Title: The Beneficial Effects Of Photobiomodulation To Reduce Intraocular Pressure In Primary Open-Angle Glaucoma.

ABSTRACT:

Purpose

The aim of this trail was to study the efficacy of photobiomodulation (PBM) treatment to reduce the intraocular pressure in subjects with primary open angle glaucoma disease.

Methods

Twenty eyes suffering from open angle glaucoma with high IOP level were selected, examined and treated with Thera-RED light diode system .The subject where divided into two groups (n=10) ; treated and placebo group respectively ; this system provide two lights (red at 660n.m continue and Near IR light micro-pulsed at 850 n.m) , the patients received two series of treatment (ten per month within three months between every series of sessions) over five months and follow up taking ocular pressure measurements after every diode delivery session .

Results

A significant decrease in IOP has been observed from the first month of the treatment compared to the placebo group (from 22.6mmHg before treatment to 15 mmHg after the tenth session) this amelioration has been also remarked during the second session of treatment (fifth month) to attempt 14.2mmHg.

Conclusion

Thera-RED light diode system treatment shows a significant decrease of IOP and remained to be stable under 14.2 mmHg in all the follow up, which confirm that photobiomodulation help in reducing the intraocular pressure in glaucomatous patients .

Key words

Photobiomodulation, intra ocular pressure, trabecular meshwork, diode light, primary open angle glaucoma, aqueous humor,

Introduction

"Primary Open Angle Glaucoma (POAG) is a degenerative and chronic optic neuropathy". (**1**) "it is a complex, multifactorial neurodegenerative disease process that leads to progressive damage to the optic nerve **(2),**

and the leading cause of irreversible blindness in the world". **(1).**

Up to date, glaucoma presents a number of cases about 76 million in 2020 and could reach 111.8 million in 2040, **(3)(4).**

"The most important risk factor for glaucoma is the increase of intraocular pressure (IOP) **(5)**, the IOP is generated by a damage of trabecular meshwork" **(6).**

"The use of photobiomodulation therapy has recently been considered in many diseases by stimulating cell migration and proliferation towards the damaged tissue, and controlling inflammation, which will eventually cure the disease" **(7).**

Our study is for the purpose of stabilized the intraocular pressure with ameliorating the aqueous humor outflow.

- **Material and methods:**

20 eyes with primary open angle glaucoma (POAG) were selected and divided into 2 groups (n=10). The first group was treated with PBM; the second group was considered as placebo group. The subjects were selected after ophthalmological exams (VA, SL, gonioscopy) and no glaucoma treatment has been stopped during the study. This study was conducted in partnership between the laboratory neurogenesis research and development and ophthalmological single center.

- **Study design**

The data were collected during 20 visits over the course of 5 months' study **(figure1)** no exclusion factors were present; a written informed consent was taking from the patients. And the good practice of Helsinki guide lines was applied .

The clinical studies were carried out within an ophthalmological clinic located in Algeria.

The device has been patented and certified by the Algerian national institute of industrial property under the reference(N°230300/26/03/2023).

Exclusion factors:

Patients with Close angle glaucoma; glaucoma with normal intraocular pressure and Mono ophthalmic patients were excluded from this study.

Subjects underwent two rounds of treatment during the study which consisted of PBM or placebo treatments with the assurance of their anonymity, 10 sessions for 31 days (1 month) with an interval of three months maximum between the series of sessions initiated at the start and repeated in the 5 th month.

The procedures involving the treatment of our patients were carried out under good hygienic and regulatory conditions, and good practice of Helsinki.

Intra ocular pressure (IOP) was taken before and after each session with aplanation tonometry and a diagram of the evolution of the ocular pressure was provided in order to establish the IOP evolution.

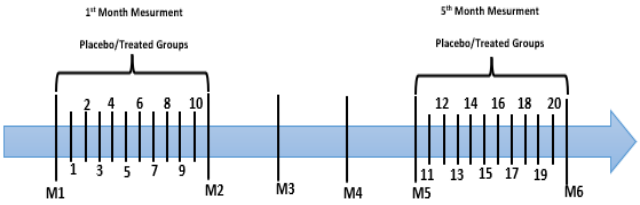


Figure1: diagram illustrating the PBM clinical study design.

