Treatment of dry Age-related Macular Degeneration with Photobiomodulation

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ABSTRACT

Objective: To evaluate if Photobiomodulation (PBM) can affect vision in patients with dry Age-Related Macular Degeneration (AMD).

Methods: Prospective interventional case series. Near Infra Red (NIR) and yellow wavelengths of low powered light were applied to eyes with AMD in serial consecutive treatments. Included were patients with dry AMD, 50 years or older and with visual acuity between 20/20 - 20/200. Primary outcome measures selected were change in visual acuity, contrast sensitivity and fixation stability.

Results: The treatment protocol was completed in 18 eyes (9 patients). Changes in visual acuity ($p<0.0001$) and contrast sensitivity ($p<0.0001$ at 3 cycles/degree and $p<0.0032$ at 1.5 cycles/degree) were positive and significant. There were no significant changes in fixation stability parameters.

Conclusions: PBM proves to be beneficial for improvement of vision and contrast sensitivity and a safe treatment for dry AMD in this pilot study. Larger studies are warranted to validate the findings from this study.

INTRODUCTION:

AMD is a retinal degenerative disease that causes irreversible, profound vision loss in people over the age of 60 years[1]. AMD occurs in two major forms: exudative (wet) and atrophic (dry) AMD. These two forms of AMD are both part of the same disease process continuum and share similar risk factors for their development. Exudative AMD is characterized by choroidal neovascularization (CNV). In contrast, atrophic AMD is characterized by retinal pigment epithelial (RPE) cell atrophy and subjacent photoreceptor degeneration. Factors involved in causing RPE cell injury and dysfunction have been shown to include oxidative stress, inflammation and genetic disposition[2]. Damage caused by oxidative stress and inflammation leads to progressive loss of cell function and thus contributes to the development of atrophic AMD.
There are no proven treatments for the dry or atrophic form of AMD to date. Potential therapeutic approaches for atrophic AMD include inhibiting inflammatory responses as well as reducing oxidative stress secondary to anoxia.
PBM otherwise known also as low level laser therapy (LLLT) when used in the red to near-IR range (630–1,000 nm) using low-energy lasers or light-emitting diode (LED) arrays has been shown to accelerate wound healing, improve recovery from ischemic injury in the heart and attenuate degeneration in the injured optic nerve [3 4 5 6 7 8].
LED treatment significantly improved rod- and M-cone- mediated ERG responses in methanol-intoxicated rats [9].
Ivandic and Ivandic have shown that LLLT with a laser diode aimed at the macular area (trans sclerally) in human subjects significantly improved visual acuity in a case series of both dry and wet AMD. Visual acuity in the control group remained unchanged. No adverse effects were observed in those undergoing therapy [10].

We designed this study as the first globally to look at the effect of PBM with low powered LED (non coherent) devices shone through the pupil in patients with dry AMD.

METHODS

The study was designed as a prospective non-randomized interventional case series. Patients were identified prospectively as they presented to clinics run by two of us (GM and RD). We selected subjects with previously diagnosed dry age-related macular degeneration (AMD).
Inclusion criteria were documented dry AMD, best corrected visual acuity (BCVA) of 20/20 to 20/200 and older than 50 years of age. Excluded from the study were subjects with previous or active wet AMD, with a previous history of epilepsy, with cognitive

impairment, other retinal disease, previous retinal surgery, significant media opacity or contraindications to dilation drops.

The non-presence of neovascularization was ascertained prior to enrollment by examination with Ocular Coherence Tomography (OCT) and Intra-venous Fluorescein Angiography (IVFA) and confirmed by a retina specialist. All subjects were assessed for Visual Acuity with ETDRS charts at 4 meter distance (Precision Vision, USA) recorded in log MAR units, contrast sensitivity at 1.5 and 3 cycles per degree (Stereo Vision Optec 6500, USA) recorded as log contrast sensitivity and for fixation stability with the Nidek MP1 micro perimeter (Nidek Technologies, Padova, Italy). Accurate estimates of fixation stability could be obtained from raw data provided by the instrument by calculation of a Bi-Curve Ellipse Area (BCEA) [11]. Calculations are based on the minor and major axes of an ellipse area covering fixational eye movements and takes into account two standard deviation measures of each recorded eye movement. The results are expressed in square degrees. Measurements took place prior to treatment, immediately following the treatment protocol (6weeks), 4, 6 and 12 months after.

