

Effect of Low-Level Laser Therapy on Inflammatory Reactions during Wound Healing: Comparison with Meloxicam

VINICIUS NERY VIEGAS, M.S.,¹ MARCELO EMIR REQUIA ABREU, M.S.,¹ CHRISTIAN VIEZZER,² DENISE CANTARELLI MACHADO, Ph.D.,² MANOEL SANT'ANNA FILHO, Ph.D.,³ DANIELA NASCIMENTO SILVA, Ph.D.,³ and ROGÉRIO MIRANDA PAGNONCELLI, Ph.D.¹

ABSTRACT

Objective: This study evaluated the action of low-level laser therapy (LLLT) on the modulation of inflammatory reactions during wound healing in comparison with meloxicam. **Background Data:** LLLT has been recommended for the postoperative period because of its ability to speed healing of wounds. However, data in the literature are in disagreement about its anti-inflammatory action. **Methods:** Standardized circular wounds were made on the backs of 64 Wistar rats. The animals were divided into four groups according to the selected postoperative therapy: group A—control; group B—administration of meloxicam; and groups C and D—irradiation with red ($\lambda = 685$ nm) and infrared ($\lambda = 830$ nm) laser energy, respectively. The animals were killed at 12, 36, and 72 h and 7 days after the procedure. **Results:** Microscopic analysis revealed significant vascular activation of irradiated sites in the first 36 h. Only group B showed decreases in the intensity of polymorphonuclear infiltrates and edema. Group D showed a higher degree of organization and maturation of collagen fibers than the other groups at 72 h. The animals in group C showed the best healing pattern at 7 days. The anti-inflammatory action of meloxicam was confirmed by the results obtained in this research. The quantification of interleukin-1 β (IL-1 β) mRNA by real-time polymerase chain reaction (PCR) did not show any reduction in the inflammatory process in the irradiated groups when compared to the other groups. **Conclusions:** LLLT improves the quality of histologic repair and is useful during wound healing. However, with the methods used in this study the laser energy did not minimize tissue inflammatory reactions.

INTRODUCTION

DURING THE INFLAMMATORY PROCESS, tissue and cell lesions, circulatory disorders, exudation, and proliferative and healing events occur in a chronological sequence. Inflammation is defined as the combination of all these events.^{1,2} The reactions that occur in tissues as a result of an inflammatory process are beneficial to the organism because they lead to the regeneration of injured tissues. However, to minimize postoperative discomfort and improve the quality of tissue healing, this process should be modulated, and not exacerbated.^{3,4}

Numerous intercellular interactions of the immunologic system are controlled by soluble mediators called cytokines. These

important regulating molecules form a diverse group of intercellular signaling proteins that regulate not only the local and systemic inflammatory and immunologic responses, but also wound healing, hematopoiesis, and many other biological processes.^{5–7}

The most important cytokines involved in the inflammatory process are tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, and IL-8.⁷ The presence of soft tissue injury promotes an increase in the production of proinflammatory cytokines, reaching maximal levels between 12 and 72 h post-injury.^{8–11} Some studies showed a reduction in the expression of mRNA of these cytokines after treatment with anti-inflammatory drugs in experimental models.⁸

¹School of Dentistry, Laser Center, ²Biomedical Researches Institute, and ³School of Dentistry, Oral and Maxillofacial Surgery Department, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil.



FIG. 1. Photomicrograph of central site of a wound from the control group (12 h). H&E stain, approximately 40 \times .

