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The Effect of Topical Brimonidine on the Haemodynamics of Optic Nerve Head and Retinochoroidal Circulation Using Optical Coherence Tomography Angiography in Glaucoma Patients.

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Abstract:

Introduction: Glaucoma is a chronic progressive optic neuropathy in which elevated intraocular pressure (IOP) is an important modifiable risk factor. So far, lowering IOP is the mainstay of glaucoma management, with the aim of lowering the rate of progression. Neuroprotection is a promising non-IOP-based approach to the management of glaucoma through increasing the longevity of retinal ganglion cells (RGCs) and increasing their resistance to various stressors. Brimonidine is both an ocular hypotensive and a neuroprotectant of RGCs. However, the exact mechanism through which brimonidine exerts its neuroprotective effect is not fully understood.

Aim of the study: To investigate the hemodynamic effects of brimonidine on the optic nerve head (ONH) and retinochoroidal circulation, which may add to our understanding of its neuroprotective properties.

Subjects and Methods: This is a prospective longitudinal interventional study where 22 brimonidine-naïve primary open angle glaucoma (POAG) patients underwent optical coherence tomography angiography (6*6mm macula and 4.5*4.5mm ONH) at baseline and three months after brimonidine. Superficial and deep macular ONH radial peripapillary capillary (RPC) vascular densities as well as subfoveal choroidal thickness (SCT) were compared between baseline and follow-up.

Results: Compared to baseline, there was a statistically significant increase in superficial macular vascular density (SVD) and a decrease in deep macular vascular density (DVD) at three-month follow-up. There was no statistically significant change in either ONH RPC vascular density (RPCVD) or SCT.

Conclusions: Brimonidine was associated with an increase in SVD, which may constitute a novel mechanism for its neuroprotective properties on RGCs through improved perfusion.

Keywords: Brimonidine; Glaucoma; Optical Coherence Tomography; Angiography.

1. Introduction

Glaucoma is a chronic, progressive optic neuropathy. Characteristic features of glaucomatous optic neuropathy (GON) include advancing optic nerve head (ONH) cupping, which results from progressive loss of retinal ganglion cells (RGCs) and retinal nerve fiber layer (RNFL). Such progressive structural damage is paralleled by progressive functional visual field constriction that can eventually lead to complete blindness [1].

In the context of GON, elevated intraocular pressure (IOP) is considered an important modifiable risk factor. Lowering IOP is therefore the main therapeutic intervention available for the management of GON. However, lowering IOP has been shown to only lower the rate of progression rather than halt the disease process altogether [2]. Therefore, interest is growing in other potential therapeutic options, e.g.,

neuroprotection. Neuroprotectants are agents that can increase the longevity of nerve cells through anti-apoptotic, antioxidant, and myriad other mechanisms [3]. Brimonidine, besides being a well-established ocular hypotensive, is also a known neuroprotectant of RGCs. However, the exact mechanism of its neuroprotective effects hasn't been adequately investigated [4].

In this study, we aim at testing the hypothesis that brimonidine may exert its neuroprotective effect by improving the perfusion of RGCs since brimonidine is essentially an alpha-2 receptor agonist with vasoactive properties [5]. Optical coherence tomography angiography (OCTA) is a non-invasive, optical interferometry-based angiography modality that we used to study the potential effects of brimonidine on the macular, ONH, and choroidal vasculature.

2. Subjects and methods

2.1. Subjects

A total of twenty-two primary open angle glaucoma (POAG) patients (thirty-five eyes) were included in the study. The sample size calculation was done using Stata software version 17.0 for Windows. The statistical power was set at 0.9 and the significance level at 0.05. The effect size was set to a mean difference of 3 and a standard deviation of difference of 4.48 based on scientific literature data regarding OCTA reproducibility and coefficient of variation as well as OCTA studies of brimonidine. The two-sample paired-means t-test sample size estimation tool of Stata

software version 17.0 for Windows yielded an estimated sample size of 26 eyes, which our sample exceeded by including 35 eyes.

Inclusion criteria

1. A confirmed diagnosis of POAG.
2. Brimonidine-naïve patients.
3. In case of patients already on antiglaucoma medication, only patients who had been on a single medication for at least three months prior to adding brimonidine were included.
4. Image quality index (IQI) of OCT angiograms of at least 5.

Exclusion criteria

1. Ocular vascular diseases e.g. retinal vein or artery occlusion, retinal vasculitis.
2. Systemic vascular diseases e.g. hypertension, diabetes mellitus, ischemic heart disease, vasculitis.
3. Retinal dystrophies and non-glaucomatous optic neuropathies.
4. Previous glaucoma surgeries.