- **Evaluated parameters**

tonometry by applanation tests as well as a visual field with 24/2 program (Zeiss) were taken in order to establish a statistical study highlighting the results of our study.

- **Photobiomodulation treatment**

The subjects were treated with PBM ''*Thera-Red*'' which delivers two distinct wavelengths, a red range (660 n.m) and a near IR range (850

n.m), with emitted energy of 300mW/cm² pulsed for the near IR, and an emitted energy of 250mW/cm² for red light. The treatment consists of projecting red and Near IR lights in 4 distinct phases under a well-established protocol. **Table 01**

The first phase includes the projection of continuous red diode light for 100 seconds (eye closed), followed by a second phase in which a pulsed near IR light is projected for 40 seconds (eye open). A third phase follows comprising continuous red light for 100 seconds (eye closed), and the fourth and final phase consists of a second projection of near IR light for 40 seconds (eye open).

Figure 2: *Thera-Red*

Table 01: 'Thera- Red'system specifications.

Parameter	**Specifications**
Light source	Diode light emission.
Light emission	660 n.m output 300mW/cm2 850 n.m output 250mW/cm2
Treatment exposure time	Total of 280 seconds (4 minutes 40 seconds). Dispatched into 4 phases: **1:** 100 seconds with closed eye continuous RED wavelength. **2:** 40 seconds with open eye pulsed Near IR wavelength. **3:** 100 seconds with closed eye continuous RED wavelength. **4:** 40 seconds with open eye pulsed Near IR wavelength.

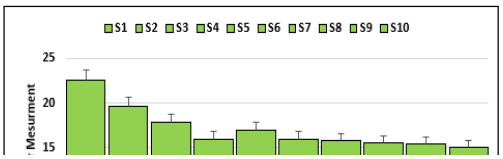
- **Statistical analyses**

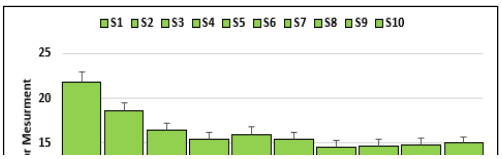
The statistical results were carried out with the EXCEL-Stat software, the average; the histograms and the P value ($p < 0.05$) were applied in order to highlight the results of our study.

- **Results**

20 patients aged (66±8) (60% men and 40% women) were recruited in this study, divided into two groups (one group treated with PBM and the other considered as placebo group). with an IOP measurement before and after each treatment session.

- The results obtained from IOP in summer marked and presented in the histograms below.





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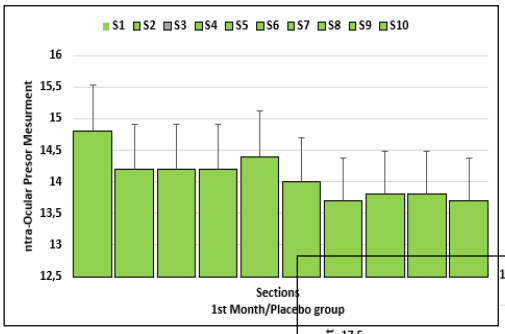