Intramuscular administration of nonsteroidal anti-inflammatory drugs (NSAIDs) is often given for rapid pain relief and modulation of the inflammatory process.¹² Meloxicam is an NSAID of the enolic acid group that shows preferential inhibition of cyclooxygenase-2, imparting analgesic, antipyretic, and anti-inflammatory properties. This drug has a plasma half-life of approximately 20 h, making it convenient for once-daily administration.¹³ The excellent tolerability of intramuscular administration of meloxicam together with its rapid and complete absorption may provide an alternative to oral administration of the drug.¹²

Low-level laser therapy (LLLT), an alternative for the modulation of inflammatory processes, has also been recommended for use postoperatively because of its capacity to biomodulate healing.^{14–16} However, data in the literature are not in agreement about the anti-inflammatory effect of laser energy on wound healing. Some studies suggest that laser therapy may minimize inflammatory reactions,^{17,18} whereas others report that LLLT accelerates inflammation in the healing process, and makes it more severe initially, thus decreasing healing time. Thus the application of laser energy to injured tissues may provide earlier healing with better histologic quality.^{19–23}

This study evaluated the action of LLLT on the modulation of inflammatory reactions during wound repair, and analyzed the histological pattern of the healing process, as well as IL-1 β mRNA levels.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of the School of Dentistry of Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS). Sixty-four young adult male Wistar rats weighing 200–250 g were kept in individual cages at room temperature and normal room lighting, and were fed laboratory chow and water *ad libitum* throughout the experiment. The animals underwent surgical procedures under general anesthesia (0.025 mL/100 g 10% xylazine and 0.05 mL/100 g 2% ketamine, IM). After the anesthetic effect was confirmed, the back of the animal was shaved, washed with 2% chlorhexidine diglu-

conate, and dried with sterile gauze. A standardized circular wound 8 mm in diameter was created on the dorsum of each rat using a surgical punch. The animals were divided into four groups according to the postoperative therapy each group received. Group A was the control group; group B received IM injection of meloxicam (1 mg/0.1 mL) immediately after surgery and at 48 h; group C was irradiated with red InGaAlP laser energy ($\lambda = 685$ nm); and group D was irradiated with infrared GaAlAs laser energy ($\lambda = 830$ nm); groups C and D received therapy immediately after surgery and at 48 h post-injury. Laser energy was focused transcutaneously on four equidistant points around the wound, according to the following protocol: continuous mode, 35 mW of power and 4 J/cm² of total energy density per session (spot size of approximately 0.02827 cm²).

At each experimental time point (12, 36, and 72 h, and 7 days), the animals in each group were humanely killed in a CO₂ chamber. The specimens were removed, coded, and kept in 10% buffered formalin for 24 h, and then were routinely processed for paraffin embedding, and stained with hematoxylin and eosin (H&E). The microscopic analysis was made by two previously calibrated observers and their findings were confirmed by an experienced pathologist. For animals killed at 12, 36, and 72 h, data were recorded about the degree of the tissue healing seen. For polymorphonuclear and mononuclear cells, hyperemia, and edema seen microscopically, the following intensity criteria were used: 0, absent or nearly absent; 1, minor; 2, moderate; and 3, intense.

The expression of IL-1 β mRNA in the specimens obtained was evaluated by real-time polymerase chain reaction (PCR). The initiating oligonucleotides used in this research were: forward, 5'-CAACAAAAATGCCTCGTGC-3', and reverse, 3'-TGCTGATGTACCAGTTGGG-5'.

The specimens were cut into small fragments, placed in microtubes of 1.5 mL capacity containing 500 μ L of the organic solvent Trizol Reagent (Invitrogen, Carlsbad, CA, USA), and later were macerated to facilitate RNA extraction. After vigorous maceration of the tissues, the liquid content was removed from the macerator, placed in a new microtube, and centrifuged

