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Research Article

CLINICAL RESULTS FROM LOW-LEVEL LASER THERAPY IN PATIENTS WITH AUTOSOMAL DOMINANT CONE- ROD DYSTROPHY

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ABSTRACT

Purpose. The objective of this study is to examine long-term effects of low-level laser therapy (LLLT) in patients with autosomal dominant cone-rod dystrophy (CRDs).
Methods. LLLT, a He-Ne Laser with continuous emission at 633 nm (01 mW/cm2) was used in five patients autosomal dominant pedigree of Romani origin with non syndromic CRDs.
Laser radiation was applied transpupillary for 6 times for 3 min once in two days to the macula. The research was implemented for a period of three years. Clinical evaluation included best corrected visual acuity determination, funduscopy, Humphrey perimetry, Farnsworth Hue-28 color testing, fluoresce in angiography, and full-field electroretinogram (ERG).
Results. All affected individuals presented reduced visual acuity (0.01 - 0.4) and photophobia with slightly variable. Funduscopic examination and fluorescein angiography revealed advanced changes including bone spicule-like pigment deposits in the midperiphery and macular area along with retinal atrophy, narrowing of the vessels, and waxy optic discs. Visual fields demonstrated central scotoma. Electrophysiologic examination of the patients detected an abnormal cone-rod ERG (20-30μV) with photopic amplitudes more markedly reduced than the scotopic. Flicker responses were missing and Farnsworth Hue-28 test found protanopia. There was a statistically significant increase in visual acuity ($p<0.001$, end of study versus baseline). For CRDs patients for the period of 3 years after the treatment with LLLT. Central absolute scotoma in CRDs was reduced after LLLT. The prevalence of metamorphopsia in CRDs was reduced after LLLT.
Conclusion. This study shows that LLLT may be a novel long-lasting therapeutic option for both forms of CRDs . This is highly effective treatment that improves visual acuity for a long time.

INTRODUCTION

Cone rod dystrophies (CRDs) characterized by the loss of cone cells, the photoreceptors responsible for both central and color vision[1]. The cones and rods transform light into electric nerve messages that transfer to our brain via our optic nerve[2]. CRDs (prevalence 1/40,000) are inherited retinal dystrophies that belong to the group of pigmentary retinopathies[3]. There are more than 30 types of cone-rod dystrophy, which are distinguished by their genetic cause and their pattern of inheritance: autosomal recessive, autosomal dominant, and X-linked. CRDs are characterized by retinal pigment deposits, predominantly localized to the macular region[4,5]. There is no one effective treatment for the different types of CRD; however, there may be treatment options that may help to slow down the degenerative process, such as light avoidance and the use of low-vision aids. Dry AMD is characterized by drusen, retinal pigment epithelial (RPE) cell atrophy and subjacent photoreceptor degeneration[6]. Factors involved in causing RPE cell injury and dysfunction have been shown to include mitochondrial dysfunction, oxidative stress, inflammation and genetic disposition[7]

Photobiomodulation (PBM) was discovered almost 50 years ago by Endre Mester in Hungary [8]. For most of this time PBM was known as "low-level laser therapy" as ruby laser (694nm) and HeNe lasers (633 nm) were the first devices used. Llow-level laser therapy (LLLT) produces signi□ cant bioeffects[9,10,11,12] These effects are manifested in biochemical, physiological and proliferative phenomena in various enzymes, cells, tissues, organs and organisms [13,14]. Published studies demonstrate that mitochondrial cytochrome C oxidase (CCO) is a key photoacceptor of light at these wavelengths and improves blood flow and ATP formation, enhances O_2 binding and reduces oxidative stress and inflammation[15,16].

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Although early studies identified mitochondrial CCO as an endogenous photoacceptor for PBM, the cellular and molecular mechanisms underlying PBM are better understood[17]. Recent findings provide important new insight. First, nitric oxide has been implicated. Second, CCO, an enzyme known to reduce oxygen to water at the end of the mitochondrial respiratory chain, has been shown to have a new enzymatic activity - the reduction of nitrite to nitric oxide[18]. This nitrite reductase activity is elevated under hypoxic conditions but also occurs under normoxia. And third, low-intensity light regulates nitric oxide synthesis by CCO without altering its ability to reduce oxygen.

Purpose

The objective of this study is to examine long-term effects of low-level laser therapy (LLLT) in patients with cone-rod dystrophy.

METHODS

LLLT, a He-Ne Laser with continuous emission at 633 nm (01 mW/cm2) was used in five patients autosomal dominant pedigree of Romani origin with non syndromic CRDs. For the investigation, there was applied a new ophthalmologic system for bio-stimulation and LLLT of eye diseases based on the He-Ne laser (Mediray 04, Optella Ltd., So□ a, 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/cm2. The apparatus is developed in Bulgaria by the authors K. Koev, V. Tanev, L. Avramov (Fig.1). 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.

Fig 1 He-Ne laser "MEDIRAY 04"

Laser radiation was applied transpupillary for 6 times for 3 min once in two days to the macula. The research was implemented for a period of three years. Clinical evaluation included best corrected visual acuity determination, funduscopy, Humphrey perimetry, Farnsworth Hue-28 color testing, fluorescein angiography, and full-field electroretinogram (ERG).

