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The Role of Brimonidine Eye Drops as an Adjunctive Therapy for Optic Nerve Protection in Patients with Controlled Open Angle Glaucoma

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ABSTRACT

Objective: This study aims to evaluate the neuroprotective role of brimonidine eye drops in patients with controlled open angle glaucoma.

Methods: This study is prospective and non-randomized. It was done between January,2014 and April, 2016. It included 33 eyes with controlled open angle glaucoma who were referred to Al Zahraa University Hospital. Brimonidine eye drops (BMD) were administrated. Follow up was done every 6 months for 12 months and three visual field (VFs) examinations were done to all patients using Humphrey Visual Field Analyzer II 745.**Results:** There is a gradual decline of IOP mean values from 15.3 ± 3.6 mmHg baseline to 13.5 ± 3.0 mmHg after 6 months and to 11.7±2.1 mmHg after one year of the use of BMD eye drops. The mean values of MD measurements showed improvement after BMD eye drops use as it becomes lower than baseline values after 6 months (-7.2 ± 5.2 vs -5.1 ± 3.7 respectively), with further improvement after one year of BMD eye drops use as it becomes lower than that after 6 months (-5.1 ± 3.7 vs -3.3 ± 3.6 respectively). Similarly, PSD measurements after 6 months (4.6 ± 3.1 vs 4.0 ± 3.1). Furthermore, measurement after one year of BMD eye drops use show more improvement as it becomes lower than measurements after 6 months (4.0 ± 3.1 vs 3.4 ± 4.4).

Conclusion: Neuroprotection can be used to reduce the risk of glaucomatous progression independent of its effects on IOP as the future treatment modality.

Keywords: Glaucoma, IOP, Visual field**,** Brimonidine eye drops.

INTRODUCTION

Glaucoma is second only to cataract among visual disorders, but it is a major cause of worldwide irreversible blindness. Bilateral blindness will be present in 5.9 million people with open angle glaucoma and 5.3 million people with angle closure glaucoma in 2020 **[(1)].**

Glaucoma is the ocular disorders with multiple-factorial induce via a clinical optic neuropathy with or without enhance the intraocular pressure. Few research claims that the IOP is the best approach to treat the glaucoma **[(2)].**

Visual field loss and RGCs death continue to occur in patients with well controlled intraocular pressures and thus, a consensus has recently been reached that additional treatment strategies are needed **[(3)]**.

Recently, there has been a growing interest in using neuroprotective drugs for the treatment of glaucoma. Brimonidine (BMD) is a selective α2-adrenergic receptor agonist that is used clinically to lower the IOP by decreasing the production of aqueous humor and facilitating its outflow via the TM **[(4)].** BMD has been found to prevent progressive RGC loss and thinning of the inner retinal layer and visual impairment in a normal tension glaucoma. This was achieved through stimulation of production of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and basic fibroblast growth factor in multiple pathways **[(5)].** BMD significantly lowers the rate of visual field progression, attributed to an IOP-independent protective effect of BMD **[(6)].**

METHODS

This intervention prospective study was carried out between January,2014 and April, 2016 in *Al Zahraa University* Hospital. Thirty three eyes with controlled open angle glaucoma (16 patients with bilateral eye affection and one patient with a unilateral eye affection) were included in this study. Mean age of patients ± SD was 43.0 ± 9.4 years (Range: 29 - 64 years). All patients had a diagnosis of open angle glaucoma based on the appearance of the optic disc and reproducible perimetric defects

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characteristic of glaucoma. BMDs were administrated, and follow up was done for 12 months. Visual field (VFs) examination was done before BMDs administration, and was then repeated every 6 months using the Humphrey Visual Field Analyzer II 745.

Inclusion criteria

Cases with controlled open angle glaucoma
With no media opacities.
Refractive errors in the spherical equivalent not exceeding −6 or +3 D.
Cylindrical correction within 3.0 D.
Reliable SITA 24-2 standard tests.

Exclusion criteria

Age: <25 or >65 years:
Spherical equivalent refractive error: <−6.00 D.
Diabetic retinopathy or other diseases (as optic disc abnormalities) that could affect the visual field.
Previous intraocular surgery.
Other intraocular diseases or other diseases affecting the VF.
Treatment with miotics.
Unreliable VF tests.

