Effect of low-level laser therapy on the initial stages of tissue repair: basic principles *

Ação da terapia com laser de baixa potência nas fases iniciais do reparo tecidual: princípios básicos

Juliana Aparecida de Almeida Chaves Piva[1]
Vanessa dos Santos Silva[2]
Elizângela Márcia de Carvalho Abreu[2]
Renata Amadei Nicolau[3]

Abstract: O objetivo do estudo foi realizar uma revisão de literatura a respeito da terapia com laser de baixa potência e sua relação com as fases iniciais de reparo. Foram analisados 22 artigos, observou-se a utilização de diferentes doses e comprimentos de ondas (632,8 a 904 nm). Nos estudos in vitro foram utilizadas doses entre 2,2 e 16 J/cm². A dose de 5 J/cm² tem sido apontada como responsável por mudanças significativas in vitro, porém a dose de 16 J/cm² promove efeito inibitório sobre o crescimento celular em culturas. Em estudos in vivo, envolvendo animais foram utilizadas doses entre 0,04 a 21 J/cm². Para estudos em humanos foram utilizadas doses entre 1,8 a 16 J/cm². Conclui-se que a terapia com laser de baixa potência exerce efeitos antiinflamatórios importantes nos processos iniciais da cicatrização: redução de mediadores químicos, de citocinas, do edema, diminuição da migração de células inflamatórias e incremento de fatores de crescimento contribuindo diretamente para o processo de reabilitação tecidual. Porém, a falta de padronização dificulta a escolha de parâmetros ideais.
Keywords: Fibroblast growth factors; Inflammation; Inflammation mediators; Laser therapy, Low-level; Lasers

Resumo: O objetivo do estudo foi revisar a literatura a respeito da terapia com laser de baixa potência e sua relação com as fases iniciais de reparo. Foram analisados 22 artigos, observando-se a utilização de diferentes doses e comprimentos de ondas (632,8 a 904 nm). Nos estudos in vitro, foram utilizadas doses entre 2,2 e 16 J/cm². A dose de 5 J/cm² tem sido apontada como responsável por mudanças significativas in vitro; porém, a dose de 16 J/cm² promove efeito inibitório sobre o crescimento celular em culturas. Em estudos in vivo, envolvendo animais, foram utilizadas doses entre 0,04 a 21 J/cm². Para estudos em humanos, foram utilizadas doses entre 1,8 a 16 J/cm². Conclui-se que a terapia com laser de baixa potência exerce efeitos anti-inflamatórios importantes nos processos iniciais da cicatrização: redução de mediadores químicos, de citocinas, do edema, diminuição da migração de células inflamatórias e incremento de fatores de crescimento, contribuindo diretamente para o processo de reabilitação tecidual. Porém, a falta de padronização dificulta a escolha de parâmetros ideais.
Palavras-chave: Fatores de crescimento de fibroblastos; Inflamação; Lasers; Mediadores da inflamação; Terapia a laser de baixa intensidade

Received on 10.08.2010.
Approved by the Advisory Board and accepted for publication on 30.11.2010.
* Work conducted at the Institute for Research and Development, Universidade Vale do Paraiba (IP & D – UNIVAP) - Sao Jose dos Campos (SP), Brazil.
Financial Support / *Suporte Financeiro*: Fellowship Program of Coordination for the Improvement of Higher Education Personnel - CAPES.
Conflict of interest: None / *Conflito Interesses: Nenhum*

[1] Specialist - M.Sc. student, Universidade do Vale do Paraiba - UNIVAP (University of Vale do Paraiba) - Sao Jose dos Campos (SP), Brazil.
[2] M.Sc. in Biomedical Engineering - Professor at Universidade Paulista – UNIP (Paulista University) - Sao Jose dos Campos (SP), Brazil.
[3] M.Sc. and PhD in Biomedical Engineering and Ph.D. in Basic Medical Sciences - Professor at Universidade do Vale da Paraiba (UNIVAP) - Sao Jose dos Campos (SP), Brazil.

