequencies from the frequency range of 37.5-70 GHz were less effective or not effective at all. At fixed frequency of 42.2 GHz and intensity of  $0.1 \text{ mW/cm}^2$ , the effect had bell-shaped dependence on exposure duration with a maximum at 20-40 min. Reduction of intensity to  $0.01 \text{ mW/cm}^2$  resulted in a change of the effect dependence on exposure duration to a linear one. Combined action of cyclooxygenase inhibitor sodium diclofenac and EHF EMR exposure caused a partial additive effect of decrease in footpad edema. Combined action of antihistamine clemastine and EHF EMR exposure caused a dose-dependent abolishment of the anti-inflammatory effect of EHF EMR. The results obtained suggest that arachidonic acid metabolites and histamine are involved in realization of anti-inflammatory effects of low-intensity EHF EMR.

J Photochem Photobiol B. 2007 Nov 12;89(1):50-5. Epub 2007 Sep 6.

# **Anti-inflammatory effects of low-level laser therapy (LLLT) with two different red wavelengths (660 nm and 684 nm) in carrageenan-induced rat paw edema.**

Albertini R, Villaverde AB, Aimbire F, Salgado MA, Bjordal JM, Alves LP, Munin E, Costa MS.

## **Source**

Instituto de Pesquisa & Desenvolvimento, IP&D, Universidade do Vale do Paraíba, UNIVAP, Av. Shishima Hifumi, 2911, CEP: 12244-000 São José dos Campos, SP, Brazil.

## **Abstract**

It has been suggested that low-level laser therapy (LLLT) can modulate inflammatory processes. The aim of this experiment was to investigate what effects red laser irradiation with two different wavelengths (660 nm and 684 nm) on carrageenan-induced rat paw edema and histology. Thirty two male Wistar rats were randomly divided into four groups. One group received a sterile saline injection, while inflammation was induced by a sub-plantar injection of carrageenan (1 mg/paw) in the three other groups. After 1 h, LLLT was administered to the paw in two of the carrageenan-injected groups. Continuous wave 660 nm and 684 nm red lasers respectively with mean optical outputs of 30 mW and doses of 7.5 J/cm<sup>2</sup> were used. The 660 nm and 684 nm laser groups developed significantly ( $p < 0.01$ ) less edema (0.58 ml [SE $\pm$ 0.17] ml and 0.76 ml [SE $\pm$ 0.10] respectively) than the control group (1.67 ml [SE $\pm$ 0.19]) at 4h after injections. Similarly, both laser groups showed a significantly lower number of inflammatory cells in the muscular and conjunctive sub-plantar tissues than the control group. We conclude that both 660 nm and 684 nm red wavelengths of LLLT are effective in reducing edema formation and inflammatory cell migration when a dose of 7.5 J/cm<sup>2</sup> is used.

Biofizika. 2007 Sep-Oct;52(5):947-52.

# **Dependence of anti-inflammatory effects of high peak-power pulsed electromagnetic radiation of extremely high frequency on exposure parameters**

[Article in Russian]

Gapeev AB<>, Mikha?lik EN<>, Rubanik AV<>, Cheremis NK<>.

## **Abstract**

A pronounced anti-inflammatory effect of high peak-power pulsed electromagnetic radiation of extremely high frequency was shown for the first time in a model of zymosan-induced footpad edema in mice. Exposure to radiation of specific parameters (35, 27 GHz, peak power 20 kW, pulse widths 400-600 ns, pulse repetition frequency 5-500 Hz) decreased the exudative edema and local hyperthermia by 20% compared to the control. The kinetics and the magnitude of the anti-inflammatory effect were comparable with those induced by sodium diclofenac at a dose of 3 mg/kg. It was found that the anti-inflammatory effect linearly

increased with increasing pulse width at a fixed pulse repetition frequency and had threshold dependence on the average incident power density of the radiation at a fixed pulse width. When animals were whole-body exposed in the far-field zone of radiator, the optimal exposure duration was 20 min. Increasing the average incident power density upon local exposure of the inflamed paw accelerated both the development of the anti-inflammatory effect and the reactivation time. The results obtained will undoubtedly be of great importance in the hygienic standardization of pulsed electromagnetic radiation and in further studies of the mechanisms of its biological action.

Photomed Laser Surg. 2007 Aug;25(4):245-9.