The intervention consisted of using LLLT in the yellow and red to near-IR range using low-energy delivery with the Warp10 (Quantum Devices) and the Gentlewaves (Light Bioscience) instruments. The instruments used are commercially available and have been approved for use in other conditions by the FDA and Health Canada. The FDA considers one of the devices a non -significant risk device for using on the eye. The other device is of even lower power.
The treatment parameters followed for the Warp10 delivery system were 670nm +/- 15nm at 50-80 mW/cm2, 4-7.68 J/cm2, for 88 +/- 8 seconds.
The treatment parameters followed for the Gentlewaves delivery system were 590nm +/- 8nm at 4mW, 790nm +/- 60nm at 0.6mW, for 35 seconds, pulsed at 2.5 Hz (250 milliseconds on, 150 milliseconds off) while delivering 0.1J/cm2/treatment.
All subjects were treated with the two devices used sequentially at each treatment visit for a total of 18 treatments over a six-week period (3 times per week for 6 weeks).

The primary outcome measures selected for analysis were visual acuity, contrast sensitivity and fixation stability estimates. Data analysis was based on descriptive statistics that include frequency distributions, a measure of central tendency (mean) and a measure of dispersion (standard deviation). A statistical comparison of means between populations was made by t-test and repeated measures analysis of variance (repeated measures ANOVA). Differences were considered to be statistically significant at p values of less than 0.05. The study was performed in adherence to the guidelines of the Declaration of Helsinki. The study protocol was approved by an independent Research Ethics Committee (IRB Services, Aurora, Canada). Informed consent was obtained from all participants.

RESULTS

Over a span of 12 months 18 AMD study eyes (6 males and 12 females) were recruited and treated; aged 61 to 90 years old (mean 74.3 years/ SD 7.7).

Average ETDRS BCVA for the AMD group was measured at 0.25 log Mar units before the treatment and at 0.13 log Mar units 12 months after the treatment ($p<0.0001$). Repeated Measures ANOVA yielded **F (4,68) = 18.86, p less than 0.0001.** See figure 1

Contrast sensitivity:
Repeated measures ANOVA for Contrast sensitivity (3cycles/degree):
F (4,68) = 11.44, p less than 0.0001. See figure 2

Repeated measures ANOVA for Contrast Sensitivity (1.5 cycles/degree):
F (4,68) = 4.39, p less than 0.0032. See figure 3

Fixation stability:
Repeated measures ANOVA for Fixation Stability (BCEA): F (4,68) = 0.90, p less than 0.4661.

Correlation analysis between Fixation Stability and ETDRS VA:
Pearson R value of 0.6776, p less than 0.001.

DISCUSSION

Potential therapeutic approaches for atrophic AMD include neutralizing ROS, promoting cell survival, and inhibiting inflammatory responses that could potentially delay the progression of this disease and even improve cellular function.
Photobiomodulation (PBM) also known as low level laser therapy (LLLT) has both primary and secondary effects on cellular responses to disease including anti inflammatory, anti oxidant and anti apoptosis effects.

The precise biochemical mechanisms underlying the therapeutic effects of LLLT are not yet well established[12]. At the most basic level, LLLT acts by inducing a photochemical reaction in the cell, a process referred to as biostimulation or photobiomodulation. When a photon of light is absorbed by a chromophore in the treated cells, an electron in the chromophore can become excited and jump from a low-energy orbit to a higher-energy orbit [13 14]. This stored energy can then be used by the system to perform various cellular tasks.
The influence of LLLT on the electron transport chain extends far beyond simply increasing the levels of ATP produced by a cell. Oxygen acts as the final electron acceptor in the electron transport chain and is, in the process, converted to water. Part of the oxygen that is metabolized produces reactive oxygen species (ROS) as a natural by-product. ROS are chemically active molecules that play an important role in cell signaling, regulation of cell cycle progression, enzyme activation, and nucleic acid and protein synthesis.

Within the cell, there is strong evidence to suggest that LLLT acts on the mitochondria [15] to increase adenosine tri- phosphate (ATP) production [16], modulation of reactive oxygen species (ROS), and the induction of transcription factors [17].
These transcription factors then cause protein synthesis that triggers further effects down-stream, such as increased cell proliferation and migration, modulation in the levels of cytokines, growth factors and inflammatory mediators, and increased tissue oxygenation [18].
Dosimetry in LLLT is highly complicated. The large of number of interrelated parameters has meant that there has not yet been a comprehensive study reported that examined the effect of varying all the individual parameters one by one, and it is unlikely there will ever be such a study carried out. This considerable level of complexity has meant that the choice of parameters has often depended on the experimenter's or the practitioner's personal preference or experience rather than on a consensus statement by an authoritative body. Nevertheless, the World Association of Laser Therapy (WALT) has attempted to provide dosage guidelines (http://www.walt.nu/dosage-recommendations.html).
In vitro studies, animal experiments and clinical studies have all tended to indicate that LLLT with fluences of red or NIR as low as 3 to 5 J/cm2 will be beneficial in vivo, but a large dose like 50 to 100 J/cm2 will lose the beneficial effect and may even become detrimental.
LLLT is also being considered as a viable treatment for serious neurological conditions such as traumatic brain injury (TBI), stroke, spinal cord injury, and degenerative central nervous system disease.
Further experiments have tried to pinpoint the mechanism underlying these results. As expected, increased mitochondrial activity has been found in brain cells irradiated with LLLT [19], indicating that the increased respiration and ATP production that usually follow laser therapy are at least partly responsible for the improvement shown in stroke patients. However, there is still the possibility that LLLT has other effects specific to the brain. Several groups have suggested that the improvements in patient outcomes are because of the promotion of neurogenesis, and migration of neurons [20]. This hypothesis is supported by the fact that the benefits of LLLT following a stroke may take 2– 4 weeks to manifest, reflecting the time necessary for new neurons to form and gather at the damaged site in the brain [21] [22]. However, the exact processes underlying the effects of LLLT in a stroke patient are still poorly understood.