INTRODUCTION

Clinical practice with low-level laser therapy (LLLT) has been investigated and employed for about 20 years. The growing interest in the effects of this therapy has been demonstrated by the significant amount of scientific publications in the area. However, researchers and therapists have questioned the clinical benefits of laser therapy due to divergent results in the literature caused by lack of methodological standardization in studies as well as by its clinical applicability, especially when it comes to using this resource in the early stages of tissue repair. [1-4]

The initial effects of laser interaction with biological tissue may cause the release of pre-forming substances such as histamine, serotonin, bradykinin and modify normal enzymatic reactions, accelerating or delaying these reactions and promoting an increase in ATP production. This leads to increased efficiency of the sodium-potassium pump; consequently, the difference in electric potential between the inside and outside of the cell is maintained with better results. [5]

The first stage of tissue repair is inflammation, which is essential to preserve the integrity of the organism. It involves an interaction between inflammatory cells (neutrophils, lymphocytes, monocytes/macrophages) and vascular cells (endothelial cells and smooth muscle). Initially, the inflammatory cells migrate to the target tissue by chemotaxis, induced by chemical mediators (histamine, prostaglandins - PGE2, leukotrienes - LTD4, interleukins - IL-1 and IL-6, nitric oxide - NO) that bind endothelial and cell receptors, stimulating an inflammatory response. [2]After that, there is activation of other mediators of lipid (eicosanoids) and peptide (cytokines, growth factors and neuropeptides) nature, externalization of adhesion proteins for leukocytes in endothelial cells on the surface of the membrane facing the lumen of the vessels. As a result of the trauma itself or cellular activation, the microenvironment has its physicochemical composition changed (low O_2 tension, decreased pH, presence of reactive nitrogen and oxygen species), which is another form of signaling that activates the cells involved in the process. [6]

LLLT has shown to be an anti-inflammatory alternative with effects similar to those observed in therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), inhibiting and/or decreasing the concentration of prostaglandin ES2 (PGE_2), cyclooxygenase 2 (COX2) and histamine. [7-9]

Mizutani et al. suggest that LLLT inhibits the arachidonic acid cascade in damaged tissue, leading to decreased production of PGE2. [10] Later, this phenomenon interferes with the production of bradykinin and many kinds of inflammatory cytokines. In addition, the increase in local blood flow improves acidosis and, simultaneously, promotes both the release and removal of substances related to pain.

Viegas et al. suggest that LLLT promotes early activation of the inflammatory phase in the tissue repair process, thus causing exacerbation of its signs. [11] This activation was due to substantial vascular activation in the first 36 hours of the repair process.

According to Gavish et al, LLLT has shown to reduce inflammation in a variety of clinical situations. [12] Their studies have shown that LLLT modifies some fundamental aortic aneurysm processes, progressively increasing matrix protein and smooth muscle cell proliferation, as well as secretion and expression of matrix metalloproteinase. Inhibition of gene expression of proinflammatory cytokine interleukin-1β from these cells was also observed.

Rocha Jr. et al. observed a greater amount of fibroblasts in irradiated cells, showing a significant increase in fibroblast proliferation and decreased inflammatory infiltrate, concluding that LLLT accelerates the process of tissue repair. [13]

Thus, LLLT seems to be able to modulate inflammation in various tissues. Also, it has advantages, since it is a noninvasive, nonpharmacologic method with a low rate of side effects. [3,7,8] Therefore, this study aims to review the publications of the last 14 years in order to provide scientific foundation for the use of low-power laser radiation in processes that assist tissue healing in the initial phase.

MATERIALS AND METHODS

The material used was obtained by researching scientific papers in databases such as Medline, Lilacs and Scielo. We selected publications dating from 1995 to 2009. In order to perform the search, we used a combination of the following keywords: low-level laser, inflammation, chemical mediators, growth factors.

RESULTS

We analyzed 22 articles, according to the data shown in table 1. We observed that the areas studied varied a lot, no matter whether the studies were *in vitro* or *in vivo* (animal or human). We found relevant differences regarding the area of study and irradiation parameters (wavelength and dose used). The objects of study varied from cells such as monocytes, macrophages and fibroblasts to membranes, mucosa, diabetic and skin wounds, cartilage, tendons, muscles, fluids such as human blood, organs and arteries.

Graphs 1 and 2 show that *in vivo* studies corre-

spond to approximately 74% of the total. Of this percentage, 76.5% were conducted in animals (5.9% rabbits, 70.6% rats) and only 23.5% were conducted in humans. As for *in vitro* studies, they correspond to 26% of the studies surveyed.

Among the studies analyzed, we found that different wavelengths (no. = 12) ranging from 632.8 to 904 nm were used. The most widely used wavelength was 830 nm, when compared separately. As for spectral range, the most used was that between 632.8 and 685 nm, *lasers* in the red range of the electromagnetic spectrum.