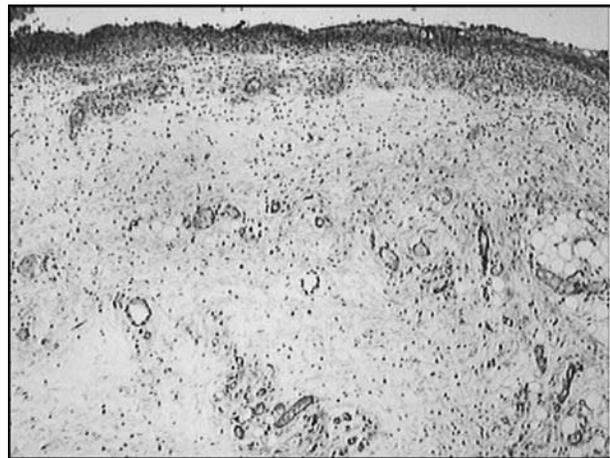


FIG. 2. Photomicrograph of central site of a wound from the group irradiated with red laser energy (12 h post-injury). The hyperemia is more severe than that seen in the control group. H&E, approximately 40 \times .

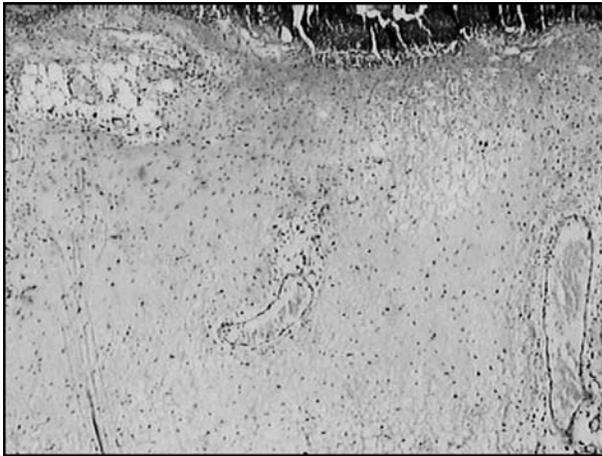


FIG. 3. Photomicrograph of central site of a wound from the group treated with meloxicam (36 h). A reduction in the amount of polymorphonuclear infiltrate is seen. H&E, approximately 40 \times .

at 4 $^{\circ}$ C for 20 sec at 14,000 rpm. The supernatant was treated with 120 μ L of cold chloroform to dissolve the greasy component. The supernatant obtained after a second centrifugation was placed in another microtube and treated with 200 μ L of cold isopropanol and 2 μ L of glycogen to promote precipitation of nucleic acids. After extraction of all RNA from the cells, a reverse transcriptase reaction was used for the synthesis of complementary DNA (cDNA). The real-time PCR was performed in a thermocycler (iCycler iQ; Bio-Rad Laboratories, Hercules, CA, USA) with the addition of the following reagents, totaling 25 μ L for each sample: 12.5 μ L of SYBR Green (Platinum SYBR Green qPCR Supermix UDG; Invitrogen), 2.5 μ L of initiators of the oligonucleotides (forward) to IL-1 β (50 pM), 2.5 μ L of initiators of the oligonucleotides (reverse) to IL-1 β (50 pM), 2.5 μ L of cDNAs, and 5 μ L of MilliQ ultrapure water (Millipore, Billerica, MA, USA).

The reactions were performed according to following protocol: 95 $^{\circ}$ C (3 min), 30 cycles of 95 $^{\circ}$ C (10 sec) and 42 $^{\circ}$ C (1 min), 95 $^{\circ}$ C (1 min), 42 $^{\circ}$ C (1 min), increase in temperature of 1 $^{\circ}$ C/10 sec, from 42 to 100 $^{\circ}$ C, and maintenance of the samples at 4 $^{\circ}$ C. The quantification of IL-1 β mRNA levels was performed in the second step of this process.

RESULTS

At 12 h, all groups showed intense inflammation, edema, and hyperemia of the entire wound site, with an intense polymorphonuclear infiltrate. The number of mononuclear cells present was small. Superficial necrosis was seen in the upper portion of the lesion in all slides. The groups irradiated with red and infrared laser energy showed more hyperemia than the control group and the meloxicam group (Figs. 1 and 2).

