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Original Article

Features of Cellular and Molecular Mechanisms of Regulation of Reparative Processes in Chronic Wounds Using Photobiomodulation Therapy

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Abstract

Introduction: Treatment of chronic wounds is an urgent worldwide problem for medicine. Among the many efforts in wound healing techniques, photobiomodulation therapy has shown promising results.

Aim: To study the effect of photobiomodulation therapy on optimisation of the regulation of reparative processes in chronic wounds by cytokines (through the example of interleukin-1β, tumour necrosis factor-alpha, interleukin-6, interleukin-4, interleukin-10, and granulocyte macrophage colony stimulating factor).

Materials and methods: The study involved 12 Wistar rats. A trophic wound was modelled in the animals. After the operation, the animals were divided into two groups of 6 animals each. The wound defects of animals in the experimental group were exposed to low-intensity laser radiation. Photobiomodulation therapy was applied once a day for 5 days, starting the day after wound modelling. The device Lika-therapist M (Ukraine) was used in a continuous mode at a wavelength of 660 nm, an output power of 50 mW, and an energy density of 1 J/cm^2, and 60 s exposure time.

Results: The study showed the following changes in the expression of intercellular mediators in the blood serum of animals with chronic wounds when using photobiomodulation therapy: a decrease in the levels of interleukin-1β ($p>0.05$) and tumour necrosis factor-alpha ($p<0.05$); increased concentrations of interleukin-4 ($p<0.05$); the concentrations of interleukin-6, granulocyte macrophage colony stimulating factor, and interleukin-10 were not significantly changed. The histological study showed better organization of collagen fibers in the experimental group.

Conclusions: Photobiomodulation therapy can be an instrument for optimizing the reparative process by correcting the regulation by intercellular mediators.

Keywords

collagen, cytokines, rats, wound healing

INTRODUCTION

Treatment of chronic wounds is an urgent worldwide problem for medicine. The rise in the incidence and prevalence of chronic wounds, in the aging population[1], the economic costs of treating long-term non-healing wounds[2], the threat of antibiotic resistance and undesired side effects of pharmaceuticals[3] necessitate the development of new and more cost-effective treatments for chronic wounds. Among the many efforts in wound healing techniques, photobiomodulation (PBM) therapy, also known as low-level laser therapy (LLLT), has shown promising results. It may be applied in a wide range of treatments including wound healing, inflammation, and pain reduction.[4] However, the cellular-molecular mechanisms underlying tissue repair using low-intensity laser radiation are still not well understood.

Physiological regulation of skin wound healing is a process that depends on many types of cells and mediators interacting in a very complex time sequence. Dysregulation can lead to delayed wound healing.[5] Wound healing usually goes through the phases of hemostasis, inflammation, proliferation, and remodelling. The effectiveness of healing processes is largely determined by the balance of pro-inflammatory and pro-regenerative signals mediated by cytokines.[6] Low-intensity laser radiation can significantly induce the production of cytokines, such as growth factors, interleukins, and various macromolecules.[7] Investigation of the effect of PBM therapy on the processes of chronic wound repair at cellular and molecular level will improve the understanding of the signalling pathways by which the immune system controls the wound healing process. This knowledge can contribute to the development of standardized protocols for the treatment of patients with long-term non-healing wounds, providing a possibility to use the entire therapeutic potential of the method.

AIM

The aim of the present study was to investigate the effect of photobiomodulation therapy on optimisation of the regulation of reparative processes in chronic wounds by cytokines (through the example of interleukin-1β (IL1β), tumour necrosis factor-alpha (TNFα), interleukin6 (IL6), interleukin4 (IL4), interleukin10 (IL10) and granulocyte macrophage colony stimulating factor (GMCSF)).

MATERIALS AND METHODS

Animals and wound surgery

The study involved 12 white Wistar rats weighing 250±30 g at the age of 9 months. The experiments were carried out in accordance with the principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) and the General Principles of Animal Experiments, approved by the First National Congress on Bioethics (Kiev, 2001). The experimental study was conducted after approval by the Bioethical Committee of Kharkiv Medical Academy of Postgraduate Education.

A trophic wound was modelled in animals, with the reproduction of conditions of local hypoxia and microcirculation disorders.[8] The animals were depilated, then the skin was excised with surgical scissors to the superficial fascia in the form of a circle with a diameter of 20 mm in the proximal part of the back of rats. Then, a purse string suture was used along the edges of the wound to create a picture of circulatory disorders which would reduce the normal blood supply in the area of the simulated trophic wound. The fascial cutaneous nodes were sutured to hold the edges of the wound and prevent their convergence. On the surface of the bottom of the formed wound, the superficial fascia was dissected with transverse and longitudinal, mutually perpendicular incisions, which formed cells measuring 5×5 mm to create a picture of trophic changes not only in the skin but also in a part of the superficial fascia, as well as underlying tissues. The operations were performed under general anesthesia (mononarcosis with zoletil at a rate of 10 mg/kg body weight). The wound remained open throughout the experiment.