The effects found were slightly different, varying according to the area studied, model and wavelength. The effect was classified as positive (+), negative (-) or null. Positive effect corresponds to anti-inflammatory action, negative effect corresponds to proinflammatory action and null effect corresponds to no change or significant effect. Among the main positive (+) effects presented in Table 1 are reduction of pro-inflammatory cytokines (TNF-α, IL-6, IL-2) and chemical mediators such as PGE2 and increase in growth factors (bFGF, IGF-1).

Doses of 2.2, 5.0, 6.32 and 16 J/cm² were used in *in vitro* studies, and the dose of 5 J/cm² did not cause any significant changes. However, when diabetic wounds and wound cells were irradiated with 16 J/cm², they suffered an inhibitory effect, presenting significant decrease in cell proliferation. Studies involving rats presented a greater variety of doses (0.04 to 21 J/cm²), with the dose of 7.5 J/cm² being the most employed. For studies in humans, doses of 1.8, 5.0, 8.7 and 16 J/cm² were used. For doses of 8.7 and 16 J/cm², the results were null. It was observed that different doses produced similar physiological results. The positive effect was evident, i.e., the anti-inflammatory effect of LLLT in the early stages of tissue repair. However, the wide variety of doses used demonstrates the lack of standardization of the studies and, consequently, the difficulty in comparing the results obtained.

DISCUSSION

To investigate the mechanism of action of laser on experimental edema (carrageenan), Albertini et al. conducted studies in rats with intact adrenal glands and in adrenalectomized rats, treated with diclofenac sodium and LLLT. [14] The doses that produced anti-inflammatory effect were 1 and 2.5 J/cm², reducing edema by 27% and 45.4%, respectively. The best result in terms of edema reduction was that obtained with irradiation 1 hour after inflammation induction. The energy density of 2.5 J/cm² produced anti-inflammatory effects similar to those produced by diclofenac sodium at a dose of 1 mg/kg. In adrenalectomized animals, LLLT failed to inhibit the edema, suggesting that low-level laser irradiation possibly exerts its anti-inflammatory effects, stimulating the release of adrenal corticosteroid hormones. In another study, Albertini et al. demonstrated that the edema was significantly smaller in the groups treated with LLLT, compared to the control group. [2] The percentage was 65.3% for the group treated with a wavelength of 660 nm and 54.5% for the 684-nm group compared with the control group 4 hours after induction of inflammation by carrageenan. A significant reduction of inflammatory cells in the irradiated groups was also demonstrated.

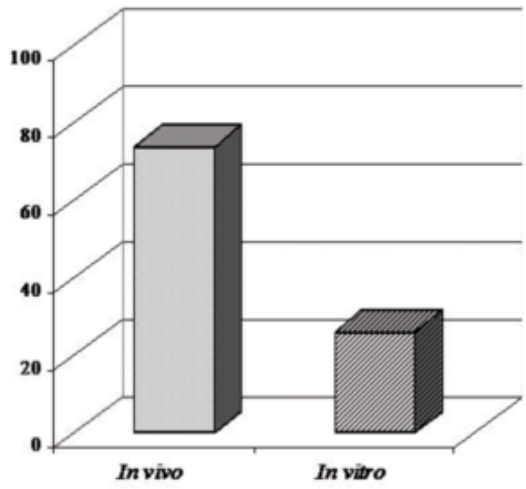
In their studies, Zhevago and Samoilova concluded that one of the major mechanisms responsible for the anti-inflammatory effects of LLLT is the decrease in the plasma level of proinflammatory cytokines (TNF-α, IL-6 and IL-2). [15]

Studies by Saygun et al. suggest that the biomodulation effects of LLLT may be associated with an increased production of growth factors such as bFGF and IGF-1. [16] These studies confirm the findings observed in Table 1, according to which the action of LLLT and its anti-inflammatory effects are directly related to reduction of pro-inflammatory cytokines, as well as the amount of chemical mediators. Other relevant items demonstrated by Albertini et al. were observed, such as decreased TNFα, IL-1β and IL-6 mRNA expression after laser therapy, both with wavelengths of 660 nm and 684 nm. [17] These results indicate that LLLT induces an inflammatory reaction that may modulate transcription factors linked to mRNA expression of proinflammatory cytokines. These data are corroborated by previous studies conducted by Nomura, Yamaguchi and Abiko, which suggest that laser therapy can reduce the production of inflammatory mediators and events that contribute to the inhibition of IL-1β. Studies by Aimbire et al. confirm these findings as they show that LLLT significantly reduced the levels of TNFα compared with the control group. [7] The authors suggest that the therapeutic potential of LLLT regarding the suppression of TNFα is necessary in various inflammatory diseases in internal medicine. They also highlight that it is important to note that this effect is highly dependent on the dose used.