At 36 h, the control group showed an intense inflammatory infiltrate, with a predominance of neutrophils and a moderate amount of mononuclear cells. Edema and hyperemia were also seen. The meloxicam group showed the least intense inflam-



FIG. 4. Photomicrograph of central site of a wound from the group irradiated with infrared laser energy (36 h). Vascular activation and intense polymorphonuclear infiltrate are more apparent here than in the non-irradiated groups. H&E, approximately 40 \times .

matory process and a reduction of the polymorphonuclear infiltrate (Fig. 3). Hyperemia was, on average, moderate; mean edema values were lower than those of the other groups.

The irradiated groups showed intense polymorphonuclear infiltrate. Mononuclear infiltrate and edema intensities were similar to those found in the control group. The hyperemia was more intense, on average, than in the non-irradiated groups. The group irradiated with infrared laser energy showed the most intense hyperemia (Fig. 4).

At 72 h, all groups showed a decrease in polymorphonuclear infiltrate and a predominance of mononuclear inflammatory cells, such as macrophages, lymphocytes, and plasmacytes. Minor to nearly absent edema was seen in all groups. The irradiated groups were in a more advanced stage of tissue repair. The group irradiated with infrared laser energy had better organized and more mature collagen fibers (Figs. 5 and 6).

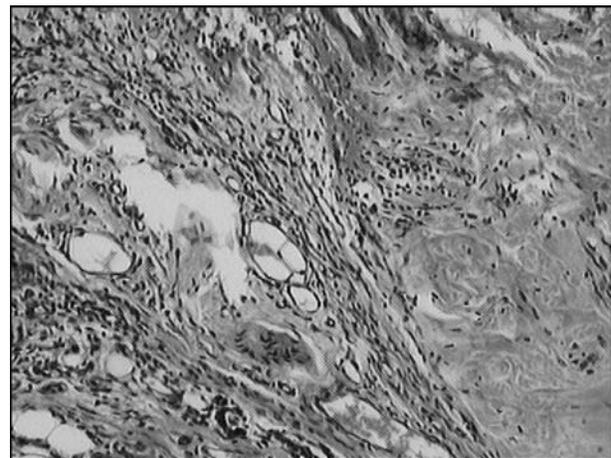


FIG. 5. Photomicrograph of a wound edge from an animal in the control group (72 h). Less maturation of collagen fibers is seen here than in the other groups. H&E, approximately 40 \times .

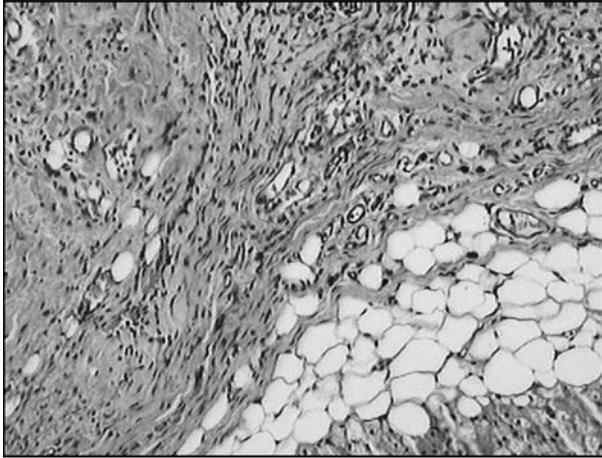


FIG. 6. Photomicrograph of a wound edge from the group irradiated with infrared laser energy (72 h). Thicker and more organized collagen fibers can be seen, and this group was in a more advanced stage of tissue repair. H&E, approximately 40 \times .

At 7 days, all groups showed formation of granulation tissue, with evident plasmablast infiltrate, neovascularization, fibroblasts, and rare polymorphonuclear cells. No group showed complete epithelialization of the lesion. Epithelialization was slower in the control group, with no differences between the other three groups. The group irradiated with red laser energy showed the best healing pattern. Collagen fibers were predominantly organized and parallel to the basal layer of epithelium, suggesting less wound contraction, less scar production, and increased tensile strength (Figs. 7 and 8).