All cases were subjected to the following: -

History taking: age, sex, family and medical history.
A comprehensive ophthalmic examination: Best corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure (IOP) measurement using Goldmann applanation tonometry, gonioscopy and dilated fundoscopic examination using a 78-diopter (D) lens.
Standard automated perimetry (SAP) with 24-2 Swedish Interactive Threshold Algorithm (Humphrey, Carl Zeiss Meditec, Inc., Dublin, CA) were collected.

The studied cases showed controlled IOP by either beta blocker, prostaglandin analogs or carbonic anhydrase inhibitors eye drops. Brimonidine (BMD) α2 adrenergic receptor agonists (α2ARAs) 0.2% eye drops twice daily was introduced to all patients. Patients were followed up with ophthalmological examination after 6months & after one year of brimonidine eye drops use.
Perimetry: White in white visual fields (Humphrey Field Analyzer) was performed using the conventional test procedures (full-threshold test strategy). An optimal lens correction was placed before the tested eye, and the fellow eye was occluded with an eye patch. All tests utilized a 24-2 stimulus presentation pattern.

Glaucomatous visual field was defined by two of the following three criteria:

The presence of a cluster of three points on pattern deviation probability plot with a P-value of less than 5%, one of which had a P-value less than 1%, or a pattern standard deviation with a P-value less than 5%, or a glaucoma hemi-field test result outside normal limits.

The study was done after approval of ethical board of Al-Azhar university and an informed written consent was taken from each participant in the study.

Statistical analysis

Statistical analysis was done by using the Statistical Package for Social Science; version 17 for windows.
Descriptive statistics: Quantitative data were presented as mean ± standard deviation (mean ± SD).
Analytical statistics: Comparison between the ophthalmological measurements at different study time points was done by using paired t-test.
The level of significance was taken at P value of < 0.05; p values less than 0.05 was considered statistically significant.

RESULTS

Table (1): Age and ophthalmological examination of the studied cases

Items	Mean ±SD	Range
Age/ years	43.0 ± 9.4	29.0 - 64.0
Best Corrected Visual acuity	0.70 ± 0.15	0.50 – 1.00
CD ratio	0.58 ± 0.13	0.40 - 0.80

CD ratio: cup/disc ratio**.**

This table shows the age, visual acuity and CD ratio measurements among the studied cases. The mean age of the studied cases ± SD was 43.0 ± 9.4 years (Range: 29.0 - 64.0 years).

Table (2): Baseline and follow up measurements of IOP, MD and PSD of the studied cases

Items	Baseline Measurements **before** BMD eye drops use	Measurements **after 6 months of** BMD eye drops use	Measurements **after 1 year of** BMD eye drops use
IOP (mmHg) Mean ±SD	**IOP1**	**IOP2**	**IOP3**
	15.3 ± 3.6	13.5 ± 3.0	11.7 ± 2.1
MD(dB) Mean ±SD	**MD1**	**MD2**	**MD3**
	-7.2 ± 5.2	-5.1 ± 3.7	-3.3 ± 3.6
PSD(dB) Mean ±SD	**PSD1**	**PSD2**	**PSD3**
	4.6 ± 3.1	4.0 ± 3.1	3.4 ± 4.4

MD: mean deviation, **PSD:** pattern standard deviation, **IOP:** Intraocular pressure

Table 2 and figures 2.3,4 demonstrate measurements of IOP, MD and PSD of the studied cases at different study times. There is a gradual decline of IOP mean values from 15.3 ± 3.6 to13.5 ± 3.0 after 6 months and to 11.7±2.1 after one year of the use of BMD eye drops. The mean values of MD measurements showed improvement after BMD eye drops use as it becomes lower than baseline values after 6 months (-7.2 ± 5.2 vs -5.1 ± 3.7 respectively), with further improvement after one year of BMD eye drops. Similarly, PSD measurements were improved after 6 months with further improvement after one year of BMD eye drops.

