LOW LEVEL LIGHT THERAPY IN OPHTHALMOLOGY

EFFECTS AND RESULTS OF AN INNOVATIVE TECHNOLOGY

Report by
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Introduction

Low-level light therapy (LLLT) has gained attention in recent years as a novel tool for therapeutic applications in a variety of medical conditions. Low-level light therapy (LLLT) using red to near-infrared light energy has been used as a new scientific approach with therapeutic applications in ophthalmology. The ongoing therapeutic revolution spearheaded by LLLT is largely propelled by progress in the basic science fields of photobiology and bioenergetics. Photoneuromodulation of cytochrome oxidase is the primary photoacceptor of light in the near-infrared region of the electromagnetic spectrum. It is also a key mitochondrial enzyme for cellular bioenergetics, especially for nerve cells in the retina.

Recent research is reviewed that supports LLLT potential benefits in retinal disease. LLLT has potential significant applications against retinal damage by counteracting the consequences of mitochondrial failure[30].

LLLT was effective in controlling the corneal conditions and the degree of inflammation in DED. Such findings may suggest therapeutic effects of LLLT on DED. After LLLT, the amount of tear volume was increased, and corneal surface irregularities were restored. Also, the number of neutrophils and the level of inflammatory cytokines significantly decreased as well.

Inflammation in particular is thought to be the major cause of DED. When there are damages on the ocular surface and tear film, a chain inflammation reaction begins in a way that inflammatory cytokines are generated from the activated inflammatory cells. This may result in a destruction of lacrimal glands and impairment of conjunctival epithelium[1,2]. Considering that controlling the inflammation is crucial in treating patients, many options have been chosen to accomplish the goal. Low level light (laser) therapy (LLLT) has been widely used recently not only to reduce inflammation but also to relieve pain, without complications. LLLT is non-invasive, non-ablative and only requires a short period of time to treat the symptoms. It is effective in promoting contractions of untreated wounds, suggesting an indirect effect on surround tissues[3,4]. Currently there are a number of studies reported regarding the use of low-level light on different eye conditions:

- **Tear volume measurements** – the tear volume was significantly decreased.
- **Corneal surface irregularities** – the corneal irregularities gradually recovered.
- **Corneal staining scores** – Fluorescein staining of the cornea was significantly increased.
- **The effect of LLLT on the lacrimal gland** - LLLT in dry eye treatment group showed reduced number of neutrophils.
- **The effect of LLLT on inflammatory cytokines expression** - Immunohistochemistry showed the level of inflammatory cytokines in the lacrimal gland. The expressions of IL-1β, IL-6α, and TNF-α were increased.

Discussion

DED is a multifactorial disease with complex patho-physiological process, which hinders patients' quality of life through various symptoms. Numerous treatment options are currently available for DED and some of the treatments involve many side effects, which can worsen the conditions[5].

LLLT is one of the known methods to treat DED with no side effects reported so far, and so this study aimed to confirm the effects of LLLT in vivo on DED mouse model[31]. LLLT in dry eye group showed significant increase of tear volume after 17 days, with the recovery of corneal surface irregularities and decrease in corneal surface irregularities and decrease in corneal fluorescein scores. In addition, the degree of desquamation and the number of detached epithelial cells decreased after LLLT, showing the increased density and epithelial tissue stabilization. The activation of neutrophils is a complex process involving sequential phases with different signaling mediators[7], and such phases can recruit neutrophils at damages tissues in various conditions such as autoimmune diseases like Sjogren's syndrome or even radioactive treatments[8]. IL-6α and TNF-α are the major factors affecting dry eye related inflammation and LLLT may reduce inflammation through controlling the level of TNF-α in its mechanism[9,10].LLLT is effective in reducing TNF-α expression and controlling the degree of inflammation[11,12]. The LLLT was considered effective in treating DED, increasing tear volume, improving corneal surface irregularities and symptom scores, alleviating inflammation through decreasing the levels of neutrophils and inflammatory cytokines such as IL-1β, IL-6α, and TNF-α[31].

Effects of LLLT in Ophthalmology

Treatment of MGD often involves application of heat to the eyelids, using warm compresses, with or without lid massage to melt the abnormal meibum and facilitate its re-entry into the tear film[13].