Although variations were found in the intensity of polymorphonuclear or mononuclear infiltrates, hyperemia, and edema, no statistically significant differences were found ($p > 0.05$, Fischer's exact test).

As a rule, the IL-1 β mRNA levels were low after 12 h in all groups evaluated, with no significant difference between them. At 36 h, there was a peak in the levels of IL-1 β in all groups. After 72 h, the IL-1 β mRNA levels detected decreased and they remained steady until the seventh postoperative day. The animals treated with meloxicam had the lowest levels in all periods analyzed. The irradiated animals did not show results similar to those of the group that received meloxicam. Nevertheless, the levels of IL-1 β mRNA expression detected at 72 h and 7 days in the irradiated animals was lower than that of the control group (Table 1 and Fig. 9).

The samples from the control group at 12 h and the group irradiated with red laser at 7 days were not included in the analysis of the results of this study. These samples showed levels of IL-1 β mRNA expression that were inconsistent with the periods evaluated. It is possible that during preparation of the specimens for PCR analysis, degradation occurred with loss of some nucleic acids.

Upon analysis of the values of IL-1 β mRNA levels at all time periods studied, using the ANOVA and Tukey multiple comparison tests, the results showed a statistically significant difference between the control group and the group treated with meloxicam ($p = 0.03$). No statistically significant difference was observed between the other groups.

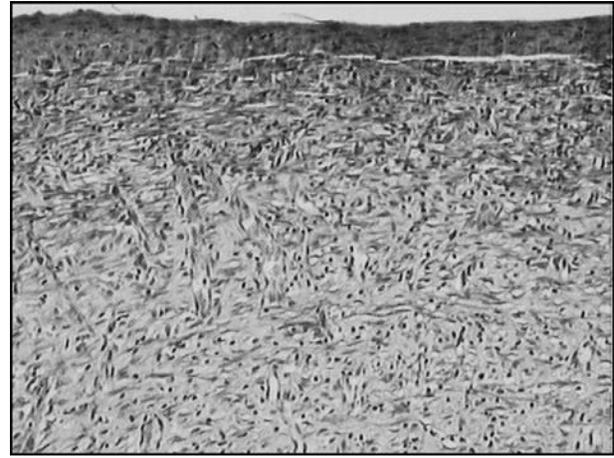


FIG. 7. Photomicrograph of central site of a wound from the control group (7 days). H&E, approximately 100 \times .

DISCUSSION

Surgical wound healing that is free of infection and with reduced inflammation and pain is extremely important for the success of modern surgical procedures.^{1,22,24–26} Several drugs have been used effectively to modulate the postoperative inflammatory response.^{3,4} Laser therapy has been recommended in such clinical situations because of the well-known biological effects of the interaction between laser energy and injured tissues. Laser light stimulates cellular activity and leads to the release of growth factors by macrophages.^{21,23} It also induces keratinocyte proliferation, angiogenesis, and mast cell activation and degranulation,²⁰ which may also accelerate wound healing.^{10,21–23,27,28} This acceleration is the result of a shorter acute inflammation phase and earlier commencement of the prolifer-

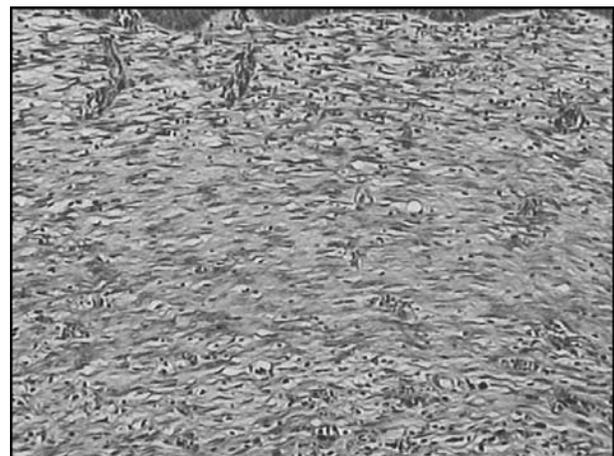


FIG. 8. Photomicrograph of central site of a wound from the group irradiated with red laser energy (7 days). Collagen fibers parallel to epithelial basal layer can be seen. H&E, approximately 100 \times .