RESULTS

All affected with CRDs individuals presented reduced visual acuity (0.01 - 0.4) and photophobia slightly variable. Funduscopic examination and fluorescein angiography revealed advanced changes including bone spicule-like pigment deposits in the midperiphery and macular area along with retinal atrophy, narrowing of the vessels, and waxy optic discs. Visual fields demonstrated central scotoma. Electrophysiologic examination of the patients detected an abnormal cone-rod ERG (20-30μV) with photopic amplitudes more markedly reduced than the scotopic. Flicker responses were missing and Farnsworth Hue-28 test found protanopia. There was a statistically significant increase in visual acuity ($p<0.001$, end of study versus baseline) for CRDs patients for the period of 3 years after the treatment with LLLT. After LLLT, visual acuity improves in a larger proportion of patients.

In patients visual acuity improved optotypes in 9/10 eyes (90%; p _ 0.001)
Eyes: by one row of optotypes in 3/10 (30,%),
by two rows in 4 /10 (40 %),
by three rows in 2/10 (20 %),
Visual acuity remained unchanged in 1/10 eyes (1.0%).
Central absolute scotoma in CRDs was reduced after LLLT.
The prevalence of metamorphopsia in CRDs was reduced after LLLT.

DISCUSSION

In this study we report a family of Gypsy origin affected by autosomal dominant cone-rod dystrophy with application on the LLLT. For the first time, publish clinical results from the use of LLLT in patients with autosomal dominant CRDs.

LLLT improvement in visual acuity in most patients with (_90%) CRDs. An increase of two to three rows of optotypes was observed in 6/10 (60%) eyes with CRDs.

We found that central absolute scotoma and metamorphopsia in CRDs was reduced after LLLT.

The first signs and symptoms of cone-rod dystrophy, are usually decreased sharpness of visual acuity and photophobia[2]. These features are typically followed by impaired color vision (dyschromatopsia), scotomas in the center of the visual field, and peripheral vision loss[3]. Photobiomodulation (PBM) utilizes very low energy levels causing no tissue damage[14]. The local reduction of edema, and reductions in markers of oxidative stress and pro-inflammatory cytokines are well established after LLLT[18]. PBM stimulates cellular processes that provide an approach to target the underlying degenerative pathology with disease-modifying potential[19]. A recent review paper of PBM in retinal diseases has reported that the literature supports the conclusion that the low cost and non-invasive nature of PBM coupled with the first promising clinical reports and the numerous preclinical studies in animal models make PBM well poised to become an important player in the treatment of retinal disorders[20].. There is no evidence of LLLT in patients with CRDs in the literature. Ivandic is administered LLLT in a patient with retinitis pigmentosa[7]. Visual acuity improves in a patient with retinitis pigmentosa after LLLT[7].

PBM also known as low-level level laser therapy is the use of red and near-infrared light to stimulate healing, relieve pain, and reduce inflammation [14,22,23]. The primary chromophores have been identified as cytochrome c oxidase in mitochondria, and calcium ion channels (possibly mediated by light absorption by opsins). Secondary effects of photon absorption include increases in ATP, a brief burst of reactive

oxygen species, an increase in nitric oxide, and modulation of calcium levels. Tertiary effects include activation of a wide range of transcription factors leading to improved cell survival, increased proliferation and migration, and new protein synthesis. Many wavelengths in the red (600-700 nm) and near-infrared (NIR, 770-1200 nm) spectral regions have shown positive results, however there is a region in between (700-770 nm) where broadly speaking, the results are likely to be disappointing[24]. Some studies have looked at animal models of neuropathic pain such as the "spared nerve injury" [25]. This involves ligating two out of three branches of the sciatic nerve in rats and causes long lasting (>6 months) mechanical allodynia [27].

Authors[26] used a transgenic mouse strain (FVB/N-Tg(iNOS-luc) that had been engineered to express luciferase under control of the inducible nitric oxide synthase promoter, to allow bioluminescence imaging of PBM of the zymosal-induced arthritis model in mice knees[26]. They compared the same fluence of 635, 660, 690, and 905 nm (CW0 and 905 nm (short pulse). Animals younger than 15 weeks showed mostly reduction of iNOS expression, while older animals showed increased iNOS expression. Pulsed 905 nm also increased iNOS expression. In recent years the use of PBM as a treatment for traumatic brain injury, and other brain disorders including stroke, neurodegenerative diseases and even psychiatric disorders has increased markedly [25,27,28,29].

Photoneuromodulation of cytochrome oxidase activity is the most important primary mechanism of action of LLLT[12]. Cytochrome oxidase is the primary photoacceptor of light in the red to near-infrared region of the electromagnetic spectrum. It is also a key mitochondrial enzyme for cellular bioenergetics, especially for nerve cells in the retina and the brain. Evidence shows that LLLT can secondarily enhance neural metabolism by regulating mitochondrial function, intraneuronal signaling systems, and redox states. In contrast to laser treatment, PBM utilizes very low energy levels causing no tissue damage[14]. Photobiomodulation stimulates cellular processes that provide an approach to target the underlying degenerative pathology with disease-modifying potential. A recent review paper of PBM in retinal diseases has reported that the literature supports the conclusion that the low cost and non-invasive nature of PBM coupled with the first promising clinical reports and the numerous preclinical studies in animal models make PBM well poised to become an important player in the treatment of retinal disorders[28]. The good clinical results that we have found show that LLLT can be successfully used in CRDs.

CONCLUSION

This study shows that LLLT may be a novel long-lasting therapeutic option for both forms of CRDs. This is highly effective treatment that improves visual acuity for a long time.

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