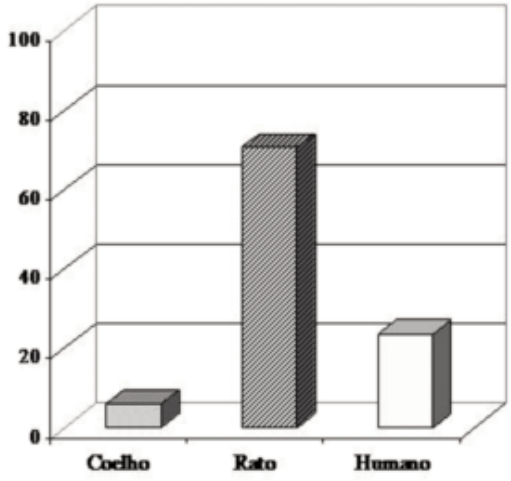
Fukuda and Malfatti reported that one of the most relevant aspects and main divergence is the dose. [19] A dose may be defined as the amount of radiation given to the tissue. Also, according to the authors, the ideal dose to be used should be based on the literature describing successful laboratory practices, in which it is estimated in accordance with the tissue to be irradiated, the energy absorbed for each

Table 1: Effect of LLLT on growth factors and chemical mediators related to the early stages of tissue repair

Area investigated	Growth factor / mediator	Model	Wavelength (nm)	Effect	Author(s) and year
Subplantar muscle	↓ edema, TNFα, IL-1β, IL-6, Citocine mRNA	Rat	660 and 684	+	Albertini et al.[17]
Subplantar muscle	↓ Kinin B2 Receptor mRNA	Rat	660 and 684	+	Bortone et al.[23]
Gastrocnemius muscle	↓ edema, ↓ number of leukocytes and polymorphonuclear cells	Rat	685	+	Barbosa et al.[24]
Monocytes and macrophages	↓ MCP-1, IL-1α, IL-1β, IL-6, IL-10; ↑ ON; TNFα.	*In vitro*	780	+ + Null	Gavish et al.[12]
Acute pleuritis	↓ protein, exudate, leukocytes, neutrophils, ON, MCP-1, IL-6, IL-10, TNFα.	Rat	660	+	Boschi et al.[25]
Gingival fibroblasts	↑ b FGF, IGF-1, IGFBP3, fibroblast proliferation	*In vitro*	685	+	Saygun et al.[16]
Surgical wounds	Pro-inflammatory cytokine mRNA IL-1α, IL-1β	Rat	685 and 830	Null	Viegas et al.[11]
Diabetic wounds	↓ IL-6	*In vivo-human*	632, 8	+	Houreld e Abrahamse[22]
Cells of diabetic wounds	↓proliferation and cell migration; ↑IL-6	*In vitro*		–	
Gastrocnemius muscle	↓ inflammatory cells	Rat	660 and 684	+	Albertini et al.[2]
Gums and labial mucosa	↓IL-1β, IFN-γ ↑PDGF, TGF-β TNF-α, bFGF	Rat	632,8	+ + Null	Safavi et al.[26]
Peritoneum	↓ células inflamatórias	Mouse	904	+	Correa et al.[8]
Surgical wounds	↑FGF	Rat	870	+	Rocha Jr et al.[13]
Human peripheral blood	↓ proinflammatory cytokines TNF-α, IL-6, IL-12 e IFN-γ; ↑ TGF-β	*In vitro*	340 and 480	+	Zhevago e Samoilova[15]
Lung	↓ TNFα	Rat	650	+	Aimbire et al.[7]
Achilles Tendonitis	↓ PGE2	Human	904	+	Bjordal et al.[27]
Gingival crevicular fluid	MMP-8, IL-1 and elastase	Human	635 and 830	Null	Qadri et al.[20]
Femoral artery	↑ adenosine, GH and FGF	Rabbit	904	+	Ihsan[28]
Subplantar muscle	↓ edema	Rat	650	+	Albertini et al.[14]
Orthopedic and rheumatologic diseases	↓ PGE2	Human	830	+	Mizutani et al.[10]
Gingival fibroblasts	IL-1β	*In vitro*	830	-	Nomura, Yamaguchi e Abiko[18]
Gingival epithelium	↓ PGE2	*In vitro*	830	+	Sakurai et al.[29]
Ear	↓histamines	Rat	632,8	-	Sakihama[9]