## **Low-level laser therapy (GaAs lambda = 904 nm) reduces inflammatory cell migration in mice with lipopolysaccharide-induced peritonitis.**

Correa F, Lopes Martins RA, Correa JC, Iversen VV, Joenson J, Bjordal JM.

### **Source**

University Nove Julho, São Paulo, Brazil.

### **Abstract**

#### **OBJECTIVE:**

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This study was designed to study the effect of an infrared low-level laser (GaAs lambda = 904 nm, 4 mW) on inflammatory cell migration in lipopolysaccharide (LPS)-induced peritonitis in mice.

#### **BACKGROUND DATA:**

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It has been suggested that red wavelengths of low-level laser therapy (LLL) can exert anti-inflammatory effects, but little is known about the anti-inflammatory effects of infrared lasers. Peritonitis is a potentially life-threatening inflammatory condition that may be suitable for studying anti-inflammatory effects of infrared lasers.

#### **METHODS:**

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Sixty male mice were randomly divided into five groups, and one group was given an intraperitoneal sterile saline injection. In the remaining four groups, peritonitis was induced by an intraperitoneal LPS injection. Animals in three of the LPS groups were irradiated at a single point over the peritoneum with doses of 3 J/cm<sup>2</sup>, 7.5 J/cm<sup>2</sup>, and 15 J/cm<sup>2</sup>, respectively. The fourth group injected with LPS was an LPS-control group.

#### **RESULTS:**

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At 6 hours after injection the groups irradiated with doses of 3 J/cm<sup>2</sup> and 7.5 J/cm<sup>2</sup> had a reduced number of neutrophil cells in the peritoneal cavity compared with the LPS-control group, and there were significant differences between the number of neutrophils in the peritoneal cavity between the LPS-control group and groups irradiated with doses of 3 J/cm<sup>2</sup> (-42%) and 7.5 J/cm<sup>2</sup> (-70%). In the group irradiated with 15 J/cm<sup>2</sup>, neutrophil cell counts were lower than, but not significantly different from, LPS controls (-38%;  $p = 0.07$ ). At 24 hours after injection, both neutrophil and total leukocyte cell counts were lower in all the irradiated groups than in the LPS controls. The 3-J/cm<sup>2</sup> exposure group showed the best results at 24 hours, with reductions of 77% in neutrophil and 49% in leukocyte counts.

## **CONCLUSION:**

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Low-level laser therapy (904 nm) can reduce inflammatory cell migration in mice with LPS-induced peritonitis in a dose-dependent manner.

Photomed Laser Surg. 2007 Apr;25(2):112-7.

## **Effect of low-power laser therapy on hemorrhagic lesions induced by immune complex in rat lungs.**

Aimbire F<>, Lopes-Martins RA<>, Albertini R<>, Pacheco MT<>, Castro-Faria-Neto HC<>, Martins PS<>, Bjordal JM<>.

Laboratory of Animal Experimentation, Research and Development Institute (IP&D), Vale do Paraíba University (UNIVAP), São José dos Campos, Brazil.

**OBJECTIVE:** The aim of this study was to investigate if low-level laser therapy (LLLT) can modulate formation of hemorrhagic lesions induced by immune complex.

**BACKGROUND DATA:** There is a lack of information on LLLT effects in hemorrhagic injuries of high perfusion organs, and the relative efficacy of LLLT compared to anti-inflammatory drugs.

**METHODS:** A controlled animal study was undertaken with 49 male Wistar rats randomly divided into seven groups. Bovine serum albumin (BSA) 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 Ga-Al-As laser with LLLT doses of 2.6 Joules/cm<sup>2</sup> to celecoxib, dexamethasone, and control groups for hemorrhagic index (HI) and myeloperoxide activity (MPO) at 24 h after injury.

**RESULTS:** The HI for the control group was 4.0 (95% CI, 3.7-4.3). Celecoxib, LLLT, and dexamethasone all induced significantly ( $p < 0.01$ ) lower HI than control animals at 2.5 (95% CI, 1.9-3.1), 1.8 (95% CI, 1.2-2.4), and 1.5 (95% CI, 0.9-2.1), respectively, for all comparisons to control. Dexamethasone, but not celecoxib, induced a slightly, but significantly lower HI than LLLT ( $p = 0.04$ ). MPO activity was significantly decreased in groups receiving celecoxib at 0.87 (95% CI, 0.63-1.11), dexamethasone at 0.50 (95% CI, 0.24-0.76), and LLLT at 0.7 (95% CI, 0.44-0.96) when compared to the control group, at 1.6 (95% CI, 1.34-1.96;  $p < 0.01$ ), but there were no significant differences between any of the active treatments.