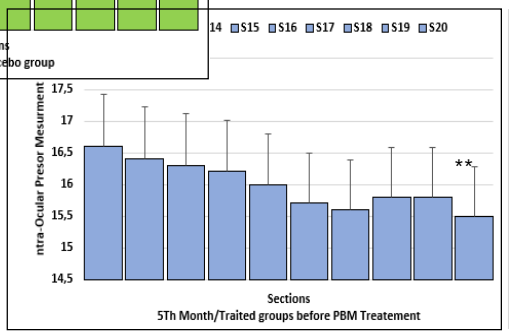

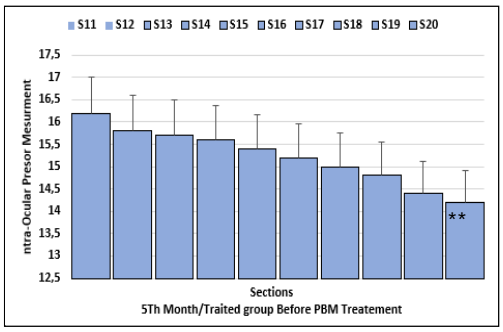

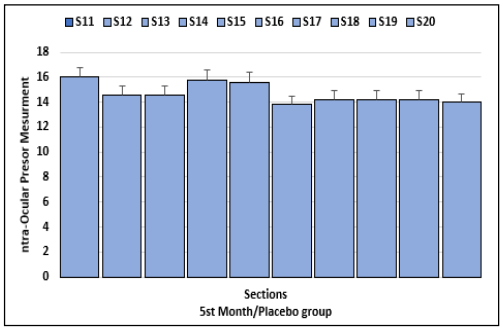

* :significant

** :high significant

* : p ≤0.05

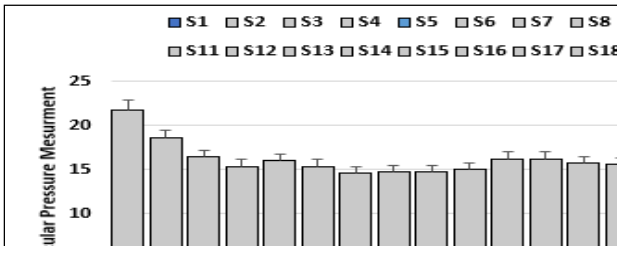

Fig. 3. Histograms showing IOP in summer marked

The results show a decrease in eye pressure, compared to the first session (from 22.6 mmHg before treatment to 15 mmHg after treatment session 10) during the first month.

On the other hand, an insignificant decrease in the placebo group (from 14.8mmHg to 13.7 mmHg).

After 5 months the intraocular pressure was measured and the treatment was taking back the intraocular pressure content decreased significantly (from 16.6 mmHg to 14.2 mmHg). With an average of 2.2 mmHg.

the placebo group showed improvement (a slight decrease in intraocular pressure). From 16 mmHg to 14 mmHg with an average of 2 mmHg.

Discussion:

"Glaucoma is an optic neuropathy in which the primary risk factor is increased intraocular pressure (IOP), attributed to increased resistance to trabecular outflow of aqueous humor (AH). This resistance is believed to result from trabecular degeneration secondary to chronic oxidative stress and cellular senescence but may also involve inflammatory mechanisms whose roles are little known" **(8).**

"One of the major causes of the degeneration and cell loss of the glaucomatous trabecular meshwork would be the existence of chronic oxidative stress secondary to aging, and amplified in the event of glaucoma". **(9)** "Indeed, in case of chronicity, chronic oxidative stress would promote senescence of trabecular tissue **(10)** cell apoptosis, accumulation of extracellular matrix (ECM) and stiffening of the cytoskeleton, leading to increased resistance to evacuation of the HA and thus to an elevation of the IOP". **(9) (11) (12).**

"The TM is the most sensitive tissue to oxidative damage in the anterior chamber" **(13).** "Oxidative stress to the TM can cause much damage, such as reduce TM mitochondrial respiratory activity, leading to growth arrest **(14),** affect ECM structure **(15)** and lead to ECM accumulation (**16),** damage TM cellular DNA **(17),** alter membrane permeability **(18),** cause the rearrangement of TM cell cytoskeletal structures, cause the loss of cell-matrix adhesion (**19),** affect cell cycle progression **(20),** cause inflammatory cytokine release **(21, 22),** and trigger apoptosis **(23,24),** as well as many forms of cell death" (**25).** "Cell death may cause a free radical attack **(26, 27)** and the loss or altered functionality of TM cells, leading to even more oxidative stress, thus beginning a vicious cycle" **(28).** "At least, ROS alter the morphology, function and drainage of the anterior chamber filter channel that eventually leads to an increase in IOP" (**29). "**In patients with glaucoma, the levels of mitochondrial DNA (mtDNA) damage and lipid peroxidation products in the TM are significantly higher compared with the controls **(30; 31)** and their visual field

defects, due to retinal ganglion cell degeneration, are directly proportional to oxidative damage to the TM" **(32).**

"An important principle of photobiomodulation therapy is that the dose of light administrated does not exceed the damage threshold not be defined by their output power per session , but by the effective dose delivered to the target tissue at the specified wavelength".(33).