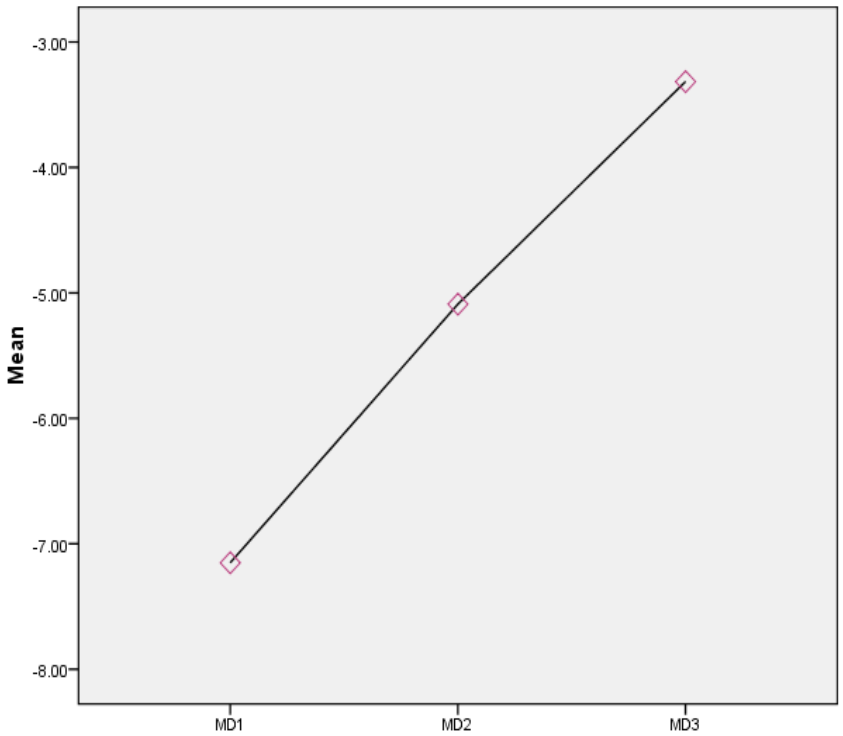

Figure 1. Values of mean deviation at follow up visits

This figure shows the gradual improvement of MD values along the follow up visits with the use of BMD eye drops.

Table (3): Comparison of MD, PSD and IOP measurements at different follow up visits by paired t-test

Items	Mean difference	p-value
MD comparison**		
MD1- MD2	-2.1± 3.7	0.004*
MD1- MD3	-3.8 ± 4.1	< 0.001*
MD2- MD3	-1.7 ± 2.5	<0.001*
PSD comparison**		
PSD1-PSD2	0.59 ± 2.3	0.161
PSD1-PSD3	1.18 ± 3.8	0.084
PSD2-PSD3	0.58 ± 3.78	0.381
IOP comparison**		
IOP1 - IOP2	1.8 ± 1.12	< 0.001*
IOP1 - IOP3	3.6 ± 2.1	<0.001*
IOP2 - IOP3	1.7 ± 1.5	< 0.001*

MD: mean deviation, **PSD:** pattern standard deviation, **IOP:** Intraocular pressure
**paired t-test *Significant p-value

This table shows comparison between MD and PSD and IOP measurements at different study times by paired t-test. There is a significant difference (P < 0.05) between baseline MD and IOP measurements and the follow up measurements after 6 months and after one year of the use of BMD eye drops. The mean difference between the baseline MD and IOP values and after one year was significantly higher than the mean difference between baseline measurements and after 6months of the use of BMD eye drops (P < 0.05). Similarly, the mean difference of PSD measurements was higher between baseline and after one year (3.6 ± 2.1) than between the baseline and after 6 months (1.8 ± 1.12) with a non-significant p-value (P> 0.05).

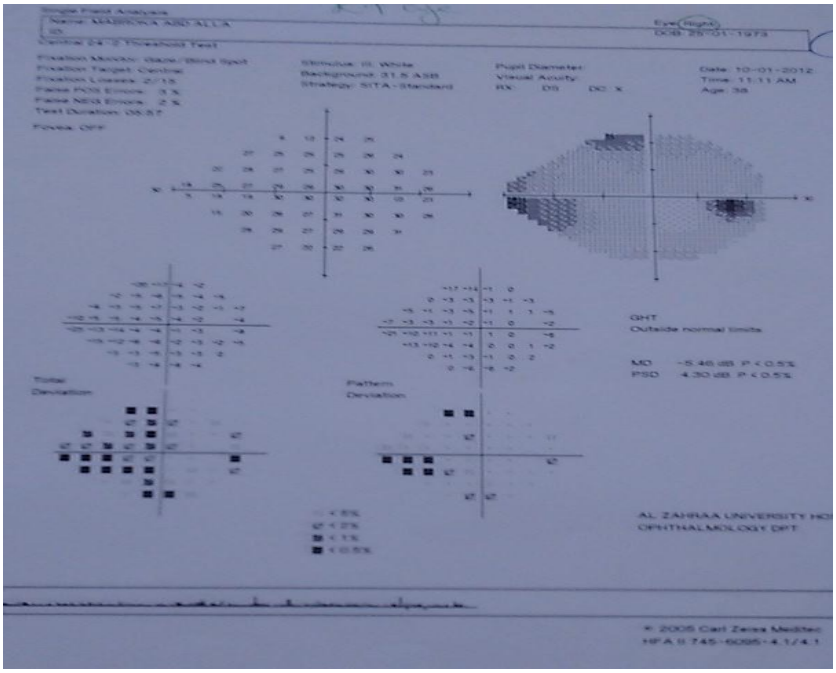

Figure (2): Visual field at the first examination of the patient.

