

Analgesic Effect of He-Ne (632.8 nm) Low-Level Laser Therapy on Acute Inflammatory Pain

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ABSTRACT

Objective: The aim of this study was to evaluate the analgesic effect of the low level laser therapy (LLLT) with a He-Ne laser on acute inflammatory pain, verifying the contribution of the peripheral opioid receptors and the action of LLLT on the hyperalgesia produced by the release of hyperalgesic mediators of inflammation. **Background data:** All analgesic drugs have undesired effects. Because of that, other therapies are being investigated for treatment of the inflammatory pain. Among those, LLLT seems to be very promising. **Material and methods:** Male Wistar rats were used. Three complementary experiments were done. (1) The inflammatory reaction was induced by the injection of carrageenin into one of the hind paws. Pain threshold and volume increase of the edema were measured by a pressure gauge and plethysmography, respectively. (2) The involvement of peripheral opioid receptors on the analgesic effect of the laser was evaluated by simultaneous injection of carrageenin and naloxone into one hind paw. (3) Hyperalgesia was induced by injecting PGE₂ for the study of the effect of the laser on the sensitization increase of nociceptors. A He-Ne laser (632.8 nm) of 2.5 J/cm² was used for irradiation. **Results:** We found that He-Ne stimulation increased the pain threshold by a factor between 68% and 95% depending on the injected drug. We also observed a 54% reduction on the volume increase of the edema when it was irradiated. **Conclusion:** He-Ne LLLT inhibits the sensitization increase of nociceptors on the inflammatory process. The analgesic effect seems to involve hyperalgesic mediators instead of peripheral opioid receptors.

INTRODUCTION

THE INFLAMMATORY PROCESS induces an increase in the sensitization of nociceptors to mechanical, thermal, or chemical stimulation, which it manifests as inflammation and pain.¹ Analgesic drugs with peripheral activity can act by two different mechanisms. One produces analgesia by preventing the sensitization of nociceptors^{2,3} through the use of drugs that inhibit the chemical mediators of the inflammation, such as cyclo-oxygenase inhibitors (COX).⁴

The other mechanism is by the direct blocking of the hyperalgesia.^{5–7} Opioids and drugs that promote an increase in nitric oxide act by this mechanism, through via L-arginine/nitric oxide/cyclic GMP.^{8,9}

All drugs cause undesirable side effects.^{4,9} Aspirin-like drugs frequently induce gastric or intestinal ulceration, and para-aminophenol may cause skin rash, and in a few isolated

cases neutropenia.¹⁰ Because of that, other therapies are being investigated for treatment of the inflammatory pain. Among those new treatments, the low level laser therapy (LLLT) seems to be very promising.

The therapeutic effect of the LLLT has been studied since the 1960s. Mester¹¹ showed in his pioneering work in 1966 that LLLT presented beneficial effects on tissue; since then, other researchers have found that LLLT affects tissue healing,^{12,13} anti-inflammatory action, and analgesic effects.^{16–19} Although different studies have shown the efficacy of that treatment, particularly of inflammatory pain, the mechanism by which radiation produces analgesia and anti-inflammatory effects remains elusive. Previous studies in the 1980s suggested that laser radiation could promote release of neurotransmitters, such as serotonin¹⁹ or β -endorphin.²⁰ Later, it was proposed that laser radiation could produce biomodulation of enzymatic, photochemical, and photophysical activities.²¹ Those works formed

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the theoretical basis for the development of many other studies that concluded that laser radiation produced the same analgesic and anti-inflammatory effects of drugs that inhibit cyclo-oxygenase (COX).^{14,17,22,23} Recent studies have suggested that radiation can interfere with the pituitary-hypothalamus-adrenal axis²⁴ or promote the increase of the NO synthesis.²⁵

The aim of the present study is to evaluate the analgesic effect of the LLLT with a He-Ne laser on acute inflammatory processes, investigating the contribution of the peripheral opioid receptors, and LLLT action on hyperalgesia produced by the release of hyperalgesic mediators during the inflammatory process.

