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ORIGINAL ARTICLE

Effects of dorzolamide/timolol fixed combination on retrobulbar hemodynamics in pseudoexfoliative glaucoma

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Abstract In our study we aimed to evaluate the short-term effects of dorzolamide/timolol on ocular perfusion pressure and retrobulbar blood flow in patients with pseudoexfoliative glaucoma (PXG). This prospective observational cross-sectional study enrolled 22 eyes of 22 newly-diagnosed patients with PXG in a single center. All of the patients received a fixed combination of dorzolamide/timolol. Besides routine ophthalmologic examination, the retrobulbar hemodynamic parameters in the ophthalmic artery, central retinal artery, and short posterior ciliary arteries were measured in all participants at baseline and the 3rd month using color Doppler imaging. The mean intraocular pressure (IOP) was 22.3 ± 2.1 mmHg at baseline and reduced to 17.4 ± 2.3 mmHg at the 3rd month ($p < 0.05$). None of the retrobulbar parameters, except peak systolic velocity and resistive index in temporal short posterior ciliary arteries, changed significantly on therapy with dorzolamide/timolol fixed combination when the results were analyzed at Month 3. The drug significantly decreased the peak systolic velocity ($p = 0.044$) and reduced the resistive index in 0.04 units, 95% confidence interval 0.03–0.05, ($p < 0.001$) in the temporal short posterior ciliary arteries. This study reports that the retrobulbar hemodynamics might be affected less than expected by dorzolamide/timolol fixed combination in patients with PXG although the reduction of IOP was statistically significant.

Conflicts of interest: All authors declare no conflicts of interests.

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Introduction

Pseudoexfoliation syndrome is one of the most commonly identifiable causes of glaucoma overall [1]. Secondary chronic open-angle glaucoma as a result of blockage of the outflow channels by pseudoexfoliation material has been reported between 20% and 25% of all glaucomas [2]. Some previous studies have shown the accumulation of pseudoexfoliation material in the wall of central retinal artery, short posterior ciliary arteries, and vortex veins. A possible role in disturbance in the blood flow has been reported in patients with pseudoexfoliation syndrome.

The major role of carbonic anhydrase inhibitors (CAIs) on intraocular pressure (IOP) is reducing aqueous humor secretion by inhibition of carbonic anhydrase in the ciliary processes. In addition to IOP lowering effect of this group drugs, dorzolamide and brinzolamide also increase the retrobulbar ocular blood flow by arterial vasodilation [3–6]. Several studies, using different methods, indicated that dorzolamide reduced retrobulbar ocular blood flow [7–9].

The purpose of this study was to compare the effects of dorzolamide/timolol fixed combination on retrobulbar ocular blood flow parameters in patients with pseudoexfoliative glaucoma (PXG) using color Doppler imaging.

Materials and methods

This prospective observational cross-sectional study included 22 eyes of 22 patients (12 females, 10 males) with PXG, who are newly diagnosed at Medipol University School of Medicine, Department of Ophthalmology, Istanbul.

The inclusion criteria were having a white pupillary ruff and the presence of a manifest pseudoexfoliation deposition pattern in the anterior lens capsule, intraocular pressure (IOP) $>$ 21 mmHg with a typical glaucomatous disk, an open chamber angle, and characteristic glaucomatous visual field loss.

Exclusion criteria were eyes lacking clear corneas or those having posterior segment pathologies, previous intraocular surgery, ocular trauma or other intraocular pathology, or who were unable to understand the study or communicate. The study protocol was approved by the Ethics Committee of Medipol University. The tenets of the Declaration of Helsinki were followed and all patients provided informed consent prior to enrollment.

All patients underwent routine ophthalmic examinations including visual acuity, Goldmann tonometry, slit-lamp biomicroscopy, and fundoscopy. Color Doppler imaging measurements were performed by an experienced radiologist with a 7.5-MHz linear transducer using acoustic gel at baseline and 3rd month using Color Doppler imaging (LOGIQ P6; GE Healthcare, Milwaukee and Wisconsin, USA). For the measurements, patients were in the supine position with their eyes closed while looking straight ahead. During the examination minimal pressure was applied on the eye so as not to cause any alterations in retrobulbar blood flow measurements.

Ophthalmic artery blood flow parameters were obtained ~25 mm behind the globe, from the point where the artery crossed the optic nerve. The central retinal artery and vein were measurable ~10 mm behind the retrolaminar portion of the optic nerve. The nasal and temporal short posterior ciliary arteries were examined ~10–20 mm behind the globe just before they branched. Values for each artery, peak systolic velocity, and end diastolic velocity were obtained from the color Doppler signals. The resistive index was calculated by Pourcelot's formula [Resistive Index = (Peak Systolic Velocity − End Diastolic Velocity)/Peak Systolic Velocity]. Mean central retinal vein velocity was calculated from the color Doppler signals.

All statistical analyzes were performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). A Kolmogorov–Smirnov test was used to test for normality between samples, followed by a Levene test to assess equal variances. Wilcoxon test was used to compare the variables. All p values were two-sided and were considered statistically significant when $p < 0.05$.