2.2. Study design

This is a prospective, longitudinal, interventional study conducted at Fayoum University Hospitals. It was approved by the ethical committee of the Faculty of Medicine, Fayoum University (IRB M488). A written informed consent was obtained from all participants. Each participant underwent full ophthalmological examination including anterior and posterior

segment examination, gonioscopy and IOP measurement at baseline. Furthermore, OCTA 6*6 mm macula and 4.5*4.5 mm ONH were performed at baseline. Brimonidine tartrate 0.15% bid was prescribed to participants at baseline to achieve better control of IOP. The same ophthalmological examination and OCTA imaging protocol were repeated at a follow-up visit three months after starting brimonidine. Baseline intraocular pressure (IOP), superficial macular vascular density (SVD), deep macular vascular density (DVD), radial peripapillary capillary vascular density (RPCPVD) and subfoveal choroidal thickness (SCT) were then statistically compared to their corresponding follow-up values three months after brimonidine (**Figure 1**).

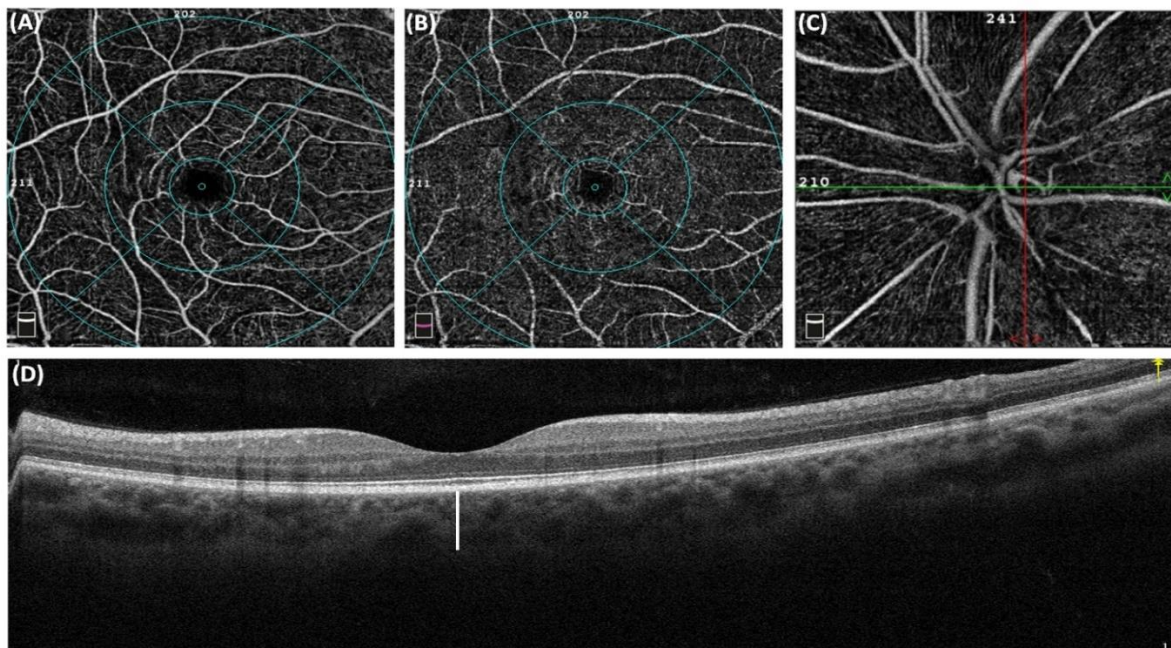


Figure 1. Superficial vascular plexus (A), deep vascular plexus (B), optic nerve head and radial peripapillary capillary plexus (C), B-scan optical coherence tomography with white line representing subfoveal choroidal thickness (D).

2.3. Statistical Methods

Descriptive data were presented as numbers and percentages for categorical variables. Means and standard deviation (SD) were used for numerical variables.

3. Results

A total of 35 eyes from 22 patients were included in the analysis. Nine eyes were excluded because of low-quality OCTA images (IQI less than 5) due to poor fixation or significant media opacity. The median and range of age were 62, 27–80

years. Sixteen (72.73%) patients were males, and nineteen (54.29%) eyes were right eyes. The mean and standard deviation of average retinal nerve fibre layer thickness (RNFLT) were $88.20 \pm 21.74 \mu\text{m}$ (**Table 1**).

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Table 1. Characteristics of participants.

Variables	Frequency (%)
Total number of patients N (%)	22 (100%)
Sex N (%)	
Male	16 (72.73%)
Female	6 (27.27%)
Total number of eyes N (%)	35 (100%)
Eyes N (%)	
Right	19 (54.29%)
Left	16 (45.71%)
Average RNFLT (mean \pm SD)	88.20 ± 21.74

Counterintuitively, IOP showed no statistically significant difference between baseline and follow-up. On the other hand, there was a statistically significant increase in SVD from 41.85 ± 6.04 to 42.64 ± 6.38 ($P = 0.03$). (**Figure 2**). Conversely, there was a statistically significant decrease in DVD

from 43.90 ± 7.57 to 42.56 ± 7.19 ($P = 0.02$). (**Figure 3**). No statistically significant change could be demonstrated for RPCPVD. Similarly, subfoveal choroidal thickness (SCT) showed no statistically significant change from baseline to follow-up (**Table 2**).

Table 2. Comparison between different measures at baseline and follow-up.