Graph 1: Percentage of studies conducted *in vitro* and *in vivo*



Graph 2. Percentage of studies conducted *in vivo*

tissue, irradiation time and size of the affected area. This data confirm a study by Qadri et al. in which it was observed that there were no changes in IL-1 or elastase, probably because more appropriate parameters were not used, as stated by the authors. [20] Still, with regard to dose, Correa et al. demonstrated that the best results with LLLT were obtained using a dose of 3J/cm², 24 hours after induction of inflammation by lipopolysaccharide (LPS) in the peritoneum of rats, with a reduction of 77% in neutrophils and 49% in leukocytes. [8]

LLLT also exerts a stimulatory effect on TGF-β and PDGF. It should be noted that stimulation of these growth factors is directly related to the repair process. In a study by Numata *et al*., specific aspects of wound healing were evaluated, which refer to macrophage infiltration, keratinocyte migration, angiogenesis, fibroblast and growth factor (bFGF), under the effect of histamine. [21] The authors found that, clinically, it is important to reduce the area of the lesion as quickly as possible in order to relieve stress and reduce the possibility of infection. Specifically, skin wound healing is a complex process, involving a series of overlapping events that include leukocyte recruitment, matrix deposition, epithelialization and, finally, resolution of the inflammation with formation of a mature scar. Normal wound repair includes a vigorous angiogenic response that delivers nutrients to the inflammatory cells and damaged tissue.

For Houreld and Abrahamse, the use of lasers to stimulate *in vivo* and *in vitro* healing of diabetic wounds and diabetic wound cells promoted cell migration and proliferation, stimulation of cytokine (IL-6) and fibroblasts (WS1). [22] The aim of the study was to determine the importance of proteases and growth factors in the regulation and equilibrium of the tissue repair process, which, according to the authors, if interrupted, may delay healing and lead to degradation, which is a characteristic of chronic wounds. Also according to the authors, cytokines are involved in all of the wound phases, from migration, proliferation, differentiation and cell metabolism to healing. In this study, the authors report that proper fluence of phototherapy stimulates IL-6 expression, cell proliferation and migration in cells of diabetic wounds. A fluence of 5 J/cm² stimulates the healing of diabetic wounds *in vitro,* whereas a fluence of 16 J/cm² is inhibitory. The authors believe that laser parameters can be optimized and standardized and the underlying mechanisms better understood. According to them, phototherapy can become a safe alternative for the treatment and healing of wounds of slow evolution, such as those in patients with diabetes.

In their studies, Bortone et al. used laser on experimental edema (carrageenan) to promote an inflammatory process in the subplantar muscle of rats. After laser therapy, they found that there was a decrease in B2 kinin receptors mRNA expression when using both wavelengths of 660 nm and 684 nm. Their results suggest that the expression of both kinin receptors is modulated by LLLT, possibly contributing to its anti-inflammatory effect.[23]

Barbosa et al. reports the effect of LLLT on the formation of edema and leukocyte influx caused by the venom of the jararacussu snake *(Bothrops jararacussu)* in rats. The site of injury was irradiated with a wavelength of 685nm and a dose of 4.2J/cm². A combined therapy including LLLT and serum was also

studied. The results showed that LLLT significantly reduced edema formation by 53% and 64% in 3 and 24 hours, respectively, and in reduced accumulation of neutrophils ($P < 0.05$). The combined therapy was more effective than the therapy used separately. In conclusion, LLLT significantly reduced edema and leukocyte influx in the muscle being studied, suggesting that LLLT should be considered as a potential therapeutic approach for the treatment of local effects of the Bothrops species. [24]

Boschi et al. investigated the possible effects of LLLT in the modulation of pro-inflammatory and anti-inflammatory mediators in rats with pleurisy. Inflammation was induced by carrageenan injected into the pleural cavity. A continuous wave (20 mW) of laser diode with a wavelength of 660 nm was used in four groups employing different doses and forms of treatment 1, 2 and 3 hours after inflammation induction. A group received a single dose of 2.1 J, and other three groups received a total energy of 0.9, 2.1 and 4.2 J. Subsequently, the volume of exudate, differential and total leucocytes, concentration of protein, NO, IL-6, IL-10, TNF-alpha and MCP-1 were measured from the aspirated liquid. The results showed that LLLT in a wavelength of 660 nm significantly reduced the volume of exudate, inducing an anti-inflammatory effect characterized by differential or total inhibition of leukocyte influx, exudation, total proteins, NO, IL-6, MCP-1, IL-10 and TNF-alpha in a dose-dependent mode. That is, laser treatment with 2.1 J was more effective than 0.9 and 4.2 J [25]