MATERIAL AND METHODS

Animals

Seventy male Wistar rats, weighing between 170 and 190 g, were used throughout this study. Groups with seven animals each were formed.

Three different experiments were carried out. In the first, rats were separated into four equal groups and were studied. Analgesic and anti-edematogenic effects of the laser radiation were verified when a solution of carrageenin was injected in the rats.

To investigate how the laser radiation promotes the analgesia in an inflammatory process, the contribution of the peripheral opioid receptors was verified. Twenty-eight rats divided into four equal groups were also used for this second experiment.

The third experiment aimed at determining the laser radiation effect on pain threshold when an inflammatory process is absent; to achieve this goal, a metabolite from the arachidonic acid/cyclo-oxygenase that increases only the sensibility of nociceptors in an inflammatory process was used in the experiment. Two groups of seven rats each were studied. The experimental procedures were previously submitted and authorized by the Bioethics Council of Universidade do Vale do Paraíba (UNIVAP). The three experiments are described in detail below.

Radiation laser effect on the inflammation of rat paws. The inflammatory reaction was induced by an intraplantar (i.pl.) administration of 0.1 ml of sterile saline solution containing carrageenin (1 mg) into one of hind paws. The contralateral paw received the same volume of sterile saline solution (control paw).¹⁴

The pain threshold was measured using an Ugo Basile pressure gauge before carrageenin injection and 2, 4, and 6 h thereafter, following essentially the methodology described by Randall and Selitto.²⁶ Briefly, a force with increasing magnitude (16 g/s) was applied to the paw and the force (in grams) needed to induce the animal to withdraw its paw was considered to be the pain threshold.

The volume increase (edema) of paws up to the tibiotarsal articulation was measured plethysmographically before the injection of the irritant and 2, 4, and 6 h thereafter. Results were expressed as the percent increase of the paw volume when compared to the control one.

Evaluation of the contribution of peripheral opioid receptors to the analgesic LLLT (632.8 nm) effect. Saline solutions of carrageenin (0.1 mg) and naloxone ([Rhodia do Brasil, São

Paulo, Brazil]) 1 µg), a nonspecific opioid receptor antagonist, were simultaneously injected (0.1 ml of each) into one hind paw of the rats.²⁷ The pain threshold was measured before carrageenin and naloxone injections and 2, 4, and 6 h thereafter using an Ugo Basile pressure gauge.

Radiation laser effect on the hyperalgesia induced by prostaglandin E₂ (PGE₂). Hyperalgesia was induced by i.pl. administration of 0.1 ml of sterile saline solution containing PGE₂ (Marine colloids, 100 ng/paw) into the one hind paw. The pain threshold was measured before PGE₂ injection and 2, 4, and 6 h thereafter, using the same pressure gauge as before.⁸

He-Ne laser irradiation: laser parameters

A continuous wave He-Ne laser operating at the wavelength of 632.8 nm was used for stimulation. Laser parameters were: power of 12 mW with a spot size of 0.7 mm and irradiation time of 80 s, corresponding to an energy density of 2.5 J/cm². A noncontact probe was used for irradiation.^{17,23}

The paw was irradiated at the 1, 2, and 3 h after the induction of the inflammation or hyperalgesia.²⁴ The same procedure of laser irradiation was simulated for the control groups.

Data analysis

Mean and SEM values of the pain threshold or the increase of the paw volume were plotted as a function of time for all groups. Statistical evaluation of data was carried out by analysis of variance and sequential differences among mean values, according to Tukey contrast analysis at a level of $p < 0.05$.

