

# HE-NE LOW LEVEL LASER THERAPEUTIC APPLICATIONS FOR TREATMENT OF ACUTE IRIDOCYCLITIS

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**Summary.** This investigation is carried out in two groups of patients with acute anterior uveitis (acute iridocyclitis). In every group, there were included 20 eyes. In the first group, eyes were irradiated every day during a ten-day-period with He-Ne low level laser (Mediray 04, Optella Ltd., Sofia, Bulgaria) at emission wavelength of 632 nm and power density 0,1 mW/cm<sup>2</sup>. Second group was used as a control. In both groups, there was applied standard anti-inflammatory treatment of iridocyclitis in equal number of applications of the following: Tobradex, Ophthalar, Midrum, antibiotics drugs per os and non-steroid anti-inflammatory drugs per os, Dexamethazone para bulb. We observed significant suppression of the inflammatory reaction, stronger decrease of the ciliary flush, photophobia, epiphora, faster disappearance of the fibrinous exudate and posterior synechiae in the anterior chamber, as well as faster disappearance of the keratic precipitates, in the treated by low-level laser therapy (LLLT) eyes. For irradiated eyes by LLLT, we have found that the healing period is shortened significantly by 40 % ( $p < 0,001$ ). Our results revealed that LLLT application is appropriate and perspective for acute iridocyclitis treatment.

**Key words:** *low level laser therapy, acute iridocyclitis, inflammatory reaction, eyes.*

## INTRODUCTION

**U**veitis is the third leading cause of preventable blindness in the developed world. Most ophthalmologists are not trained in the diagnosis and treatment of difficult to control uveitis. Iritis is inflammation predominantly located in the iris of the eye. Inflammation in the iris is more correctly classified as anterior uveitis. The ciliary body can also be inflamed and this would then be called iridocyclitis [1].

Causes of anterior uveitis can be related to autoimmune disorder (juvenile rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome, ulcerative colitis,

psoriasis, sarcoidosis), infections (syphilis, tuberculosis, herpes zoster, herpes simplex, adenovirus), malignancy (masquerade syndrome-retinoblastoma, leukemia, lymphoma, malignant melanoma), trauma, gout, idiopathic or other [2].

Acute iridocyclitis is usually unilateral and is characterized by a history of pain, photophobia, epiphora, blurring of vision, a red eye (circumcorneal flush) without purulent discharge, and a small, variably irregular shaped pupil. The presence of keratic precipitates on the posterior surface of the cornea as well as flare and cell in the anterior chamber can be seen with the slit lamp [2].

Low-level laser therapy (LLLT) – also known as cold or soft laser, used for bio-stimulation, or photobiomodulation – is an emerging therapeutic approach in which cells or tissue are exposed to low-levels of red and near – infrared light from lasers. It might either stimulate or (less likely) inhibit cellular function, leading to reduction of cell and tissue death, improved wound healing, increasing repair of damage to soft tissue, nerves, bone, and cartilage, and relief for both acute and chronic pain and inflammation [3].

Low-energy laser irradiation produces significant bioeffects. These effects are manifested in biochemical, physiological and proliferative phenomena in various enzymes, cells, tissues, organs and organisms [4].

After burning the corneas with alkali, without stimulating the regeneration, some authors (5) find out that in the front epithelium and the stroma of the cornea the activity of lactatdehydrogenase, malatedehydrogenase, glutamatdehydrogenase, and glucose-6-phosphate-dehydrogenase is sharply reduced, and at the same time the activity of flavin-dependent succinatdehydrogenase is increased, which was estimated as a protective adaptation phenomenon which helps the tissues preserve their viability in extreme conditions, and conduces to decrease the deficiency of macroenergy compounds.

It was established that after a chemical burn of the cornea, the activity of some phosphatases – adenosinetriphosphatase, was permanently decreased [6], and the activity of other phosphatases – the acidic phosphatase, varies within certain limits [7].