CONCLUSION: LLLT at a dose of 2.6 Joules/cm<sup>2</sup> induces a reduction of HI levels and MPO activity in hemorrhagic injury that is not significantly different from celecoxib. Dexamethasone is slightly more effective than LLLT in reducing HI, but not MPO activity.

Biofizika. 2006 Nov-Dec;51(6):1055-68.

## **Pharmacological analysis of anti-inflammatory effects of low-intensity extremely high-frequency electromagnetic radiation**

[Article in Russian]

Gapeev AB<>, Lushnikov KV<>, Shumilina IuV<>, Chemeris NK<>.

### **Abstract**

The anti-inflammatory effect of low-intensity extremely high-frequency electromagnetic radiation (EHF EMR, 42.0 GHz, 0.1 mW/cm<sup>2</sup>) was compared with the action of the known anti-inflammatory drug sodium diclofenac and the antihistamine clemastine on acute inflammatory reaction in NMRI mice. The local inflammatory reaction was induced by intraplantar injection of zymosan into the left hind paw. Sodium diclofenac in doses of 2, 3, 5, 10, and 20 mg/kg or clemastine in doses of 0.02, 0.1, 0.2, 0.4, and 0.6 mg/kg were injected intraperitoneally 30 min after the initiation of inflammation. The animals were whole-body exposed to EHF EMR for 20 min at 1 h after the initiation of inflammation. The inflammatory reaction was assessed over 3 – 8 h after the initiation by measuring the footpad edema and hyperthermia of the inflamed paw. Sodium diclofenac in doses of 5 – 20 mg/kg reduced the exudative edema on the average by 26% as compared to the control. Hyperthermia of the inflamed paw decreased to 60% as the dose of was increased diclofenac up to 20 mg/kg. EHF EMR reduced both the footpad edema and hyperthermia by about 20%, which was comparable with the effect of a single therapeutic dose of diclofenac (3 – 5 mg/kg). The combined action of diclofenac and the exposure to the EHF EMR caused a partial additive effect. Clemastine in doses of 0.02-0.4 mg/kg it did not cause any significant effects on the exudative edema, but in a dose of 0.6 mg/kg it reduced edema by 14 – 22% by 5 – 8 h after zymosan injection. Clemastine caused a dose-dependent increase in hyperthermia of inflamed paw at doses of 0.02-0.2 mg/kg and did not affect the hyperthermia at doses of 0.4 and 0.6 mg/kg. The combined action of clemastine and EHF EMR exposure caused a dose-dependent abolishment of the anti-inflammatory effect of EHF EMR. The results obtained suggest that both arachidonic acid metabolites and histamine are involved in the realization of anti-inflammatory effects of low-intensity

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## **Assessment of Anti-Inflammatory Effect of 830nm Laser Light Using C-Reactive Protein Levels**

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INTRODUCTION<> | MATERIAL AND METHODS<> | RESULTS<> | DISCUSSION<> | RESUMO<> | REFERENCES<>

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The anti-inflammatory effect of non-surgical lasers has been proposed previously, however it was not scientifically proven. One method to assess levels of inflammation is the measurement of C-reactive protein (CRP), which is increased with the course of inflammation. The aim of this study was to assess the effect of 830nm laser irradiation after the removal of impacted third molars using the CRP as the marker of inflammation. Twelve patients were irradiated with 4.8 J of laser light per session 24 and 48 h after surgery. A control group (N=12) was treated with a sham laser. Blood samples were taken prior to, and 48 and 72 h after surgery. CRP values were more symmetric and better distributed for the irradiated group (0.320 mg/dl) than for the control (0.862 mg/dl) 48 h after surgery, however there was no statistically significant difference. After 72 h, both groups had statistically similar CRP levels (0.272 and 0.608 mg/dl), because of the normal tendency of decreasing CRP levels.

Key Words: dental surgery, inflammation, non-surgical lasers.

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## INTRODUCTION

Lasers have been used in several medical specialties and recently the dental profession has used laser both as a surgical tool and a biomodulating agent (1). Laser development began in 1917, when Albert Einstein proposed the principles of the stimulated emission of radiation. In 1958, Shawlow and Townes suggested the basic principles of light amplification (2).