RESULTS

Hyperalgesia and edema formation induced by the administration of carrageenin

Analgesic effect of He-Ne LLLT. Figure 1 shows the pain threshold as a function of time for the four groups: (i) injection of a saline solution; (ii) the same as before followed by a laser irradiation; (iii) a saline solution containing carrageenin being injected; and (iv) the same as the group before but rats received a treatment with low power laser irradiation. It can be observed that the i.p.l. injection of carrageenin caused a significant decrease in the pain threshold. The peak of hyperalgesia was achieved 4 h, after injection of the irritant. The LLLT analgesic effect presented a maximum after 4 h, with an increase of 95% of the pain threshold for the irradiated group. Mean values from the irradiated and control groups, when carrageenin was administered, were statistically different at the 0.1% level. Error bars in the figure stand for the SEM values of the data. Groups to which a saline solution was injected, both irradiated and nonirradiated, did not present with hyperalgesia.

Effect of LLLT (632.8 nm) on edema. The administration of a solution of carrageenin also induced an edematogenic response, as expected. Figure 2 shows the time evolution of the edema volume for rats with an i.p.l. injection of carrageenin, irradiated and nonirradiated with the He-Ne laser. The peak of the edema was observed 4 h after injection of the irritant and then the edema gradually decreased. The irradiation with LLL

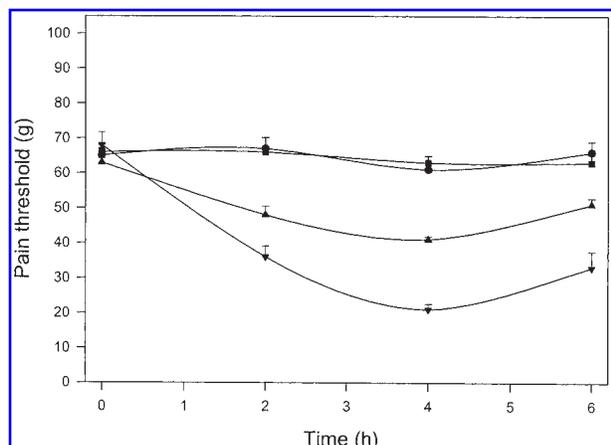


FIG. 1. Plot of the pain threshold as a function of time for rats after an i.p.l. injection of carrageenin, irradiated and control groups. Points and error bars represent mean and SEM values for seven rats per group, respectively. Only positive error bars were plotted to avoid superposition. Solid lines are used only to guide the eye. (■) Saline solution; (●) saline solution + laser; (▼) carrageenin; and (▲) carrageenin + laser.

produced a significant decrease on the edema volume. That reduction reached its maximum intensity between the second (38% difference) and fourth (35% difference) hours after the drug administration. The saline solution did not produce any detectable edema.

Effect of opioid receptors antagonists on the antinociceptive action of LLLT (632.8 nm)

Figure 3 plots the pain threshold as a function of time for the four groups: (i) injection of a saline solution containing naloxone; (ii) same as before with laser irradiation; (iii) injection of a mixture of naloxone and carrageenin, and (iv) the same as the group before; but the rats received a treatment with a He-Ne laser irradiation. The administration of naloxone, a nonspecific

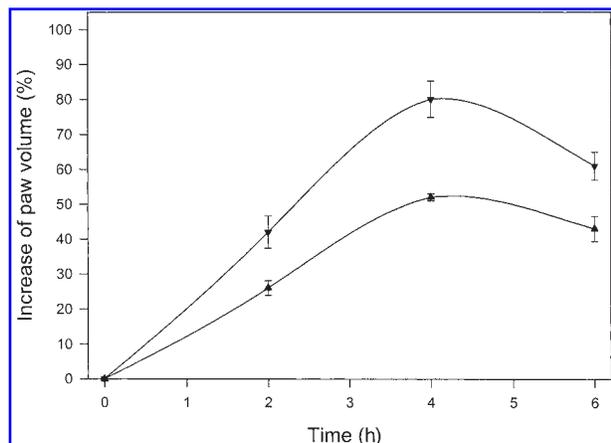


FIG. 2. Plot of the percent increase in paw volume versus time for the same rats in Fig. 1. Points and error bars represent mean and SEM values, respectively, for seven rats per group. Solid lines are only to guide the eye. (▼) Carrageenin and (▲) carrageenin + laser.