## **MATERIALS AND METHODS**

Inflammation of the uveal tract has many causes and may involve one or all three portions (iris, ciliary body and choroids) simultaneously. The most frequent form of uveitis is acute anterior uveitis (also termed as iridocyclitis acuta). A randomized study was carried out which included 34 patients (40 eyes) with active acute iridocyclitis. The patients were divided into two groups each including 20 eyes. The first group included idiopathic acute anterior uveitis (8 eyes), sarcoidosis (2 eyes), herpes simplex (2 eyes), juvenile rheumatoid arthritis (2 eyes), and one eye each of tuberculosis, Crohn's disease, ankylosing spondylitis, Behcet's, Reiter's syndrome, Fuchs heterochromic.

The second group included idiopathic acute anterior uveitis (8 eyes), herpes simplex (3 eyes), Reiter's syndrome (2 eyes), and one eye each of juvenile rheumatoid arthritis, ankylosing spondylitis, Fuchs heterochromic, tuberculosis, Crohn's disease, Behcet's, sarcoidosis.

Both groups included patients with acute iridocyclitis with the following symptoms: painful red eye, ciliary flush, marked photophobia, epiphora, posterior synechiae. Slit lamp showed anterior chamber reaction manifested by inflammatory cells, flare (protein leakage), keratic precipitates, fibrinous exudate in the anterior chamber. In cases with acute herpes simplex keratoiridocyclitis, the test with fluorescent stain was applied to rule out corneal abrasion and herpes simplex dendrite. In both groups, visual acuity was investigated.

For the investigation, there was applied a new ophthalmologic system for bio-stimulation and LLL therapy of eye diseases based on the He-Ne laser (Mediray 04, Optella Ltd., Sofia, Bulgaria) with emission wavelength of 632 nm. The system has an opportunity to regulate the size of the laser spot and laser power density from 0,05 to 0,4 mW/cm<sup>2</sup>. The apparatus is developed in Bulgaria by the authors K.Koev, V. Tanev, L. Avramov. The system is compact, portable and with minimal optical losses and high reliability. The device is convenient in exploitation, both for the patients and for the treating personnel. In the first group, eyes are irradiated every day during ten days with Mediray 04 with power density 0,1 mW/cm<sup>2</sup>. Second group is used as a control. In both groups, there was applied standard anti-inflammatory treatment of iridocyclitis in equal number of applications of the following: Tobradex, Ophthalar, Midrum, antibiotics drugs per os and non-steroid anti-inflammatory drugs per os, Dexamethazone para bulb.

## RESULTS

We observed a significant suppression of the inflammatory reaction, stronger decrease of the ciliary flush, photophobia, epiphora, faster disappearance of the fibrinous exudate and posterior synechiae in the anterior chamber, as well as faster disappearance of the keratic precipitates in the treated by low-level laser therapy (LLLT) eyes. For irradiated eyes by LLLT, we have found that the healing period is shortened significantly by 40 % ( $p < 0,001$ ).

In cases with acute keratoiridocyclitis herpetica, treated with LLLT, fluorescein colorization disappearance and earlier epithelization setting was observed.

In the group with combined LLLT best-corrected visual acuity improved in 20 eyes, of which in 19 eyes (95%) attained final visual acuity was better than or equal to 0,3, mean 0,5.

No improvement in visual acuity was seen in one eye with Behcet's. In the control group, the final corrected visual acuity was mean 0,1.

The combined LLLT with Tobradex, Ophthalar, Midrum, antibiotics *per os* and non-steroid anti-inflammatory *per os*, Dexamethazone *para bulb* showed significant additional effect on the recovery rate. (Table1).

**Table 1.** Time needed for recovery in dependence on treatment procedure applied in the case of acute iridocyclitis therapy

Group number	Treatment applied	Average days for recovery
1	Tobradex, Ophthalar, Midrum, antibiotics <i>per os</i> and non-steroid anti-inflammatory <i>per os</i> , Dexamethazone <i>para bulb</i> and LLLT	13,4±0,7
2	Tobradex, Ophthalar, Midrum, antibiotics <i>per os</i> and non-steroid anti-inflammatory <i>per os</i> , Dexamethazone <i>para bulb</i>	22,3±0,5

## DISCUSSION

From the results obtained during this investigation we could ascertain the fact that the combined treatment with the best effect on the patients with acute iridocyclitis was obtained in group one using Tobradex, Ophthalar, Midrum, antibiotics *per os* and non-steroid anti-inflammatory drugs *per os*, Dexamethazone *para bulb* and LLLT. This combination led to earlier disappearing of the inflammatory reaction, in comparison with the control group.