After the operation, the animals were randomly divided into two groups of 6 animals each. Wound defects of animals in the experimental group were exposed to low-intensity laser radiation, and the wounds of control animals were sham irradiated. The animals were removed from the experiment after 28 days. They were euthanized by inhalation of chloroform in a confined space. Day 28 was chosen to study the repair processes at the remodelling stage at the standard wound closure time for all the animals.

PBM

PBM therapy was administered once a day for 5 days, starting the day after wound modelling. The device Lika-therapist M (Ukraine) was used in a continuous mode at a wavelength of 660 nm, an output power of 50 mW, an energy density of 1 J/cm², and exposure time of 60 seconds. The laser tip was held perpendicular to the surface of irradiated tissue. The distance from the head of radiator to the wound was so chosen as to radiate the entire area of the wound. The parameters of the photobiomodulation therapy was chosen according to the results of the analysis of previously published studies.[9-11]

The effectiveness of PBM therapy in wound healing was evaluated using planimetric methods, cytokine level studies, and histologic studies.

Measurement of wound area

To assess the dynamics of wound area reduction, digital macrophotography of the wound surface was performed.

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The area of the wound surface was measured in photographs using the ImageJ software (NIH, USA). The relative area of the wounds (S) was calculated by the following formula:

$$S=St/So\times100\%$$

where So is the area of the wound immediately after its application, and St is the area of the wound surface at a given healing period.

Studies of the cytokine levels were carried out by enzyme-linked immunosorbent assay (ELISA) in the blood serum of animals. Blood for laboratory tests was taken from the heart. The levels of IL1β, TNFα, IL4, IL6, and IL10 were determined using reagent kits Vector-Best (Russia). The GMCSF level was determined using the eBioscience kit (USA). All studies were carried out according to the manufacturer's protocols.

Histological evaluation

For histological evaluation, a skin flap with a wound area was taken. Histology of the skin was performed in samples fixed in 10% neutral formalin, and then dehydrated in increasing strengths of alcohol (50°, 70°, and twice 96°), then alcohol with chloroform was used, then chloroform, followed by paraffin embedding.[12] Five-to-seven-micron-thick sections were stained with hematoxylin and eosin, or picric acid/acid fuchsin, following the Van Gieson's method. The sections were visualized using a Primo Star microscope (Carl Zeiss). Photomicrographs of the preparations were obtained using a Microocular digital camera (magnification ×400).

Statistical analysis

Statistical analysis of results was performed using Statistica 6.0. To describe the results, the data were presented as M±SE, where M is the arithmetic mean, SE is the standard error of the arithmetic mean. The significance of differences between groups (statistical significance) was determined using the non-parametric Kruskal-Wallis ANOVA test for independent samples. Differences were considered statistically significant at $p<0.05$.

RESULTS

The concentration of cytokines in the blood serum of animals of the experimental and control groups are presented in **Table 1**.

The study showed the following changes in the expression of intercellular mediators in the blood serum of animals with chronic wounds when using photobiomodulation therapy: a decrease in the levels of IL1β ($p>0.05$) and TNFα ($p<0.05$); increased concentrations of IL4 ($p<0.05$); concentrations of IL6, GMCSF, and IL10 were not significantly changed.

Histological examination showed that after 28 days, the wounds in all animals were completely epithelialized, the epidermis was not uniform in thickness in different areas of the wound. The formation of hair follicles and sebaceous glands was observed from the periphery of the wound defect to the center. At the same time, in the control group, the rounded central part of the wound remained without hair, while in the experimental group only a narrow scar remained. Wound defects in animals of both groups were filled with mature connective tissue. In the control group, areas of maturing granulation tissue with a moderate number of thin-walled vessels and single hemorrhages were detected (**Fig. 1**). In the experimental group of animals, a