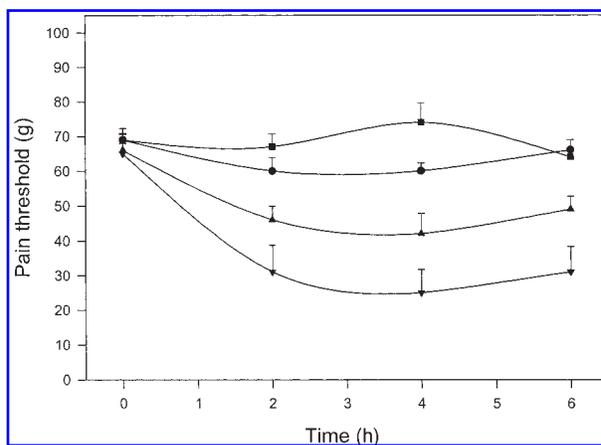


FIG. 3. Plot of the pain threshold as a function of time for rats with carrageenin and naloxone simultaneously injected. (■) Naloxone + saline solution; (●) naloxone + saline solution + laser; (▼) naloxone + carrageenin; and (▲) naloxone + carrageenin + laser.

opioid receptor antagonist, did not alter the analgesic effect of the LLLT, suggesting that the action of the laser on the inflammatory hyperalgesia did not involve a peripheral opioid receptor. The LLLT-induced analgesia was at maximum after 4 h, with an increase of 68% of the pain threshold for the irradiated groups. Mean values from the irradiated and control groups, to which naloxone and carrageenin were administered, were statistically different at the 0.1% level. Error bars in the figure stand for the SEM values of the data. The groups receiving naloxone and saline solution did not present with hyperalgesia, despite irradiation by the laser.

Analgesic effect of LLLT on hyperalgesia induced by PGE₂

PGE₂ is a hyperalgesic agent, a product of arachidonic acid/cyclo-oxygenase, that increases the sensitivity of nociceptors in an inflammatory process.²⁸ Figure 4 displays the pain threshold of the rat paw before and at 2, 4, and 6 h after an i.p.l.

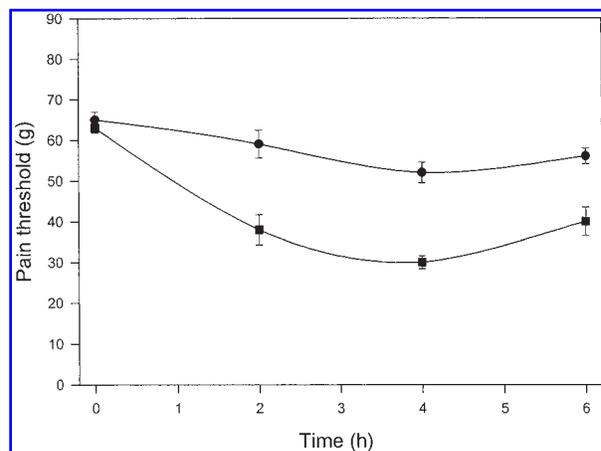


FIG. 4. Plot of the pain threshold in the rat paw as a function of time after an i.p.l. administration of PGE₂, for irradiated and control groups. (●) PGE₂ + laser; (■) PGE₂.

injection of PGE₂ (100 ng/paw). LLLT produces an analgesic effect in the hyperalgesia induced by PGE₂. The maximum effect is observed after 4 h, with a 73% increase on the pain threshold. Mean values from the irradiated and control groups are statistically different at the 0.1% level. Error bars in the figure stand for the SEM values of the data.