The combined laser treatment shows significant additional effect on the recovery rate.

The mechanisms of positive influence of LLLT are not completely understood. There are various local and systemic medico-biological processes that take place under the influence of LLLT. The action of laser light of optimal parameters has normalizing influence bringing to the total rising of adaptive potential and to the acceleration of treatment. Initial phase of any biological and clinical effect of LLLT is the absorption of quantum energy by biotissues with induction of primary photophysical and photochemical processes. The process of absorption is influenced by the optical properties of the biological object and the parameters of laser irradiation [8].

There exists a strong relationship, first, between light parameters and biostimulation effects on a cellular level, and second, between the moment of irradiation and limits of magnitude of biostimulation effects. Systemic studies with cells clearly indicate that such parameters of light as wavelength, fluence, and intensity play the most important roles in both stimulation and inhibition of cellular metabolism [9, 10].

When the iris is inflamed, white blood cells (leukocytes) are shed into the anterior chamber of the eye where they can be observed on slit lamp examination floating in the convection currents of the aqueous humor. These cells can be counted and form the basis for rating the degree of inflammation. These cells can

accumulate and cause adhesion (posterior synechiae) between the iris and the lens. It is important to make the diagnosis early and to dilate the pupil to prevent the formation of permanent posterior synechiae related to glaucoma [11].

The first law of photobiology states that for low-power visible light to have any effect on a living biological system, the photons must be absorbed by electronic absorption bands belonging to some molecular chromophore or photoacceptor. Cytochrome c oxidase, a subunit in the mitochondrial electron-transport chain, may play a role as a primary photoacceptor in mammalian cells since it has absorption bands up to 1000 nm [12].

Experimental studies on animals and *in vitro* conditions provide evidence that 633 nm laser light can enhance wound healing. Rigau et al., [13] studied the effects of the 633 nm laser on the behaviour and morphology of a primary fibroblast culture after a central scratch of 0.4-1mm and two irradiations were performed. The effect of the wounding and laser irradiation was studied using colony formation (formation of colonies in the central zone of the wound or on the edge of the scratch), haptotaxis (change of orientation of the edge cells) and chemotaxis-chemokinesis (movement or migration of cells across the wound). The number and intensity of colony formation, the haptotaxis of the edge fibroblasts and the fibroblasts present in the centre of the scratch were rated and the irradiated and non-irradiated controls compared. The group concluded that structural changes like colony formation, haptotaxis and chemotaxis-chemokinesis appear sooner in LLLT irradiated cultures than in non-treated controls. They also confirmed that LLLT induced fibroblast biological effects.

Low-intensity laser therapy is recognized as an effective therapeutic method by the FDA, particularly to improve tissue healing [14]. A large body of evidence from *in vitro* and *in vivo* studies has suggested that LLLT enhances collagen synthesis, increases the motility of keratinocytes, releases growth factors, and promotes the transformation of fibroblasts into myofibroblasts [15]. On the other hand, the idea of investigating the early phase of the skin repair process under the influence of anti-inflammatory agents (a corticosteroid or a cyclooxygenase (COX-2) inhibitor) is based on the known pharmacological properties of such drugs and on their broad clinical use and side-effects [14].

Studies have shown that during normal wound healing the inflammatory phase lasts up to two days [16]. Cell proliferation, epithelization, granulation tissue formation, and wound contraction occur during the proliferative phase. Growth of new epithelial cells across the surface of the wound and collagen remodeling occur during the maturation phase of wound healing, which lasts for months or even longer. The present results showed that He-Ne laser irradiation of the skin of mice produced beneficial effects on the macroscopic aspects of the surgical wound, such as reduction of humidity, apparent vascular modulation and effective control of the amount of clot in the injured area, during the first 24 h [17]. These data therefore, suggest that laser therapy increased the healing dynamics compared to control.

Similar results were obtained by [18] in diabetic rats, showing that laser-treated animals healed faster and better than controls. Other studies [19] using He-Ne low-energy laser have indicated that it is mainly the laser energy at 633 nm wavelength that affects the healing dynamics, producing changes in the early phase of the repair process, i.e. the inflammatory phase.