The effect of LLLT on the gene expression of mediators in the mucosal tissues and gingiva of rats was investigated by Safavi et al. Of the two groups studied, one group received irradiation twice with an interval of 24 hours, while the inflamed tissues in the other group were irradiated three times with He-Ne laser with a wavelength of 632.8 nm and dose of 7,5 J/cm^2 for 300s. It was noted that the gene expression of IL-1beta and IFN-gamma was significantly inhibited in both groups, while the gene expression of PDGF and TGF-beta significantly increased. These findings suggest that LLLT decreases the amount of inflammation and accelerates the wound healing process, altering the expression of genes responsible for the production of inflammatory cytokines. [26]

In another study, Bjordal et al. investigated the effects of LLLT in a group of seven individuals with Achilles tendinitis; a total of 14 tendons were studied. The individuals had their symptoms deliberately aggravated before starting treatment. The treatment was performed in two stages. First, they were treated with LLLT with a wavelength of 904 nm and 5.4 J per site, with a power density of 20 mW/cm^2 and then placebo LLLT (0 J) was administered to both Achilles tendons. After treatment, the authors observed that the concentrations of prostaglandin E2 were significantly reduced 75, 90 and 105 minutes after active LLLT, compared with the concentrations before treatment ($p = 0.026$) and after treatment with placebo LLLT ($p = 0.009$). According to patients' reports, pressure pain threshold had increased significantly ($p = 0.012$) after active LLLT compared to placebo LLLT: the mean difference in terms of change between the groups was 0.40 kg/cm^2 (95% confidence interval, 0.10 to 0.70). The authors suggest that the therapeutic potential of LLLT at a dose of 5.4 J per site can reduce acute pain and inflammation of Achilles tendinitis. They conclude that LLLT has a great potential in the treatment of diseases with an inflammatory component. [27]

In order to evaluate the effectiveness of LLLT in microcirculation and collateral circulation of a clogged blood vessel, Ihsan treated 34 rabbits with a wavelength of 904 nm and power of 10 mW and compared the findings with those of two rabbits in a control group. An incision was performed on the medial part of the thigh of each rabbit, and the femoral artery was exposed and ligated. The blood samples collected from the femoral artery were examined to determine the levels of growth hormones, adenosine and fibroblast growth factor. Tissue samples of the site of operation, i.e., the artery and its surrounding muscle fibers, were sent for histopathological examination to determine the fiber/capillary ratio (F/C) and capillary diameter. The results indicated that collateral circulation was accelerated and that microcirculation was enhanced with the use of LLLT. Moreover, the author concluded that there was normalization of the functional characteristics of the injured area. [28]

For Sakurai et al., the use of LLLT stimulated the production of prostaglandin E2 and cyclooxygenase-2 in human gingival fibroblasts. The aim of this study was to determine the effect of laser irradiation on the production of PGE2, cyclooxygenase (COX) -1 and COX-2, and gene expression from stimulation of LPS (lipopolysaccharide) in *in vitro* cells of human gingival fibroblasts (HGF). HGF cells were prepared from healthy gingival tissues and stimulated with LPS. Diode laser (Ga-Al-As) was irradiated at a wavelength of 830 nm on the HGF cells. Irradiation with LLLT significantly inhibited PGE2 production in a dose-dependent way, which led to a reduction of COX-2 mRNA levels. In conclusion, a low level of laser irradiation inhibited PGE2 by LPS on the HGF cells by reducing COX-2 mRNA level. The findings suggest that LLLT can be a beneficial therapy against the aggravation of gingivitis and periodontitis by bacteri-

al infection. [29]

In short, LLLT has shown to be able to modulate inflammation in various tissues and presents some advantages such as its noninvasive, non-pharmacologic nature and low rate of side effects, both in diabetic and healthy individuals. [1,3,4,7,8]