The RPE is the major local source of Complement Factor H (CFH) at the retina/choroid interface. Mutations or down regulation of CFH may increase the chance of RPE cells being attacked by activated complement systems. Damage caused by oxidative stress and inflammation lead to progressive loss of cell function and thus contributes to the development of atrophic AMD. Genes in different pathways influence progression to different stages of AMD. The genes CFH, C3, CFB, and ARMS2/HTRA1 have been associated with progression from intermediate drusen to large drusen, and from large drusen to GA or NV [23]. By altering gene expression PBM can influence factors involved in progression of AMD such as VEGF and inflammatory cytokinins.

Recently there has been interest in tissue sparing or sub threshold laser at 577nm and 810 nm to produce therapeutic effects without clinical evidence of intra retinal damage [24]. It

has been proposed that the benefits might be due to the up- and down-regulation of angiogenic growth factors (e.g., VEGF) [25] [26] [27] [28] mediated by the biological reaction of RPE cells that have been only sub lethally injured. We feel that the same benefits to cellular function can occur with PBM and that there is no damage to any cells with the low powered LED light sources used in our study.

We used fixation stability, a novel testing parameter as one of our primary outcome measures and although there were changes both in the BCEA and PRL location after the treatment these were not statistically significant, however correlation analysis between visual acuity and fixation stability was improved after the treatment – further evidence of a treatment effect. See figure 4

Average ETDRS visual acuity was statistically significantly improved immediately following the treatment and this improvement remained at statistically significant levels at 12 months although some decline in the ETDRS log MAR score is evident after 4 months.

This would suggest that some patients would benefit from re-treatment somewhere after the 4-month interval. This happened to be the case in one subject with advanced geographic atrophy in both eyes with a decline in visual acuity of four lines in the 12 months prior to enrollment in her better eye. She regained over 3 lines of visual acuity immediately following the treatment (log MAR 0.66 improving to log MAR 0.34) but when assessed at 6 months had lost any gain from her treatment (log MAR 0.7). Many patients with progressing Geographic Atrophy loose vision rapidly. She was re-treated with a non-study protocol over a ten-day period. She regained 2 lines of vision (log MAR 0.54) following this secondary treatment. As this subject was re-treated which constituted a protocol violation all data on this subject was excluded from analysis. See figure 5

The treatment appears to have revitalized, rejuvenated and improved the function of these compromised retinal cells on the border of the geographic atrophy with an immediate improvement in visual acuity however the time this effect lasted for was less than 6 months.

This could be further evaluated in the future utilizing both Auto fluorescence and Geographic Atrophy area mapping, both of which are now readily available with newer OCT scanning devices but that were not available to us at the study inception.

Contrast sensitivity was statistically significantly improved with the treatment, the response lagged a little behind the visual acuity with a peak response at the 6-month stage but again like ETDRS VA, remaining at significant levels of improvement at 12 months.

PBM is extremely well tolerated, there is no discomfort and the individual treatments are easily dispensed taking less than 5 minutes per eye.

There were no significant adverse events noted during the course of the study, one subject with a history of migraine headaches felt that she was more susceptible to getting a migraine after one treatment session however it did not occur and this sensation lasted less than one hour.

We believe the results obtained warrant further evaluation of PBM as an important, safe and effective treatment in this potentially devastating disease where there are no proven treatments to date.

Keywords: Dry age related macular degeneration, Geographic atrophy, visual acuity, low vision rehabilitation, contrast sensitivity, Low Level Light Therapy, Photobiomodulation, and NIR.

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Figure1: Repeated measures Anova of ETDRS Visual acuity (log MAR units)

Figure2: Repeated Measures Anova of contrast sensitivity at 3cpd

Figure 3: Repeated Measures Anova of contrast sensitivity at 1.5 cpd

Figure 4: fixation stability area and PRL change before (yellow) and after PBM (blue).

Figure 5: PBM improved vision in rapidly advancing GA