The suggestion that laser affects the early events in the dynamics of wound healing was partially based on the observed low-intensity laser therapy-induced attenuation of reactive oxygen species production by neutrophils in inflammatory models. This was initially suggested by another study where a diminished oxidative stress-induced apoptosis of neutrophils in acute inflammation is described [20]. Nevertheless, the basic aspects of oxidative stress and the mechanisms by which reactive oxygen species modulate physiological and pathological processes, with emphasis on wound healing, are still motive of debate.

It is well known that corticosteroids down-regulate pro-inflammatory proteins and affect gene expression, interfering with almost all phases of the inflammatory process. On the other hand, controlled laboratory trials have reported that laser photostimulation can reduce inflammation through inhibition of inducible COX-2, leading to a reduction in prostanoid levels. Additionally, experiments involving various cell culture stages have shown that laser irradiation at early stages significantly stimulates cell proliferation, alkaline phosphatase activity and osteocalcin gene expression, indicating that laser photostimulation enhances bone formation in vitro [21].

Authors [22] determined that the effects of helium-neon laser irradiation on wound healing dynamics in mice treated with steroidal and non-steroidal anti-inflammatory agents. They made the following experiment: male albino mice, 28-32 g, were randomized into 6 groups of 6 animals each: control (C), He-Ne laser (L), dexamethasone (D), D + L, celecoxib (X), and X + L. D and X were injected *im* at doses of 5 and 22 mg/kg, respectively, 24 h before the experiment. A 1 cm long surgical wound was made with a scalpel on the abdomens of the mice. Animals from groups L, D + L and X + L were exposed to  $4 \text{ J (cm}^2\text{)}^{-1} \text{ day}^{-1}$  of He-Ne laser for 12 s and were sacrificed on days 1, 2, or 3 after the procedure, when skin samples were taken for histological examination. They observed a significant increase of collagen synthesis in group L compared with C ( $168 \pm 20$  vs  $63 \pm 8 \text{ mm}^2$ ). The basal cellularity values on day 1 were: C =  $763 \pm 47$ , L =  $1116 \pm 85$ , D =  $376 \pm 24$ , D + L =  $698 \pm 31$ , X =  $453 \pm 29$ , X + L =  $639 \pm 32 \text{ U/mm}^2$ . Their results show that application of L increases while D and X decrease the inflammatory cellularity compared with C. They also show that L restores the diminished cellularity induced by the anti-inflammatory drugs. The authors suggest that He-Ne laser promotes collagen formation and restores the baseline cellularity after pharmacological inhibition, indicating new perspectives for laser therapy aiming to increase the healing process when anti-inflammatory drugs are used.

In two of the observed cases with keratoiridocyclitis herpetica of group one where LLLT treatment was applied, a decrease of the dendritic lesions was wit-

nessed in comparison to those cases with non-LLLT treatment. In cornea, colored lesions were found, as in the most cases they appeared in the form of tree branches. In similar previous investigations, we have found out that in patients with keratitis herpetica dendritica in the group treated with He-Ne laser irradiation combined with Pandavir and Acyclovir the earliest answer reaction observed was inflammation suppression and perifocal edema disappearance. Eyes treated only with Acyclovir present mean time of improvement, as the fluorescein colorization disappearance and epithelization setting is observed. Similar results were obtained on the eyes treated in double combination, Pandavir and Acyclovir. The best effect was obtained by the triple combination: Pandavir, Acyclovir and He-Ne laser (statistically proved), with the lowest mean time of improvement [23].

The combined treatment with Tobradex, Ophthalar, Midrum, antibiotics *per os* and non-steroid anti-inflammatory drugs *per os*, Dexamethazone *para bulb* and LLLT, is revealed as an efficient method for eye therapy of acute iridocyclitis. Thus the combination with He-Ne laser has strong additive effect, assuring total healing of the affected eyes with pronounced shortening of the mean duration of the disease. These excellent results most probably are related to the conjunction of the drugs and laser irradiation influences. Besides, LLLT has a stimulating regeneration effect.

**The therapeutic method proposed as a combination of medicaments and LLLT is a new alternative for treatment of acute iridocyclitis .**

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