CONCLUSION

After investigating the literature, it is possible to conclude that LLLT exerts important anti-inflammatory effects early in the wound healing process. For instance, it reduces chemical mediators (PGE2, histamine), cytokines (IL-1, IL-2, IL-6, IL -10, TNFa), migration of inflammatory cells (leukocytes, neutrophils) and edema and increases the amount of growth factors (FCF, bFGF, IGF-1, IGFBP3), thus contributing directly to the process of tissue rehabilitation. However, the lack of standardization complicates the choice of parameters to be used in its application. ❑

REFERENCES

1. Rabelo SB, Villaverde AB, Nicolau R, Salgado MC, Melo Mda S, Pacheco MT. Comparison between wound healing in induced diabetic and nondiabetic rats after low-level laser therapy. Photomed. Laser Surg. 2006;24:474-9.
2. Albertini R, Villaverde AB, Aimbire F, Salgado MA, Bjordal JM, Alves LP, et al. Anti-inflammatory effects of low-level laser therapy (LLLT) with two different red wave lengths (660 nm and 684 nm) in carrageenan-induced rat paw edema. J Photochem Photobiol B. 2007;89:50-5.
3. Dall Agnol MA, Nicolau RA, de Lima CJ, Munin E. Comparative analysis of coherent light action (laser) versus non-coherent light (light-emitting diode) for tis sue repair in diabetic rats. Lasers Med Sci. 2009;24:909-16.
4. Medeiros JL, Nicolau RA, Nicola EM, dos Santos JN, Pinheiro AL. Healing of Surgical Wounds Made with lambda970-nm Diode Laser Associated or Not with Laser Phototherapy (lambda 655 nm) or Polarized Light (lambda 400-2000 nm). Photomed Laser Surg. 2010;28:489-96.
5. Rocha JCT. Terapia laser, cicatrização tecidual e angiogênese. Rev Bras Promoção Saúde. 2004;17:44-8.
6. Balbino CA, Pereira LM, Curi R. Mecanismos envolvidos na cicatrização: uma revisão. Braz J Pharm Sci. 2005;41:27-51.
7. Aimbire F, Albertini R, Pacheco MT, Castro-Faria-Neto HC, Leonardo PS, Iversen VV, et al. Low-Level Laser Therapy Induces Dose-Dependent Reduction of TNF Levels in Acute Inflammation. Photomed Laser Surg. 2006;24:33-7.
8. Correa F, Martins RABL, Correa JC, Iversen VV, Joenson J, Bjordal JM. Low-Level Laser Therapy (GaAs =904 nm) Reduces Inflammatory Cell Migration in Mice with Lipopolysaccharide-Induced Peritonitis. Photomed Laser Surg. 2007;25:245-9.
9. Sakihama H. Effect of a helium-neon laser on cutaneous inflammation. Kurume Med J. 1995;42:299-305.
10. Mizutani K, Musya Y, Wakae K, Kobayashi T, Tobe M, Taira K, et al. A Clinical Study on Serum Prostaglandin E2 with Low-Level Laser Therapy. Photomed Laser Surg. 2004;22:537-9.
11. Viegas VN, Abreu ME, Viezzer C, Machado DC, Filho MS, Silva DN, et al. Effect of Low-Level Laser Therapy on Inflammatory Reactions during Wound Healing: Comparison with Meloxicam. Photomed Laser Surg. 2007;25:467-3.
12. Gavish L, Perez LS, Reissman P, Gertz SD. Irradiation with 780 nm Diode Laser Attenuates Inflammatory Cytokines but Upregulates Nitric Oxide in Lipopolysaccharide-Stimulated Macrophages: Implications for the Prevention of Aneurysm Progression. Lasers Surg Med. 2008;40:371-8.
13. Rocha Jr AM, Oliveira RG, Farias RE, Andrade LCF, Aarestrup FM. Modulação da proliferação fibroblástica e da resposta inflamatória pela terapia a laser de baixa intensidade no processo de reparo tecidual. An Bras Dermatol. 2006;81:150-6.
14. Albertini R, Aimbire FS, Correa FI, Ribeiro W, Cogo JC, Antunes E, et al. Effects of different protocol doses of low power gallium-aluminum-arsenate (Ga-Al-As) laser radiation (650 nm) on carrageenan induced rat paw ooedema. J Photochem Photobiol B. 2004;74:101-7.