Laser is a non-ionizing electromagnetic highly concentrated light, which, in contact with different tissues, results in several effects in tissue depending upon the wavelength and the optical properties of the irradiated tissue. Because it is a non-ionizing form of radiation, laser light can be used repeatedly within the parameters used currently because it does not induce mutagenic response. The use of laser light is not contraindicated for pregnant women, pacemaker users, and does not interfere with monitoring in the operating room (3).

Medical lasers can be classified into three main groups: Low Intensity Laser Therapy (LILT), High Intensity Laser Therapy (HILT) and Selective Laser Therapy (SLAT). LILT is also known as Low Level Laser therapy or LLLT and can modify cell metabolism, improve wound healing, reduce pain and edema, and speed inflammation and wound healing (4,5).

Inflammation occurs when immunocompetent cells are activated in response to foreign bodies or antigenic proteins. This response may have a beneficial effect (e.g. phagocytosis) or a deleterious effect (e.g. destruction of bone and cartilage in arthritis) (6).

Anti-inflammatory agents are drugs used for the treatment of non-specific inflammatory process to control signs and symptoms such as: heat, redness, pain and lack of function. There are two kinds of anti-inflammatory agents available on the market: steroids and non-steroids. The use of these drugs may result in undesirable side effects; thus, the constant search for alternative methods to control inflammation without deleterious effects to the patient.

LLLT has been used as an important tool for the control of the inflammatory process. Its anti-inflammatory effect has been studied and its ability to induce analgesia under different conditions has also been reported (7).

The serial determination of the levels of some serum proteins may be useful for the differentiation of inflammatory and non-inflammatory conditions, as well as between clinical conditions which are known to show increased or decreased acute phase response. One of these proteins is the C-reactive protein (CRP). The magnitude of the CRP response varies directly with the severity of tissue damage, type of the inflammatory stimuli, organ or tissue involved in the process, as well as on the monitoring of the natural course of the disease and the disease response to treatment (8). CRP plasma concentration is usually low (9), increases quickly at the onset of an acute inflammatory process and quickly falls when effective control of the process occurs (10,11).

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## **MATERIAL AND METHODS**

This study was approved by the Ethical Committee of the Hospital das Clínicas of the Universidade Federal de Pernambuco, Brazil. Twenty-four patients gave signed informed consent as determined by Brazilian regulations. The patients were selected according to the following criteria: lower wisdom tooth, older than 16 years of age and younger than 30 years of age, symptom free at the time of surgery, lack of pericoronaritis for at least 30 days prior to surgery. One week before surgery, a blood sample was taken to determine the baseline of CRP prior to surgery and irradiation. Patients with elevated CRP levels were dismissed from the study. Under local anesthesia, a maximum of two wisdom teeth were surgically removed using rotary and manual instruments. All patients received 500 mg of paracetamol after surgery. This drug was chosen because its very low anti-inflammatory action at usual doses (12). The drug was used immediately after surgery and repeated every six hours if necessary, not exceeding 2000 mg/day.

The patients were randomly divided into two groups (even numbered patients were placed in the test group and odd numbered patients in the control group). Twenty-four and forty-eight hours after surgery, the twelve test patients received the irradiation at the Laser Center with an 830nm diode laser (40 mW; Laser Beam, Rio de Janeiro, RJ, Brazil) for a total dose of 4.8 J/cm<sup>2</sup>. Control patients were treated with a sham laser. Forty-eight and seventy-two hours

after surgery, blood samples were taken and the CRP level was determined by nephelometry (13-15).

Statistical analysis was based upon the comparison between groups using the Kolmogorov-Smirnov, Mann-Whitney and Shapiro-Wilks tests (16).

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## RESULTS

Comparison of groups at baseline is shown in Table 1<>. Both groups had very similar levels of CRP (Kolmogorov-Smirnov = 0.17; critical value, at 5% = 0.50). Forty-eight hours after treatment (Table 2), CRP levels of irradiated patients showed a very symmetric distribution around the mean with a very small variability when compared to the controls. The Shapiro-Wilks test indicated that there was a normal distribution for the test group (S-W = 0.95; p = 0.438). However, the control group had a positive asymmetric distribution (S-W = 0.83; p = 0.021). Although there was a numerical difference between the two groups, the Mann-Whitney test did not show a significant difference between the medians of the two groups (W = 133.3; p = 0.338).