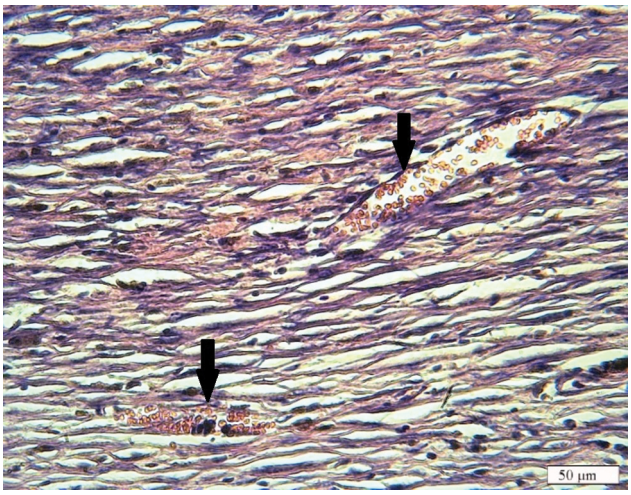

Figure 1. The site of the wound in the control group of animals after 28 days: maturing granulation tissue with capillary vessels (arrows) (magnification ×400). H&E stain.

Table 1. Cytokine levels in animal groups

Groups of animals	Indices					
	IL-1β pg/ml	TNF-α pg/ml	IL-6 pg/ml	GM-CSF pg/ml	IL-4 pg/ml	IL-10 pg/ml
Control	3.233±0.307	3.402±0.266	12.670±3.021	1.815±0.122	3.588±0.275	218.861±37.748
Experimental	2.011±0.583	2.257±0.058*	12.828±0.935	1.187±0.057	4.878±0.324*	190.384±28.666

* $p<0.05$ in comparison with the control group at 28 days

greater thickness and packing density of collagen fiber bundles were noted (**Fig. 2**).

The results of measuring the relative area of the wound surface in animals whose wounds were exposed to low-intensity laser radiation and in animals that did not receive PBM therapy are presented in **Table 2**.

DISCUSSION

Patients with chronic wounds have elevated levels of many cytokines, including IL1β, TNFα, IL6, in addition to GCSF and GMCSF. At the same time, an increase in the concentrations of pro-inflammatory IL1β is an independent predictor of the presence of chronic wounds.[13] Cytokine modulation is one of the main mechanisms by which PBM improves wound healing.[14]

In a previous study, we found an increase in the IL1β levels on days 3 and 7 in the group of animals receiving PBM therapy compared with the control group.[15] In the present study, however, on day 28, this result was reversed, and the group of animals with PBM showed lower levels of IL1β. The PBM of the parameters used is likely to induce the release of IL1β in the inflammatory focus at the initial stages of wound healing. IL1β is capable of acting on endothelial cells as well as regulating inflammation-induced angiogenesis.[14] The increase in IL1β levels induced by PBM in the early (inflammatory) phase of wound healing and the decrease in this cytokine in the remodelling phase may be related to this pro-angiogenic effect. As capillaries recover, IL1β decreases. These data are confirmed by histological studies. Skin samples in the control group showed incomplete angiogenesis (**Fig. 1**). While the histological preparations of the experimental group showed mature connective tissue.

TNFα is an acute-phase protein responsible for triggering a cascade of other cytokines. This pro-inflammatory cytokine in the early phase of wound healing increases the vascular permeability and suppresses the inflammatory process by recruiting inflammatory cells to the site of infection.[14] In the present study, PBM reduced TNFα levels in the experimental group. While low levels of TNFα may promote wound healing, higher levels, especially over an extended period of time, inhibit