15. Zhevago N, Samoilova K. Pro-and Anti-inflammatory Cytokine Content in Human Peripheral Blood after Its Transcutaneous (in Vivo) and Direct (in Vitro) Irradiation with Polychromatic Visible and Infrared Light. Photomed. Laser Surg. 2006;24:129-39.
16. Saygun I, Karacay S, Serdar M, Ural AU, Sencimen M, Kurtis B. Effects of laser irradiation on the release of basic fibroblast growth factor (bFGF), insulin like growth factor-1 (IGF-1), and receptor of IGF-1 (IGFBP3) from gingival fibroblasts. Lasers Med Sci. 2008;23:211-5.
17. Albertini R, Villaverde AB, Aimbire F, Bjordal J, Brugnera A, Mittmann J, et al. Cytokine mRNA expression is decreased in the subplantar muscle of rat paw sub jected to carrageenan-induced inflammation after low-level laser therapy. Photomed Laser Surg. 2008;26:19-24.
18. Nomura K, Yamaguchi M, Abiko Y. Inhibition of interleukin-1beta production and gene expression in human gingival fibroblasts by low-energy laser irradiation. Lasers Med Sci. 2001;16:218-23.
19. Fukuda TY, Malfatti CA. Análise da dose do laser de baixa potência em equipamentos nacionais. Rev Bras Fisioter. 2008;12:70-4.
20. Qadri T, Miranda L, Tunér J, Gustafsson A. Theshort-term effects of low-level lasers as adjunct therapy in the treatment of periodontal inflammation. J Clin Periodontol. 2005;32:714-9.
21. Numata Y, Terui T, Okuyama R, Hirasawa N, Sugiura Y, Miyoshi I, et al. The Accelerating Effect of Histamine on the Cutaneous Wound-Healing Process Through the Action of Basic Fibroblast Growth Factor. J Invest Dermatol. 2006;126:1403-9.
22. Houreld N, Abrahamse H. Irradiation with a 632.8 nm Helium-Neon Laser with 5 J/cm² stimulates Proliferation and Expression of Interleukin-6 in Diabetic Wounded Fibroblast Cells. Diabetes Technol Ther. 2007;9:451-9.
23. Bortone F, Santos HA, Albertini R, Pesquero JB, Costa MS, Silva JA Jr. Low level laser therapy modulates kinin receptors mRNA expression in the subplantar muscle of rat paw subjected to carrageenan-induced inflammation. Int Immunopharmacol. 2008;8:206-10.
24. Barbosa AM, Villaverde AB, Guimarães-Souza L, Ribeiro W, Cogo JC, Zamuner SR. Effect of low-level laser therapy in the inflammatory response induced by Bothrops jararacussu snake venom. Toxicon. 2008;51:1236-44.
25. Boschi ES, Leite CE, Saciura VC, Caberlon E, Lunardelli A, Bitencourt S, et al. Anti-Inflammatory Effects of Low-Level Laser Therapy (660 nm) in the Early Phase in Carrageenan-Induced Pleurisy in Rat. Lasers Surg Med. 2008;40:500-8.
26. Safavi SM, Kazemi B, Esmaeili M, Fallah A, Modarresi A, Mir M. Effects of low-level He-Ne laser irradiation on the geneexpression of IL-1 , TNF- , IFN- , TGF- , bFGF, and PDGF in rat's gingival. Lasers Med. Sci. 2007;23:331-5.
27. Bjordal JM, Lopes-Martins RAB, Iversen VV. A randomised, placebo controlled trial of low level laser therapy for activated Achilles tendinitis with microdialysis measurement of peritendinous prostaglandin E2 concentrations. Br J Sports Med. 2006;40:76-80.
28. Ihsan FRM. Low-Level Laser Therapy Accelerates Collateral Circulation and Enhances Microcirculation. Photomed Laser Surg. 2005;23:289-94.
29. Sakurai Y, Yamaguchi M, Abiko Y. Inhibitory effect of low-level laser irradiation on LPS-stimulated prostaglandin E2 production and cyclooxygenase-2 in human gingival fibroblasts. Eur J Oral Sci. 2000;108:29-34.

MAILING ADDRESS / ENDEREÇO PARA CORRESPONDÊNCIA:
Juliana Aparecida de Almeida Chaves Piva
Av. Shishima Hifumi, 2911- Urbanova
12244 000 São José dos Campos - SP, Brazil
Phone.: (12) 3947-1000
E-mail: juliana.piva@yahoo.com.br

How to cite this article/*Como citar este artigo*: Piva JAAC, Abreu EMC, Silva VS, Nicolau RA. Effect of low-level laser therapy on the initial stages of tissue repair: basic principles. An Bras Dermatol. 2011;86(5):947-54.