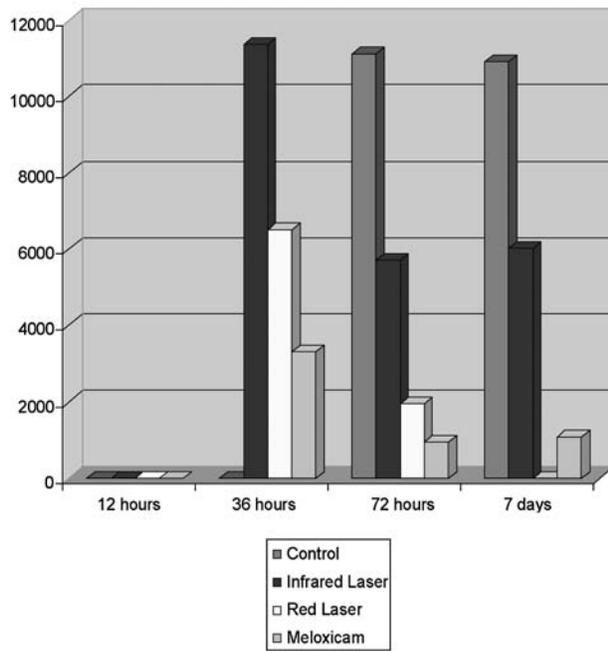


FIG. 9. Mean levels of IL-1 β mRNA expression in the tissues of the four groups ($\mu\text{g/mL}$).

ative phase of tissue repair, when granulation tissue is produced.^{21,23}

Several studies have analyzed the influence of laser energy on the biomodulation of inflammatory reactions and wound healing.^{19,22,27–29,30} Variations in wavelength, power levels, irradiation method, and exposure time may yield different results. Favorable effects on tissue repair were reported in some studies that used red lasers.¹⁹ In contrast, a meta-analysis of a large number of studies demonstrated better results in lesions irradiated with infrared lasers.²³ Also, a recent study reported improved results in lesions irradiated with a combination of different wavelengths.²²

One of the purposes of this study was to compare the effects of two wavelengths on the modulation of inflammatory reactions during wound repair ($\lambda = 685$ and $\lambda = 830$ nm). Laser power levels, as well as all other variables, were standardized according to the study method. Results were similar for the two wavelengths despite their different mechanisms of action on the cells.³¹

This study confirmed the hypothesis that LLLT promotes the early initiation and resolution of the inflammatory phase of tissue repair by making it more acute and severe and increasing collagen synthesis. No anti-inflammatory effect of LLLT was observed at 12, 36, or 72 h. In the groups analyzed at 72 h, tissue repair was more advanced. In the meloxicam group, the intensity of the polymorphonuclear infiltrate decreased at 36 h post-injury. Previous studies reported a similar decrease.^{32,33} Up to 36 h, the anti-inflammatory effect of LLLT was not the same as that of meloxicam. However, at 72 h, the polymorphonuclear infiltrate of the irradiated groups had a mean value similar to that of the group that received meloxicam, and lower values than those of the control group. Such findings suggest an earlier inflammatory recovery in the irradiated group than