Sustained heat from the level of the Meibomian glands to the posterior portion of the eyelid is highly important. The melting point of Meibomian gland secretions ranges from 32°C to 40°C [14], with melting points elevated in patients with Meibomian gland dysfunction, allowing secretion to stagnate[14,15]. Warm compresses rapidly lose heat and fall below the therapeutic temperature of 40°C within the first application[16]. Even commercially available eyelid masks microwaved for 10-20 seconds do not remain consistently above 38°C for the entire 10-min treatment[16]. An evaluation of eight methods of eyelid warming found that the method that mostly effectively maintained internal eyelid temperature, the bundle method, was also the most cumbersome[17].

The primary effect of LLLT is localized transient "heating" of the absorbing chromophore based on electric or light oscillations[18]. Beneficial effects of LLLT on the eye have been found in optic nerve trauma, methanol intoxication, optic neuropathy, retinal injury, retinitis pigmentosa, phototoxicity, and age-related macular degeneration. LLLT has also shown protective effects in a rat model of retinitis pigmentosa featuring a rhodopsin mutation inducing photoreceptor degeneration during development. Rat pups were treated with LLLT at 670 nm, 50mW/cm^2, and 4 J/ cm^2 for 5 days during the critical period of photoreceptor development. LLLT increased the concentrations of retinal cytochrome oxidase and neuroprotective factors superoxide dismutase and ciliary neurotrophic factor. In this model, LLLT also decreased the rate of photoreceptor cell death by 70%[19].

LLLT Results in MGD

After application (T 0min) of LLLT, the temperature on the upper and lower eyelids and cheek was significantly higher than before LLLT. This significant effect continued for up to 2 minutes (T 2min). From the measuring point T 5min to T 15min the temperature was higher than T before. At the next measuring point T 25min, the initial temperature was reached again. At T 2min and T 5min, a significantly ($p < 0.001$) higher temperature was measured on the upper eyelids than on the lower eyelids[32].

The tested IPL device did not increase the temperature of eyelids but the temperature of the cheek by around 4°C and of the temples by around 1.6°C. Craig J. et al.[20,32] on the other hand, after an IPL treatment with a device in which gel had to be used, reported skin warming of the cheek of less than 1°C. This may be due to the fact that Craig J. et al. had only measured the skin temperature after removing the gel. Since, according to our investigation, the skin temperature returned to normal at measuring point T 5minutes, it can be assumed that with the device used by Craig J. et al., the temperature on the cheek was higher immediately after application, but it could be measured too late. Craig J. et al. a warming of the eyelids (personal communication 12/2019)

While the LLLT had warmed the eyelids significantly, such an effect could not be found after IPL application. Nevertheless, alongside LLLT, IPL is a promising treatment for MGD according to the current study situation. In several independent studies, the tear film stability and the lipid layer as well as the symptoms of the dry eye improved significantly after IPL application.[21-22, 23, 20,32]

In this study, the "residual heat" was measured after treatment. The decisive factor is the energy that penetrates the skin.

Both IPL and LLLT generate endogenous heat at the point of use. The depth of penetration of light with a wavelength of 600 - 650 nm into the skin is 1 - 2 mm, at 650 - 950 nm it is 2 - 3 mm, at 950 - 1200nm it is 1mm[24,32]. When using IPL, a hot but extremely short "light flash" or bundled series of "light flashes" reaches the skin surface. Common devices from different manufacturers differ in terms of wavelength, energy and pulse shape / pulse duration.[25,32]

With LLLT, a light mask with red LEDs is placed over the patient's face for an average period of 15 minutes. These LEDs are also said to cause endogenous heat for the upper and lower eyelids.

If you summarize "light applications" under the light spectrum of 600 - 1070 nm[26,32] wavelength, a number of mechanisms of action are hypothetically postulated in various literature summaries related to the dry eye[6].

It could be selective photothermolysis within the fine vascular structures along the eyelids, a mild, local heat development that makes the meibomian secretion less viscous and could, therefore, lead to improved expressibility, reduction of inflammatory and neuropathic pain, stimulation of the parasympathetic nervous system affecting the meibomian glands, photobiomodulation mechanism that stimulates at the cellular and molecular level, coagulation of telangiectasias.