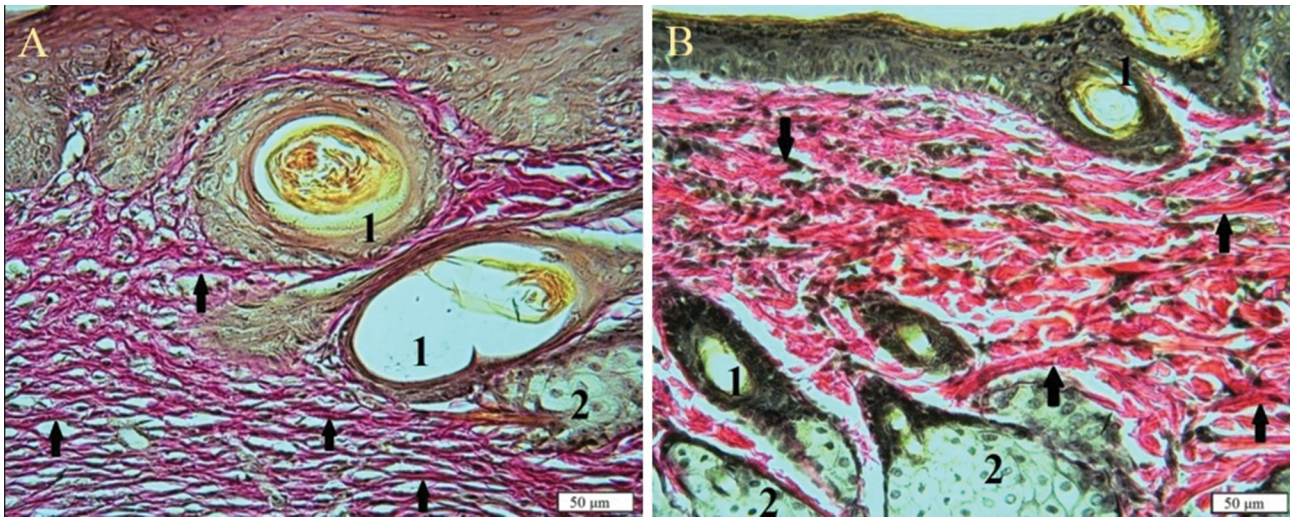

Figure 2. Areas of wounds in rats after 28 days: the formation of hair follicles (**1**) and sebaceous glands (**2**), bundles of collagen fibers (arrows) are thinner (**A**) in the control group and significant in thickness (**B**) in the experimental group (magnification ×400). Van Gieson's stain.

Table 2. Changes in the relative area of the wound surface

Groups of animals	Day										
	3	5	7	10	12	14	16	18	21	24	28
Relative area of wound surface in the control group, %	93.2±1.9	83.8±2.6	79.1±2.9	65.7±1.9	56.6±1.4	43.6±4.3	25.3±3.8	17.5±2.5	7.4±1.7	6.1±1.5	0
Relative area of wound surface in the experimental group, %	83.6±2.6	77.5±2.2	71.2±1.8	70.4±2.2	66.5±2.1	60.2±2.7	51.2±2.0	35.1±2.6	14.9±0.5	3.8±1.4	0

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the wound healing process.[16] Since IL1β and TNFα are mutual inducers, a decrease in the level of IL1β when using PBM may also be due to a decrease in the level of TNFα.

The decrease in IL1β and TNFα levels observed in our work indicates a strong anti-inflammatory effect of laser radiation at the systemic level. Also, a decrease in the concentration of these cytokines with the use of PBM therapy helps to reduce fibrosis. According to the literature, coordinated overexpression of IL1β and TNFα receptors can maintain fibrogenic phenotypes of hypertrophic scars.[17]

IL6, which is a key modulator of the inflammatory and reparative process, can also increase scarring after injury.[18,19] In our study, despite the anti-inflammatory effects of PBM therapy[20], IL6 levels did not change. This is possibly related to the complex pleiotropic function of IL6 in skin disorders.[19]

There are few studies in the literature on the effect of PBM therapy on the levels of the studied cytokines during the healing of chronic wounds at the stage of remodelling. A significant decrease in the concentration of TNFα and IL6 in the blood serum of patients with pressure ulcers was shown when using laser therapy (wavelength 658 nm) for a month.[21]

In our study, administration of PBM therapy showed a tendency to a decrease in the levels of GM-CSF known as hematopoietic growth factor and immunomodulator. The literature data on the role of this pleiotropic cytokine in wound healing are contradictory. Inhibition of GM-CSF has been shown to be beneficial in animal studies of many hyperinflammatory conditions.[22] In another study, higher systemic levels of GM-CSF are associated with faster healing of venous ulcers after multilayer compression therapy.[23]

Inhibition of proinflammatory cytokines balances the expression of anti-inflammatory cytokines such as IL4 and IL10 which are essential for the wound healing process. However, many details remain elusive due to the enormous complexity of synergistic and competitive cytokine signalling. The downward trend in anti-inflammatory cytokine IL10 levels observed in our study with PBM appears to be associated with pleiotropic and sometimes contradictory effects of IL10. IL10 appears to be a potent negative feedback regulator that influences the control and resolution of inflammation.[24] IL10 also has a protective effect against excessive collagen deposition associated with scarring when stimulated with profibrotic agents.[25] But long-term IL10 exposure may contribute to fibrotic outcomes, although they are significantly beneficial in the early stages of inflammation wound healing.[24]

Like IL10, IL4 is also involved in tissue repair. In mice, interleukin4α (IL4Rα) receptor-dependent macrophage activation controls the assembly of collagen fibrils. In mice lacking the IL4Rα receptor, skin wound healing is slowed down and vascular stability is impaired.[26]