DISCUSSION

Acute inflammatory pain is a complex process that begins at the peripheral nociceptors. A greater understanding of the phenomenon of pain reduction by low-level laser therapy has been provided. Several types of low level lasers (He-Ne, Ga-Al-As) with different wavelengths and therapeutic regimens have been used, leading to difficulty in comparing the results and formulating a theory about their mechanisms of action.^{14,16,19}

At the present time, most of the studies are based on the photochemical and photophysical theories proposed by Karu.²¹ This photophysical theory suggests that laser radiation could produce analgesia acting on the K⁺ channel. On the other hand, Breitbart et al. concluded in their work that the He-Ne laser does not induce a photophysical effect, acting directly on the mitochondria without any effect on the cell membrane.²⁹

Data seem to indicate that LLLT presents an analgesic effect on the acute inflammatory hyperalgesia induced by carrageenin. Some studies suggest that the analgesic effect of LLLT may be due to the anti-inflammatory (anti-edematogenic) activity.^{14,17,22,23,30}

The wavelength of 632.8 nm has been found to be efficient for pain relief in osteoarthritis,^{17,22} indicating that the He-Ne LLLT could also be suitable for the present experiment. Dosages and drug administration methodology used throughout this study were those already reported as being the best for decreasing the edematogenic response induced by carrageenin into the rat paw.²⁴

Acute inflammatory pain begins with the excitation of the nociceptor (e.g., rapid and direct depolarization followed by spike activity and the induction of the action potential) induced by a noxious stimuli. The hyperalgesia that ensues upon tissue injury can be accounted by changes in the transduction sensitivity, responsiveness of the nociceptors, and recruitment of "silent" nociceptors. This modulation involves complex interactions among many substances derived from damaged tissue, immunocompetent cells, the vasculature, sympathetic terminals, and the nociceptors themselves.^{31,32}

Campana *et al.*²³ proposed that this anti-inflammatory effect of LLLT could be due to inhibition of the release of chemiotactic factors. Some other studies suggested that the LLLT acts by inhibition of COX. This hypothesis is supported by measurements of the PGE₂ levels before and after laser irradiation *in vitro*^{17,30} or by the comparison of the analgesic and anti-inflammatory actions of the laser and those promoted by drugs that inhibit the COX.

The analgesic effect that was found using a direct injection of PGE₂, could imply that the inhibition of the hyperalgesia is not due to COX inhibition, once there is not direct evidence of COX modulation *in vivo*; but could modify receptor coupling, second messenger generation/action, or even modulate the ionic channels directly. The partial analgesic effect could be

explained by the multitude of substances involved in nociceptor sensitization (bradykinin, serotonin, histamine, ATP, neuropeptides, noradrenaline).^{31,32}

Our data indicate that naloxone do not inhibit the partial analgesic effect of He-Ne LLLT, suggesting that peripheral opioid receptors are not involved. These findings are not in complete accord with the data of Honmura *et al.*¹⁴ using GaAlAs LLL and naloxone overdoses.

Honmura *et al.*¹⁴ found no anti-edematogenic effect in their work, using a single irradiation of Ga-Al-As LLL, which is in disagreement with our findings using a He-Ne LLL and three irradiations. We cannot exclude the possibility of the influence of vasoconstriction on our findings, but the literature does not support this view, on the contrary, it argues in favor of vasodilation and improvement in the blood flow after LLLT.^{33,34}

A comparison of our results to those reported by Albertini *et al.*²⁴ shows that laser radiation is as effective on decreasing the edematogenic response as the administration of a diclofenac drug. Although the sensitization of nociceptors was not verified by Albertini *et al.*, there is evidence that the analgesic effect of diclofenac is by direct blocking of the hyperalgesia through the L-arginine/nitric oxide/cyclic GMP pathway.⁵

CONCLUSION

In conclusion, results from this study indicate that irradiation with 2.5 J/cm² He-Ne LLL produces an analgesic and anti-edematogenic effect, when the laser is applied at 1, 2, and 3 h after the administration of carrageenin into the rat paw. It has also been demonstrated that the analgesic effect does not involve a peripheral opioid receptor, but involves later events of PGE₂ release during the acute inflammation.

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