Other key points include reducing epithelial turnover and reducing the risk of gland obstruction, activating fibroblasts and improving collagen synthesis, minimizing demodex mite infestation, modulating the secretion of pro- and anti-inflammatory molecules, and reducing the concentration of MMPs by downregulating at the mRNA level and influencing reactive oxidative species (ROS).

	T_{before}	T_{0min}	T_{2min}	T_{5min}	T_{15min}	T_{25min}	T_{before} T_{0min}	T_{before} T_{2min}	T_{before} T_{5min}	T_{before} T_{15min}	T_{before} T_{25min}
IPL											
Lower eyelid	36.2°C ±0.72	35.7°C ±0.64	35.8°C ±0.60	36.0°C ±0.71	35.9°C ±0.69	36.1°C ±0.68	**p=0.028**	p=0.100	p=0.270	p=0.177	p=0.326
Upper eyelid	36.5°C ±0.65	36.3°C ±0.69	36.7°C ±0.67	36.4°C ±0.73	36.5°C ±0.66	36.1°C ±0.72	p=0.257	p=0.253	p=0.371	p=0.500	p=0.103
Cheek	35.5°C ±0.70	39.6°C ±0.72	37.1°C ±0.59	35.7°C ±0.68	35.6°C ±0.70	35.5°C ±0.71	***p<0.001***	***p<0.001***	p=0.262	p=0.320	p=0.323
Temple	36.0°C ±0.67	37.6°C ±0.68	36.5°C ±0.63	35.9°C ±0.65	36.1°C ±0.64	35.8°C ±0.66	***p<0.001***	**p=0.016**	p=0.316	p=0.316	p=0.171
LLLT											
Lower eyelid	35.9°C ±0.69	40.4°C ±0.58	39.6°C ±0.60	37.1°C ±0.72	36.5°C ±0.63	35.3°C ±0.72	***p<0.001***	***p<0.001***	***p=0.001***	**p=0.006**	**p=0.042**
Upper eyelid	36.2°C ±0.65	41.8°C ±0.65	40.7°C ±0.67	37.5°C ±0.69	37.5°C ±0.67	36.1°C ±0.70	***p<0.001***	***p<0.001***	***p<0.001***	***p<0.001***	p=0.371
Cheek	35.4°C ±0.79	39.8°C ±0.75	38.8°C ±0.63	36.7°C ±0.67	36.5°C ±0.71	36.1°C ±0.76	***p<0.001***	***p<0.001***	***p<0.001***	***p<0.001***	**p=0.012**
Temple	35.0°C ±0.73	37.7°C ±0.70	37.1°C ±0.69	36.1°C ±0.70	36.1°C ±0.65	35.6°C ±0.69	***p<0.001***	***p<0.001***	***p<0.001***	***p<0.001***	**p=0.025**

Table 1 *shows the measured temperatures at the different areas at the different times, as well as the standard deviation and the p-values between the repeated measurements. Significant p-values are in italics, those that would still be significant after a Bonferroni correction are additionally italic.*

Courtesy of Prof. H. PULT : "Skin temperature measurement after intensive pulse light (IPL)and low-level light therapy (LLLT) application" – die KONTAKT LINSE 4/2020

The LLLT showed a significantly higher heat effect, which was within the range recommended for the treatment of MGD with warm compresses or the like.[27,28,32] This was higher on the upper eyelids than on the lower eyelids. A warming effect was also found in the areas that are covered by IPL. The temperature to be reached in the meibomian glands during heat treatment of the MGD should be higher than 38 °C.[27,32] When using warm compresses, the surface temperature of the skin is said to be at least 40°C.[28,32] In this way, the excessively viscous meibom oil in MGD patients is liquefied and is easier to express. This seems to have been achieved by using the mask on the upper and lower eyelids. After 15 minutes of application, the warming effect continued at the temperature relevant for MGD treatment for up to two minutes after treatment, and a general effect of warming the face could be measured for up to 15 minutes. The effect of warming the face was significantly shorter with the IPL treatment. Due to the properties of LLLT, it can also be assumed that this temperature has penetrated deeper into the eyelids than when using external heat (warm compresses or similar). The LEDs on the mask have a wavelength of 633 nm, which works in normal skin at a depth of one to two millimeters.[24,32]