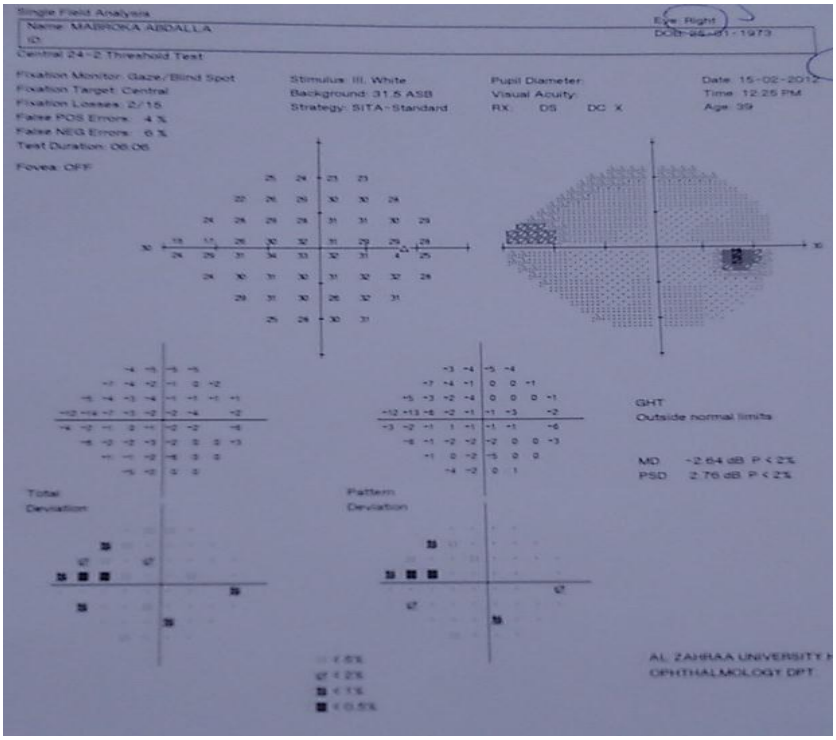

Figure (3): Visual field of the patient after 6 months

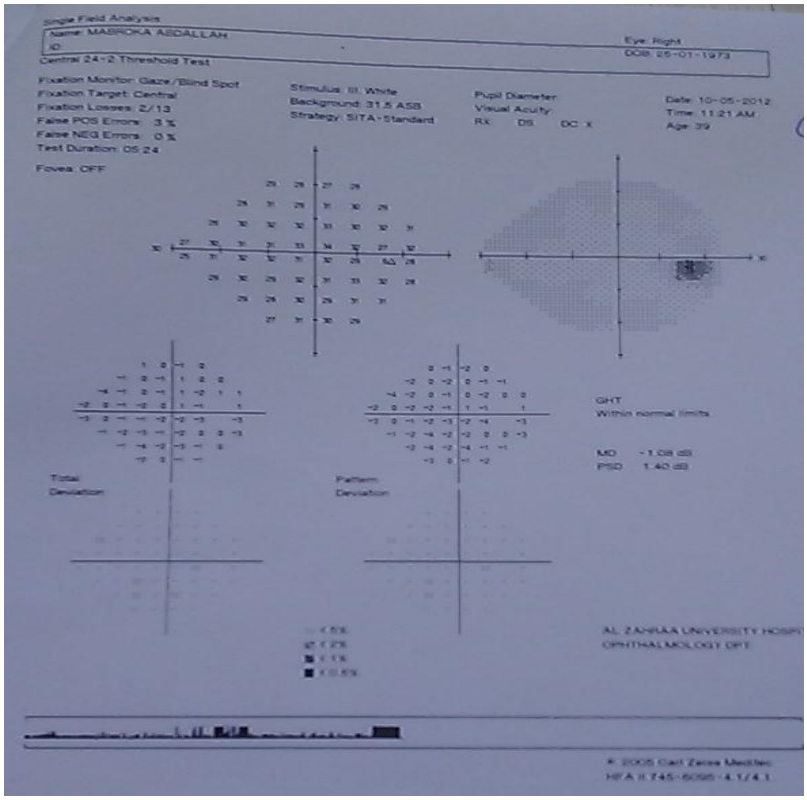

Figure (4): Visual field of the patient after one-year

DISCUSSION

Glaucoma neuroprotection must be considered independent of IOP lowering, and the target neurons should be in the central visual pathway, including retinal ganglion cells (RGCs). Chronic progressive loss of RGC is thought to be biphasic: initiation of damage is caused by a primary injury associated to the main risk factors of glaucoma (elevated IOP, cardiovascular risk factors, age, vasospasm), and there is a delayed (secondary) degeneration of neurons that either escaped the injury or were only partially damaged. The secondary degeneration may be an outcome of a hostile environment created by damaged neurons [(7)].

Brimonidine is thought to up regulate brain derived neurotrophic factor (BDNF), activating antiapoptotic genes and the cell survival signaling pathway. It is also thought to modulate the N methyl-D-aspartate receptors [(8)].

Brimonidine is also known to upregulate not only BDNF, but prosurvival factors, such as antiapoptotic factors B-cell lymphoma -2 (Bcl-2) and B-cell lymphoma extra-large (bcl-xl), basic fibroblastic growth factor (bFGF) and extracellular signal regulated kinases (ERKs). This action assists in the prevention of neuronal death and promotes cell survival [(9)].

The age of the studied cases ranged between 29.0 and 64.0 years with a mean value of 43.0 ± 9.4 years. There is a gradual decline of IOP mean values from 15.3 ± 3.6 to13.5 ± 3.0 after 6 months and to 11.7±2.1 after one year of the use of BMD eye drops; with a significant mean difference between the IOP baseline measurements and that after 6 months and one year.

Although the reduction of IOP has been the outcome of interest in previous research [(10)], it was not the primary focus of this study since lowering IOP alone is not always effective in preventing visual field loss due to glaucoma. Mean change in IOP, however, was included as a secondary outcome as it is currently the most common risk factor for glaucoma disease progression and reduction may be beneficial for some patients [(11)]. Furthermore, the **Collaborative Normal Tension Glaucoma Study (CNTGS)** [(12)] showed that a 30% reduction in IOP had significant benefit and, since that time a 30% reduction in IOP has become the standard of glaucoma care because it is a strong predictor of glaucomatous damage.