"Photobiomodulation (PBM) involves the use of red or near infrared light at low power densities to produce a beneficial effect on cells or tissues (34). The main use proposed for photobiomodulation therapy is to reduce inflammation (35) and to regenerate damaged tissues. The primary site of light absorption in mammalian cells has been identified as the mitochondria and, more specifically, cytochrome c oxidase (CCO**)". (34)** .

"Some studies show that the purified enzyme, cytochrome c oxidase (CCO) was shown to be activated in vitro by red (633 nm) (36). CCO is unit 4 of the mitochondrial respiratory chain and is a complex molecule with 13 separate protein subunits. CCO contains two different copper centers CuA and CuB and two heme centers, heme-a and heme-a3". **(37).**

"The leading hypothesis to explain how exactly light increases CCO enzyme activity is that nitric oxide (a molecule that is known to inhibit CCO by non-covalently binding between heme-a3 and CuB **(38))** can be photodissociated by absorption of a photon of red or NIR light" **(39).** to explain why PBM appears to have greater effects in diseased or damaged cells is that unhealthy or hypoxic cells are more likely to have inhibitory concentrations of NO, increasing the rate of respiration and ATP production. This proposed mechanism is illustrated in **(figure4)** which could explain the decrease in IOP after the session of PBM treatment.

"Akt/mTOR/cyclinD1, but It is not yet clear precisely how PBM activates Akt, and it is well

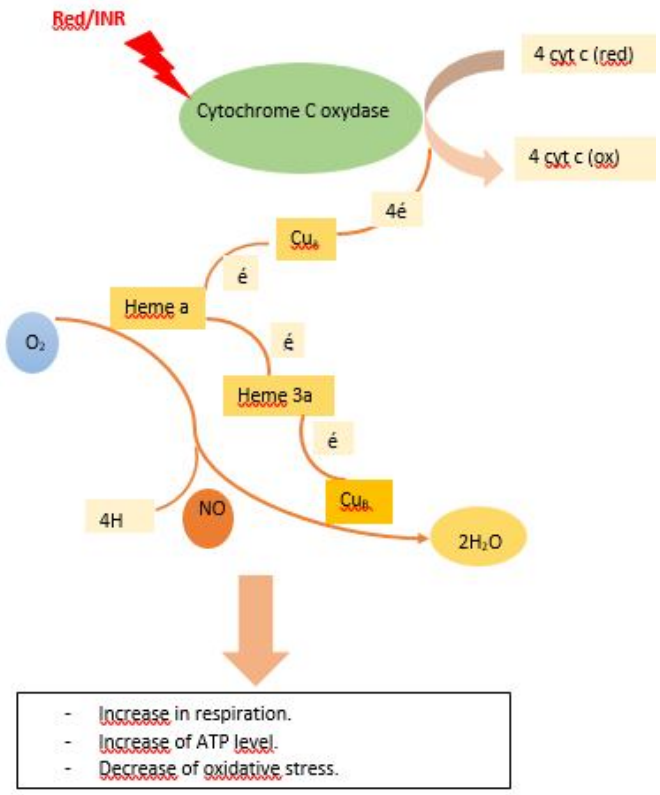

Figure4: the effect of RED/INR on the Cytochrom C oxidase.

