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RESEARCH ARTICLE

SIX YEARS FOLLOW-UP OF LOW-LEVEL LASER THERAPY (LLLT) IN PATIENTS WITH AGE-RELATED MACULAR DEGENERATION (AMD).

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Key words:-
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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 age-related macular degeneration (AMD).
Methods: The research was implemented for a period of six years. For LLLT, a He-Ne Laser with continuous emission at 633 nm (01 mW/cm2) was used in patients with AMD of all stages (dry to wet exudative forms were included). In total, 33 patients (16 men and 17 women - 66 eyes) with AMD of various stages and a mean age of 68.7 ±4.2 years were included in the study. Progressive, exudative AMD was diagnosed in 8 eyes. 58 eyes had drusen or were depigmented. Laser radiation was applied transpupillary for 6 times for 3 min once in two days to the macula. 22 patients with AMD (44 eyes) were randomly selected to receive mock treatment (control group 10 men and 12 women with a mean age of 69.3± 4.8 years). Visual acuity was followed for a 6-year period. The perimetry and Amsler test was used to screen central scotomas. Fluorescein angiography of AMD and control groups was examined.
Results: Visual acuity remained unchanged in all patients in the control group. There was a statistically significant increase in visual acuity ($p<0.001$, end of study versus baseline) for AMD patients for the period of 6 years after the treatment. The edema and hemorrhage in the patients with progressive, exudative AMD significantly decreased. No side effects were observed during the therapy. The prevalence of metamorphopsia, scotoma in AMD group was reduced.
Conclusion: In conclusion, this study shows that LLLT may be a novel long-lasting therapeutic option for both forms of AMD. This is highly effective treatment that improves visual acuity for a long time.

Introduction:-

AMD affects 30–50% of individuals 60 years or older.[1,2] Age-related macular degeneration (AMD) is diagnosed as either dry (non-neovascular) or wet (neovascular)[3]. Neovascular refers to growth of new blood vessels in an area, such as the macula, where they are not supposed to be[4]. Macular degeneration mainly affects central vision, causing "blind spots" directly ahead[5]. The dry form is more common than the wet form, with about 85 to 90 percent of AMD patients diagnosed with dry AMD[6]. The wet form of the disease usually leads to more serious

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vision loss. AMD results from defects in the choriocapillaris, Bruch's membrane, and the retinal pigmented epithelium (RPE) underneath the macula[7]. The epitheliopathy diminishes lysosomal activity and phagocytosis of the outer photoreceptors and disrupts the transportation of cell debris through the RPE to the choriocapillaris[2].Certain types of therapy including electrical stimulation and laser therapy have been developed during the recent years to decrease the regenerative process and return the function[8,9,10]. Other studies (11,12,13) 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. Helium-neon laser is red light at 632.8 nm. The incident beam can partially reach into 15 mm of tissue, causing local vascular dilation and accelerated blood flow. The laser thus plays a role in reducing inflammation, has an anti-swelling effect and promotes functional recovery. In addition, low-energy helium-neon lasers strengthen phagocytosis by macrophages and promote the absorption of inflammation[12]. Local helium-neon laser therapy contributes to the prevention of the inflammatory reaction and promotes local tissue proliferation and wound healing[13]

LLLT is a special type of laser therapy in which the irradiation used is red or near infrared beams with a wavelength of 600 - 1100 nm and an output power of 1 - 500 mW. This type of radiation is a continuous wave or pulsed light which consists of a constant beam of relatively low energy density (0.04–50 J/cm^2) [14,15,16,17]. LLLT represents a novel therapeutic method that, other than surgical laser applications, does not damage tissues[18.19].

Purpose. The objective of this study is to examine long-term effects of low-level laser therapy (LLLT) in patients with age-related macular degeneration (AMD).

Methods and Materials:-

This study of a case series was conducted in accordance with the Helsinki declaration. Informed consent was obtained from all patients before entry into the study.

The research was implemented for a period of six years. For LLLT, (Mediray 04, Optella Ltd., Sofia, Bulgaria) a He-Ne Laser with continuous emission at 633 nm (01 mW/cm2) was used in patients with AMD of all stages (dry to wet exudative forms were included). In total, 33 patients (16 men and 17 women - 66 eyes) with AMD of various stages and a mean age of 68.7 ±4.2 years were included in the study. Progressive, exudative AMD was diagnosed in 8 eyes. 58 eyes had drusen or were depigmented. Laser radiation was applied transpupillary for 6 times for 3 min once in two days to the macula. 22 patients with AMD (44 eyes) were randomly selected to receive mock treatment (control group 10 men and 12 women with a mean age of 69.3± 4.8 years). Visual acuity was followed for a 6-year period. The perimetry and Amsler test was used to screen central scotomas. Fluorescein angiography of AMD and control groups was examined.

He-Ne laser "MEDIRAY 04"

Results. Visual acuity remained unchanged in all patients in the control group. There was a statistically significant increase in visual acuity (p<0.001, end of study versus baseline) for AMD patients for the period of 6 years after the treatment. After LLLT, visual acuity improves in a larger proportion of patients.

In patients visual acuity improved optotypes in 62/66 eyes (93.9%; *p* _ 0.001):

eyes: by one row of optotypes in 18/66 (27,3%);
by two rows in 32 /66 (48,5.0%);
by three rows in 10/66 (15,2 %);
by four rows in 2/66 (2,9 %);
Visual acuity remained unchanged in 4/66 eyes (6.1%).