In the current study, the mean values of MD measurements showed improvement after BMD eye drops use as it becomes lower than baseline values after 6 months (-7.2 ± 5.2 vs -5.1 ± 3.7 respectively), with further improvement after one year of BMD eye drops use as it becomes lower than that after 6 months (-5.1 ± 3.7 vs -3.3 ± 3.6 respectively). **Prata *et al.*** [(13)] reported that a significant difference in the mean deviation index was found, but not in the pattern standard deviation, although different studies describe an improvement of visual field after reducing IOP in glaucoma eyes.

There is a significant difference ($P < 0.05$) between baseline MD measurements and at 6 months and one year after the use of BMD eye drops. This in agreement with **Araie** [(14)] who reported that the corrected pattern standard deviation measures were significantly changed within treatment groups compared with baseline (P value ≤ 0.001). Among subgroups of participants with early visual field loss or younger participants, showed some benefit in slowing visual field deterioration (mean deviation = 0.29, P value = 0.005).

The mean difference between MD1-MD3 (-3.8 ± 4.1) was higher than mean difference between MD1- MD2 (-2.1± 3.7) and MD2- MD3 (-1.7 ± 2.5). In spite of the non-significant difference of the PSD measurements at different sittings, the PSD were improved after 6 months with a further improvement after one year of the use of BMD eye drops.

This is in agreement with **Sena and Lindsley** [(15)] as they reported that corrected pattern standard deviation measures were significantly changed within treatment groups compared with baseline (P value ≤ 0.001). Among subgroups of participants with early visual field loss or younger participants, neuroprotection showed some benefit in slowing visual field deterioration.

CONCLUSIONS

The use of alpha 2 adrenergic agonists brimonidine eye drops as a neuroprotective agent showed improvement of MD measurements after 6 months of BMD eye drops use with further and continuous improvement after one year of its use.

These results are promising in prevention or controlling death of RGC in cases with open angle glaucoma.

RECOMMENDATION

Further efforts should be directed towards investigating long-term visual field preservation with neuroprotective drugs, since OAG is a chronic, progressive disease. Future studies should be performed on a large scale of population for more accurate evaluation.

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