in the control group. The analysis of hyperemia in this study showed that the laser promoted substantial vascular activation in the first 36 h of tissue repair. Specimens from the infrared and red laser groups examined at 12 and 36 h had the greatest mean values of hyperemia, which indicated an increase in local inflammatory reactions characterized by more intense vascularization. This suggests that the cardinal signs of inflammation were intensified, in contrast to previously reported findings of an anti-inflammatory effect of laser energy on this process.^{17,18} The vascular activation observed in our study can be also explained by the thermal effect of laser energy. However, several chemical mediators responsible for a series of local events, including vasodilatation, increased vascular permeability, chemotaxis of inflammatory cells, tissue destruction, and pain, are involved in the development of inflammatory reactions.^{5,7} The cardinal signs of tissue inflammation reflect the effects of cytokines on local blood vessels.^{5,34,35} The increase in IL-1 β mRNA levels in the initial phases of wound healing, as presented in this research, makes it clear that thermal effects alone do not cause vascular activation in irradiated wounds. Independently of the level of hyperemia, the level of vascularization was higher in the irradiated groups. Therefore, the inflammatory process was exacerbated, and this was important in obtaining improved results in the subsequent stages of wound healing.

The increase of IL-1 β mRNA levels in the specimens evaluated suggests an augmentation of the local inflammatory response by vascular activation and an increased number of inflammatory cells. In the initial stages of inflammation, cytokines as IL-1 and IL-6 are secreted by the cells of the tissue in which the inflammatory process occurs, predominantly by polymorphonuclear neutrophils.^{9–11} Thus, if the highest levels of proinflammatory cytokines are detected in damaged tissues, the number of neutrophils in the injured tissue will be increased, as will the local inflammatory reaction.^{5,7}

The relation between modulation of inflammatory reactions and analysis of IL-1 β levels has been corroborated in a past study.⁸ The authors observed an intense and rapid induction of higher levels of proinflammatory cytokine mRNA after cutaneous injury. The presence of IL-1 β was seen rapidly and at higher levels in animals not treated with anti-inflammatory drugs. In animals that received anti-inflammatory drugs, a reduction was seen in the expression of cytokines analyzed. In this study, at 36 and 72 h after soft-tissue injury, the animals treated with meloxicam had the lowest values of IL-1 β mRNA expression, suggesting an anti-inflammatory effect of meloxicam.

During wound healing, high levels of IL-1 α , IL-1 β , and TNF- α mRNA can be detected in macrophages and other

TABLE 1. AVERAGE VALUES OF IL-1 β mRNA EXPRESSION ($\mu\text{g/mL}$)

Group	12 hours	36 hours	72 hours	7 days
Control	0.155	0.7	11120	10910
Infrared laser	0.156	11355	5710	6032
Red laser	0.484	6505	1965	0.159
Meloxicam	1.92	3334	940	1090

mononuclear cells.⁸⁻¹¹ This fact may explain the maintenance of IL-1 β levels we found in our research, between 72 h and 7 days post-injury. The control group showed the highest levels of cytokines analyzed. A reduction in the inflammatory phase of wound healing in irradiated lesions can be explained by this fact (i.e., after 72 h the irradiated animals had decreased inflammatory reactions and increased proliferative reactions versus those of control animals).¹⁹⁻²³ In this study, the irradiated groups showed a better quality of wound healing than the control group and the group that received meloxicam. These results point to a beneficial biomodulating effect of LLLT on tissue repair, and confirms the findings of several other authors.^{18,19,21-23,27-29,36,37} However, anti-inflammatory effects of LLLT on wound healing were not confirmed in our research.

CONCLUSIONS

According to the results of this study, LLLT ($\lambda = 685$ and $\lambda = 830$ nm) used during the inflammatory phase of soft-tissue repair in rats does not reduce the inflammatory response, but it improves the quality of histologic repair.

Interleukin-1 β mRNA levels are a useful indicator of the intensity of inflammatory reactions, and the anti-inflammatory effects of meloxicam were thus confirmed.

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Address reprint requests to:
Dr. Rogério Miranda Pagnoncelli
6681 Ipiranga Avenue, Building 6, Room 209
90619-900 - Porto Alegre/RS, Brazil

E-mail: rogeriomiranda@correios.com.br