The results of the Kolmogorov-Smirnov test for two samples indicated at significance level of 5%; after 72 h the CRP levels showed the same distribution for both groups (K-S = 0.333; critical value at 5% = 0.50). Table 3 show a symmetric positive distribution for both groups. The differences of the distribution on the graphs is a reflex of the random variation.

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## DISCUSSION

Surgical removal of a wisdom tooth may result in edema, pain and slight bleeding. However, if these conditions are exacerbated or if there is the presence of infection or trismus, these can be considered as complications. The lack of previous studies comparing the use of LLLT and other types of drug treatment for inflammatory conditions of the oral cavity makes it difficult to compare the results of this study. There was modification of the CRP level immediately after the surgical removal of the wisdom teeth and increased levels of CRP were found in both groups in agreement with other reports (10,11). This inflammatory response has been reported previously (17).

The level of CRP and the clinical stage of the disease have a direct relationship to the evolution of the disease and the plasma level of CRP (18). Despite the fact that several authors consider an increase of CRP levels to be an unspecific response to infection, inflammation or tissue damage (19), in this study, CRP levels were used to assess the anti-inflammatory action of the 830nm diode laser, based on other studies that used CRP levels for monitoring inflammation (17). CRP response allows monitoring of the anti-inflammatory effect of drugs. The use of aspirin, steroids, penicillin and other non-hormonal drugs will often result in a reduction of the CRP level as these drugs will suppress the underlying inflammatory process (20). However, paracetamol was used as the analgesic drug in this study because of its very low anti-inflammatory effect in usual doses (12).

The aim of post-operative therapeutics is not the suppression of inflammation, because this process is extremely important for wound healing. Therapeutic methods and drugs used in the post-operative process aim to minimize symptoms and provide more comfort for the patient.

Thus, the use of a non-invasive treatment such as LLLT is a major step in clinical therapeutics because of the lack of side effects of LLLT.

Statistical analysis of the results detected a very symmetric distribution of CRP levels at the post-operative period of patients who had wisdom teeth surgically removed and were irradiated with 830nm laser light when compared to the levels observed for the controls.

Although this study failed to statistically confirm an anti-inflammatory effect of LLLT after surgical removal of wisdom teeth, the results show a reduction in the level of CRP in irradiated patients which may indicate attenuation of the inflammation; however, a larger sample is necessary to confirm this aspect. It is also important to observe that the complete treatment consisted of four minutes of irradiation within two days and that there was no additional cost for the patient, no need to use other drugs or any interference with routine life (3).

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## RESUMO

de Freitas AC, Pinheiro ALB, Miranda P, Thiers FA, Vieira ALB. Avaliação do efeito anti-inflamatório do laser diodo infravermelho de 830 nm através da monitorização da proteína c-reativa. *Braz Dent J* 2001;12(3):187-190.

A atividade anti-inflamatória da radiação Laser ainda não está muito bem estabelecida. Dentre as diferentes formas de avaliação da resposta inflamatória aguda encontra-se, a dosagem da proteína C-reativa (PCR), que na inflamação encontra-se elevada. O objetivo deste trabalho foi avaliar a capacidade anti-inflamatória do Laser Diodo Infra-Vermelho de 830nm no pós-operatório de cirurgias para remoção de terceiros molares retidos, através da análise cinética da variação dos níveis da PCR. A irradiação foi realizada a uma distância focal de 0,5cm, por um tempo total de dois minutos em corrente contínua, nos pontos preestabelecidos. As cirurgias foram realizadas no Bloco Cirúrgico do Departamento de Prótese e Cirurgia Buco Facial da Universidade Federal de Pernambuco. A população alvo foi de 24 pacientes divididos aleatoriamente em dois grupos. O grupo teste foi submetido à Laserterapia nas 24 e 48 horas pós-operatório (PO). O grupo controle foi submetido a uma falsa irradiação, com os mesmos intervalos do grupo teste. As amostras de sangue, para a dosagem da PCR foram colhidas antes da cirurgia e após 48 e 72 horas. Os valores da PCR no grupo teste 48 horas PO apresentou uma distribuição bastante simétrica em torno de sua média e com a variabilidade bem menor comparada com o grupo controle, porém não encontramos diferenças estatisticamente significante. Nas 72 horas PO os valores da PCR foram bastante semelhantes o que pode ser explicado, por uma tendência natural da queda desta proteína nesta fase.

Unitermos: cirurgia odontológica, inflamação, laser não cirúrgico.

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