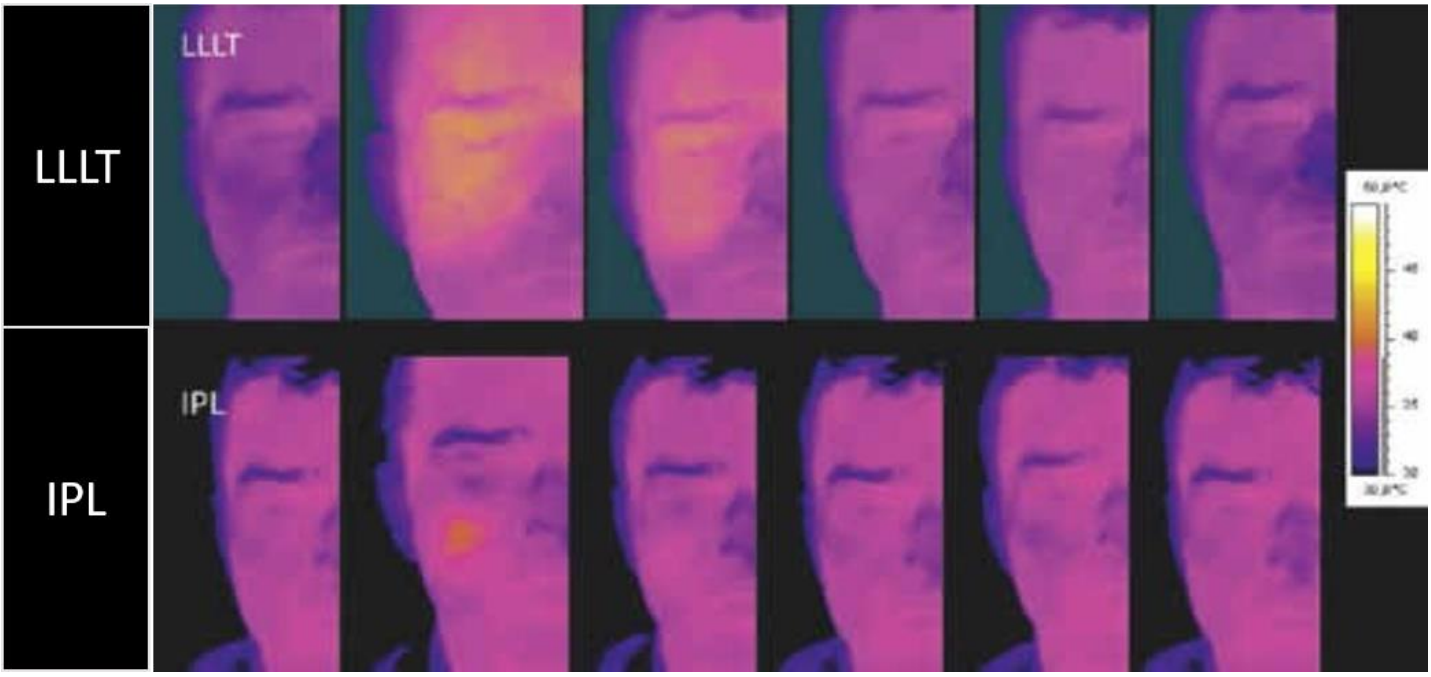

Image 4 | *Example recordings of a series of measurements before and after LLLT- (above) and IPL application (bottom row).*

Courtesy of Prof. H. PULT : "Skin temperature measurement after intensive pulse light (IPL)and low-level light therapy (LLLT) application" – die KONTAKT LINSE 4/2020

LLLT was successfully used for the treatment of chalazion and also for MGD [29,22,32].

Figure 1 A young patient before LLLT treatment (**A**), with treatment being applied (**B**) and 1 week after treatment (**C**). Images used with permission.

Courtesy of Dr. K. STONECIPHER: "Low level light therapy for the treatment of recalcitrant chalazia: a sample case summary" – Clinical Ophthalmology 2019;13:993-9

Summary

Both IPL and LLLT showed a significant skin warming effect, which lasted longer after treatment with LLLT than with IPL. Whereas after LLLT treatment sufficient warming of the eyelids was measured for MGD treatment, only warming of cheeks and temples could be measured after IPL, but not of the eyelids[32].

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