"The significant decrease in IOP level after 5 months of PBM treatment could be explaining by that PBM may exert a prosurvival effect on cells via the activation of AKT/GSK3b/b-catenin pathway. Basically, protein kinase B (also known as AKT) can be activated by PBM, and then interact with glycogen synthase kinase 3b (GSK3b), inhibiting its activity. GSK3b is a serine-threonine kinase involved in cell death" **(40).** "PBM activates Akt, which phosphorylates the Ser9 residue in GSK3b, rendering the enzyme inactive. b-catenin is an important component of Wnt signaling pathway but GSK3b-mediated phosphorylation of b-catenin or the tau protein seems to enhance TM cell death, and conversely phosphorylated GSK3b leads to cells survival"**. (41)**

Another pathway that can be activated by PBM-mediated activation of Akt is known that Akt and ROS generation are closely intertwined"**. (42).**

"Forkhead box protein M1 (FOXM1) is a transcription factor involved in the regulation of the transition from G1 to S phase of the cell cycle leading to mitotic division" **(43)** "FOXM1 is activated by epidermal growth factor via extracellular signal-regulated kinase (ERK)". **(44**). "after PBM treatment, the mitogen-activated kinase (MEK)/ERK pathway was inhibited prevented the nuclear translocation of FOXM1, suggesting that Raf/MEK/MAPK/ERK signaling is crucial for the anticell senescence effect of PBM mediated by FOXM1" **(45).**

"Peroxisome proliferator-activated receptors (PPARs) play a role in the regulation of mitochondrial metabolism" **(46)** "They are nuclear receptors that regulate gene expression. PPAR-c is involved in the generation of heat shock protein 70 (HSP-70), which is anti-inflammatory **(47)** after PBM using INR in 850n.m a marked rise in the expression of PPAR mRNA was observed, as well as increased PPAR-y activity, which decrease the inflammatory effect, by increasing the expression of a transcription factor that is signaling the synthesis of HSP70 and other anti-inflammatory proteins, leading to TM restoration". **(48). Figure5**

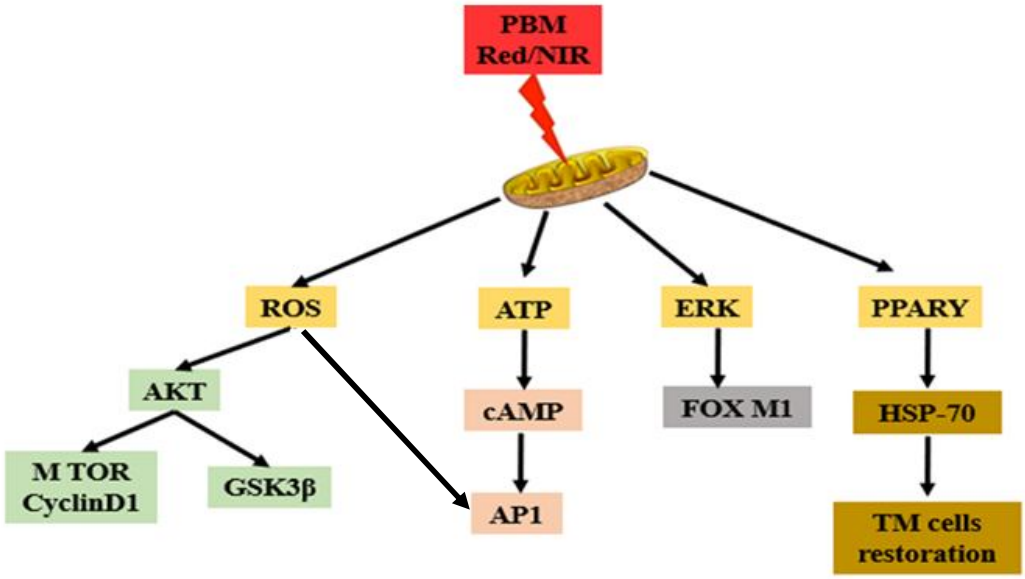

Figure5 : Activation of transcription factors and signaling pathways after PBM

In fact, all these PBM pathways could promote anti-oxidant effect, inflammatory reduction, mitochondrial activity restoration and TM cells renewal, leading to a lower eye pressure and thus treat glaucoma.

Conclusion:

in our study, photobiomodulation shows a clear improvement in the intraocular pressure compared to the placebo group, the use of this device in the daily practice of the ophthalmologist will improve the management of glaucomatous patients that could reduce the use of eye drops.

Consent

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

Disclaimer

Thera-RED light diode system was made by Laboratory Neurogenesis Research and Development patented by INAPI and certified by the national health organization (Algeria).

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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