Mean ± SD	Baseline	Follow-up	P-value*
IOP mmHg	16.94	16.46	0.67
SVD	41.85±6.04	42.64±6.38	0.03
DVD	43.90±7.57	42.56±7.19	0.02
RPCPVD	42.76±6.28	42.37±7.20	0.47
SCT μm	325.37±38.85	330.29±31.78	0.43

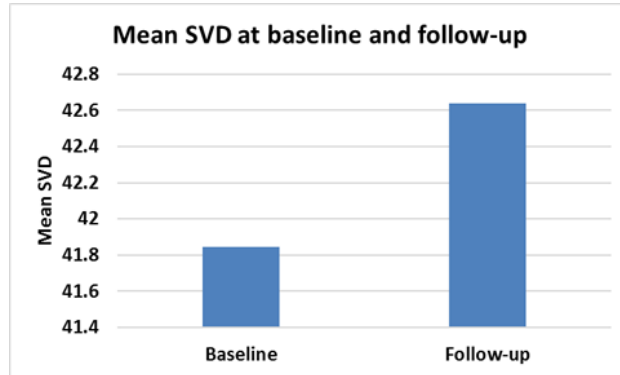


Figure 2. Bar chart comparing mean superficial vascular density (SVD) at baseline and follow-up.

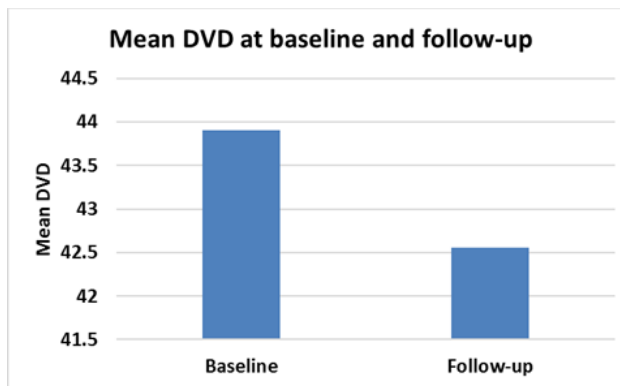


Figure 3. Bar chart comparing mean deep vascular density (DVD) at baseline and follow-up.

4. Discussion

While IOP reduction is still the main approach to the management of glaucoma based on established evidence of a lower

rate of progression in POAG and normal tension glaucoma (NTG), as well as a lower incidence of glaucomatous ONH damage in

ocular hypertension (OHT), continued progression despite lowering IOP leads to investigating alternative or complementary therapeutic approaches [2, 6, 7]. One promising add-on treatment is neuroprotection. Neuroprotectants have been shown to increase the resistance of RGCs in different types of optic neuropathies, e.g., compressive, ischemic, and GON, among others. However, the exact mechanism through which these positive effects are achieved is not clearly determined [8]. Brimonidine is a well-established neuroprotectant with evidence of better perimetric outcomes compared to other ocular hypotensives, e.g., timolol [9, 10]. Our results demonstrated that brimonidine caused a statistically significant increase in SVD, which is responsible for perfusing RGCs, the progressive loss of which is the core pathological feature of GON. However, no statistically significant increase in RPCPVD could be demonstrated, which implies that brimonidine-mediated improvement of perfusion occurred at the level of RGC somas in the macula and not retinal nerve fiber bundles in the peripapillary region. Interestingly, RGC somas are the synthetic parts of the extremely long RGC that extends from dendrites in the inner plexiform layer (IPL)

down to synapses in the lateral geniculate body (LGB), and hence somas are responsible for mitigating and combating cellular stress at any point along that exceptionally long course of the entire cell [11]. Therefore, improved perfusion of RGC soma is hypothesized to increase the resistance of the entire cell, retinal nerve fibers included, to different stressors. Conversely, brimonidine resulted in a statistically significant decrease in DVD. While the deep macular vascular plexus (DVP) is located deeper in the retina than the superficial macular vascular plexus (SVP) and is not directly involved in the perfusion of RGCs, decreased DVD implies preferential perfusion of the SVP since both SVP and DVP originate from common branches of the central retinal artery system. Therefore, the concomitant decrease in DVD and increase in SVD signify a diversion of blood flow to the SVP. On the other hand, no statistically significant effect could be attributed to brimonidine on subfoveal choroidal thickness (SCT). The evidence for retinal and ONH vascular effects of brimonidine is rather conflicting, with some studies reporting no statistically significant effects and others demonstrating improved retinal vascular autoregulatory capacity [12–15]. While this study demonstrated

brimonidine-mediated improvement of blood flow to RGCs, the lack of perimetric data precluded a definitive conclusion of functional neuroprotective properties. Therefore, future studies correlating the vascular and perimetric effects of brimonidine are needed.

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Ethical approval and consent to participate: This study was approved by the ethical committee of the faculty of medicine at Fayoum University (IRB M488). Written informed consent has been obtained from

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Conclusion

Brimonidine increases superficial macular vascular density, which may be beneficial for retinal ganglion cell viability in primary open-angle glaucoma. However, studies incorporating functional investigative modalities, e.g., perimetry, are needed to confirm functional benefits.

the patients to participate and to publish this paper.

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