The observed increase in the concentration of anti-inflammatory cytokine IL4 in the experimental group, apparently, is associated with the anti-inflammatory effect of low-intensity laser radiation and compensatory reactions that occur in response to a decrease in the levels of pro-inflammatory cytokines when exposed to PBM therapy at this stage of healing. As well as the ability of PBM to modulate extracellular matrix remodelling in the late stages of wound healing, although the effects of laser therapy may be discrete or even clinically imperceptible.[27] Histological studies confirm this assumption. In our study, at the remodelling stage, we showed better collagen structuring in a group of animals after laser therapy. Also, the formation of hair follicles and sebaceous glands from the periphery of the wound defect to its center took place faster. The literature describes that the use of low-intensity laser radiation promotes accelerated maturation of collagen and a significant increase in collagen deposition.[28] Similar results showing changes in collagen biosynthesis in the late stages of skin repair in rats under the influence of 670 nm diode laser radiation are presented in the work of Medrado et al. It has been suggested that maturation of collagen fibers and neoangiogenesis persist even 60 days after skin surgery.[29]

An important predictor of wound healing is the assessment of changes in the time course of the wound surface.[30] In our previous study, we showed a reduction in the time of wound healing when using PBM therapy in the initial healing phases.[15] However, in the present study, despite the positive effects of laser therapy (an increase in collagen deposition, cytokine modulation), there were no statistically significant differences in the area of wound contraction, compared with the same indicator in the animals of the control group. Perhaps the applied radiation parameters were not optimal for our complex wound model. Similar results were obtained by de Loura Santana C. On day 3 in the laser groups, the area of damage was significantly smaller compared to that of the control group. Beginning on day 8, there were no statistically significant differences in the lesion area between groups until day 22.[31] Other studies reported results in which laser therapy did not shorten wound healing time.[32,33] However, the variety of parameters and methodologies used in these studies does not allow comparison of the results obtained and indicates the need to standardize the use of photobiomodulation therapy.

Further studies are needed to study the effect of photobiomodulation therapy on regeneration processes, to analyse the relationship between radiation parameters and the subsequent effect on healing processes at all levels of organisation and at all phases of chronic wound healing.

CONCLUSIONS

Photobiomodulation therapy can be used as an adjunct in the treatment of long-term non-healing wounds.

Histological studies have shown that the use of PBM therapy contributes to a greater thickness and density of packing of collagen fiber bundles in animals of the experimental group.

In this study, we characterized the levels of IL1β, TNFα, IL4, IL6, IL10, GMCSF to provide a theoretical basis for the development of treatments for non-healing wounds. The results obtained indicate that the use of PBM therapy can promote wound healing by reducing TNFα levels and increasing IL4.

Further research in this area evaluating the expression of cytokines will help to elucidate the biological events associated with the action of PBM in wound healing.

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Особенности клеточно-молекулярных механизмов регуляции репаративных процессов при хронических ранах с помощью фотобиомодуляционной терапии

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Резюме

Введение: Лечение хронических ран является актуальной мировой проблемой медицины. Среди многих попыток заживления ран фотобиомодуляционная терапия показала многообещающие результаты.

Цель: Изучить влияние фотобиомодуляционной терапии на оптимизацию регуляции репаративных процессов при хронических ранах цитокинами (на примере интерлейкина-1β, фактора некроза опухоли-альфа, интерлейкина-6, интерлейкина-4, интерлейкина-10 и гранулоцитарно-макрофагальный колониестимулирующий фактор).

Материалы и методы: В исследовании приняли участие 12 крыс линии Wistar. У животных моделировали трофическую рану. После операции животные были разделены на две группы по 6 голов в каждой. На раневые дефекты животных опытной группы воздействовали низкоинтенсивным лазерным излучением. Фотобиомодуляционную терапию применяли 1 раз в сутки в течение 5 дней, начиная со следующего дня после моделирования раны. Прибор Lika-therapist M (Украина) использовали в непрерывном режиме при длине волны 660 nm, выходной мощности 50 mW, плотности энергии 1 J/cm², и времени воздействия 60 s.

Результаты: Исследование показало следующие изменения экспрессии межклеточных медиаторов в сыворотке крови животных с хроническими ранами при применении фотобиомодуляционной терапии: снижение уровня интерлейкина-1β ($p>0.05$) и фактора некроза опухоли-альфа ($p<0.05$); повышение концентрации интерлейкина-4 ($p<0.05$); концентрации интерлейкина-6, гранулоцитарно-макрофагального колониестимулирующего фактора и интерлейкина-10 существенно не изменились. Гистологическое исследование показало лучшую организацию коллагеновых волокон в опытной группе.

Заключение: Фотобиомодуляционная терапия может быть инструментом оптимизации репаративных процессов за счет коррекции регуляции межклеточными медиаторами.

Ключевые слова

коллаген, цитокины, крысы, ранозаживление