In patients treated with LLLT the improvement in visual acuity was in most cases accompanied by a decrease in metamorphopsias and scotomas.

In patients with wet AMD, edema and bleeding were reduced.

Discussion:-

The results of this retrospective analysis of a case series are encouraging. From the results obtained during this investigation carried out we could ascertain the fact that the best effect on the patients with LLLT was obtained. LLLT improvement in visual acuity in most patients with AMD (_93,9%). An increase of one to two rows of optotypes was observed in 40/66 eyes with AMD. Eye examinations revealed that LLLT diminished pigment accumulations and cystic drusen. Authors find thatuses low-powered laser light in the range of 1-1000 mW, at wavelengths from 632-1064 nm, to stimulate a biological response[20,21,23]. These lasers emit no heat, sound, or vibration. Instead of generating a thermal effect, LLLT acts by inducing a photochemical reaction in the cell, a process referred to as biostimulation or photobiomodulation[24] . Photo-biology works on the principle that, when light hits certain molecules called chromophores, the photon energy causes electrons to be excited and jump from low-energy orbits to higher-energy orbits. Absorption of photon energy by neuronal mitochondria leads to numerous downstream neuroprotective effects[25]. Red and near infrared (NIR) light are associated with significantly less safety concerns than light of shorter wavelengths and they are therefore, the optimal choice for irradiating the retina[26]. Similar results were obtained by Maiya et al.[27] in diabetic rats, showing that laser-treated animals healed faster and better than controls. LLLT accelerates wound healing in ischemic rat and murine diabetic wound healing models, attenuates the retinotoxic effects of methanol-derived formic acid in rat models, and attenuates the developmental toxicity of dioxin in chicken embryos. Potent neuroprotective effects have been demonstrated in various models of retinal damage, by red - 633/NIR light, with limited data from human studies showing its ability to improve visual function. Improved neuronal mitochondrial function, increased blood flow to neural tissue, upregulation of cell survival mediators and restoration of normal microglial function have all been proposed as potential underlying mechanisms of red/NIR light[[16,17].

Low-intensity light therapy, commonly referred to as "photobiomodulation," uses light in the far-red region of the spectrum 633 and modulates numerous cellular functions[28]. Positive effects of LLLT include acceleration of wound healing, improved recovery from ischemic injury of the heart, and attenuated degeneration of injured optic nerves by improving mitochondrial energy metabolism and production. Various *in vitro* and *in vivo* models of mitochondrial dysfunction were treated with a variety of wavelengths of LLLT. These studies were performed to determine the effect of LLLT on physiologic and pathologic processes. LLLT stimulates the photoacceptor cytochrome *c* oxidase, resulting in increased energy metabolism and production Furthermore[. The experimental results demonstrate LLLT stimulates mitochondrial oxidative metabolism *in vitro*, and accelerates cell and tissue repair *in vivo*.

A major cause of blindness in the Western world is degeneration of photoreceptors as a result of point mutations in genes coding for either phototransduction-related proteins or other proteins important for retinal function. Despite the diversity of mutated genes and proteins involved in this heterogeneous group of progressive retinal dystrophies with homologous phenotypes, the final event leading to blindness is apoptosis of photoreceptors[29]. .

Interleukin 1β (IL-1β), tumor necrotic factor-α (TNF-α), and interferon-γ (IFN-γ) play an important role in inflammation, while platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β) and blood-derived fibroblast growth factor (bFGF) are the most important growth factors of periodontal tissues. Authors investigate the effect of low- level He–Ne laser on the gene expression of these mediators in rats' gingiva and mucosal tissues[30].

Twenty male Wistar rats were randomly assigned into four groups (A_{24}, A_{48}, B_{24}, B_{48}) in which A_{24} and A_{48} were cases and B_{24}, B_{48} were controls. An incision was made on gingiva and mucosa of the labial surface of the rats' mandibular incisors. Group A_{24} was irradiated twice with 24 hours interval, while the inflamed tissues of group A_{48}

was irradiated three times with continuous He–Ne laser (632.8 nm) at a dose of 7.5 J/cm2 for 300 s. An energy of 5.1 J was given to the 68 mm^2 irradiation zone. The authors find that the gene expression of IL-1β and IFN-γ was significantly inhibited in the test groups ($P < 0.05$), while the gene expression of PDGF and TGF-β were significantly increased ($P < 0.05$). using The case and control groups did not have a significant difference in the gene expression of TNF-α and bFGF ($P > 0.05$). These findings suggest that low-level He-Ne laser irradiation decreases the amount of inflammation and accelerates the wound healing process by changing the expression of genes responsible for the production of inflammatory cytokines[30].

The combined treatment with He-Ne laser, Aftaquix and Cornergel is revealed as an efficient method for eye therapy of cornea trauma[31]. Thus the triple combination has strong additive effect, assuring total healing of the affected eyes with pronounced shortening of the mean duration of the disease[31].

LLLT may increase cellular metabolism in choroidea, RPE, and in photoreceptors, where the energy is absorbed by pigments[8].

Regular metabolic processes may be enhanced and repair processes may be triggered or accelerated. Recently, an increase in the expression of heat shock proteins was found in the retinal and choroidal layers after sub-thermal transpupillary application of laser energy[24]. In *in vitro* experiments, application of laser light was shown to increase cellular metabolic activity, the generation of adenosine triphosphate, and phagocytosis.[16]

Conclusion:-

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

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