Results

The mean age of patients was 63.15 ± 3.82 years (range, 52–68 years old) (12 females, 10 males). The mean IOP was 22.3 ± 2.1 mmHg at baseline and 17.4 ± 2.3 mmHg at the 3rd month. There was a significant decrease in IOP ($p < 0.05$). Retrobulbar hemodynamic variables at baseline and 3 months are given in Table 1. The mean blood flow velocities and resistance indices values, except peak systolic velocity and resistive index in temporal short posterior ciliary arteries, measured at baseline were not different from the values after 3 months of treatment with dorzolamide/timolol in patients with PXG ($p > 0.05$; Figures 1 and 2). The drug significantly reduced the resistive index in the temporal short posterior ciliary arteries from 0.60 (0.02) to 0.54 (0.02) and peak systolic velocity from 3 ± 6.8 cm/s to 2.7 ± 7 cm/s ($p = 0.001$ and $p = 0.044$, respectively).

Discussion

Pseudoexfoliation syndrome, an important cause of glaucoma, presents with an abnormal fibrillar extracellular material production and accumulation in anterior segment tissues pathologically [10]. Recent studies have described various intraocular complications associated with pseudoexfoliation syndrome [2,10–13]. According to electron microscopic investigations in autopsy specimens, pseudoexfoliation fibrils are observed not only in the eye, but also in the heart, lung, liver, gall bladder, and cerebral meninges [10]. Some studies suggested that, pseudoexfoliation syndrome seemed to extensively involve the vascular structures, causing a higher degree of decrease in orbital blood flow and circulation which presumably leads to glaucomatous damage faster than in primary open angle glaucoma patients without pseudoexfoliation [14]. In addition hemodynamic parameters in the retrobulbar vessels, especially in the central retinal artery and short posterior ciliary arteries which are the primary blood fund of the superficial nerve fiber layer, prelaminar, and laminar regions, are significantly lower in patients with PXG than in those healthy participants [14]. PXG has mostly worse outcomes compared with primary open angle glaucoma with high IOP levels, significant differences in pressure

Table 1 Retrobulbar hemodynamic variables at baseline and 3 months after dorzolamid/timolol administration in patients with pseudoexfoliative glaucoma.

Variables		Baseline		3rd month		p *
		Mean ± SD	Min–Max	Mean ± SD	Min–Max	
Ophthalmic artery	PSV	12.75 ± 5.2	5.4–26.7	12.05 ± 5.34	4.3–26.1	0.251
	EDV	47.61 ± 19.97	23.9–101.7	44.73 ± 14.97	20.3–85.3	0.352
	RI	0.72 ± 0.89	0.42–0.85	0.71 ± 0.08	0.49–0.84	0.153
Central artery	PSV	5.25 ± 1.56	2.30–7.40	5.27 ± 1.99	1.6–9	0.909
	EDV	19.43 ± 6.97	8.20–38.3	18.31 ± 5.45	7.1–35.4	0.254
	RI	0.71 ± 0.06	0.63–0.88	0.70 ± 0.07	0.61–0.85	0.696
Nasal posterior ciliary artery	PSV	4.57 ± 0.71	3–5.8	4.59 ± 1.06	3.2–6.8	0.653
	EDV	15.6 ± 3.37	9.5–19.7	15.15 ± 2.96	8.4–20.3	0.355
	RI	0.69 ± 0.05	0.57–0.77	0.69 ± 0.25	0.56–0.79	0.856
Temporal posterior ciliary artery	PSV	3 ± 6.8	4.75–0.95	2.7 ± 7	5.32–1.05	0.044
	EDV	8.4 ± 22	15.78–3.56	8.2 ± 22	15.32–3.09	0.897
	RI	0.61 ± 0.77	0.69–0.05	0.57 ± 0.76	0.64–0.05	0.001

EDV = end diastolic velocity (cm/s); PSV = peak systolic velocity (cm/s); RI = resistivity index; SD = standard deviation.
* Wilcoxon test.

between two eyes and also diurnal fluctuations. On the basis of these observations, it must be emphasized that modern antiglaucoma therapies should aim to affect not only intraocular pressure, but also other factors such as ocular blood flow. Although the effects of topical CAI drugs on ocular blood flow velocities were measured and the evidence obtained from these studies suggests that CAI agents increase the ocular blood flow velocities, the effect of these types of drugs was not investigated on primary open angle glaucoma patients with pseudoexfoliation [3–6,15]. The resistive index lowering effect of dorzolamide can be related to its vasodilator effect on ophthalmic and retinal vessels. Accumulation of abnormal fibrillar extracellular material in pseudoexfoliation possibly causes some changes in the vessel walls.

Since Harris et al [9] reported topical dorzolamide accelerated the blood velocity in the retinal and superficial optic nerve head but had no effect on retrobulbar hemodynamics, several studies have been conducted to achieve a clear and distinct result regarding the relationship between topical CAI and retrobulbar blood flow [3,9,16–21]. Although dorzolamide alone is not the most potent agent to lower IOP, compared with surgery or even with other topical antiglaucoma medications, it has a dual action, the

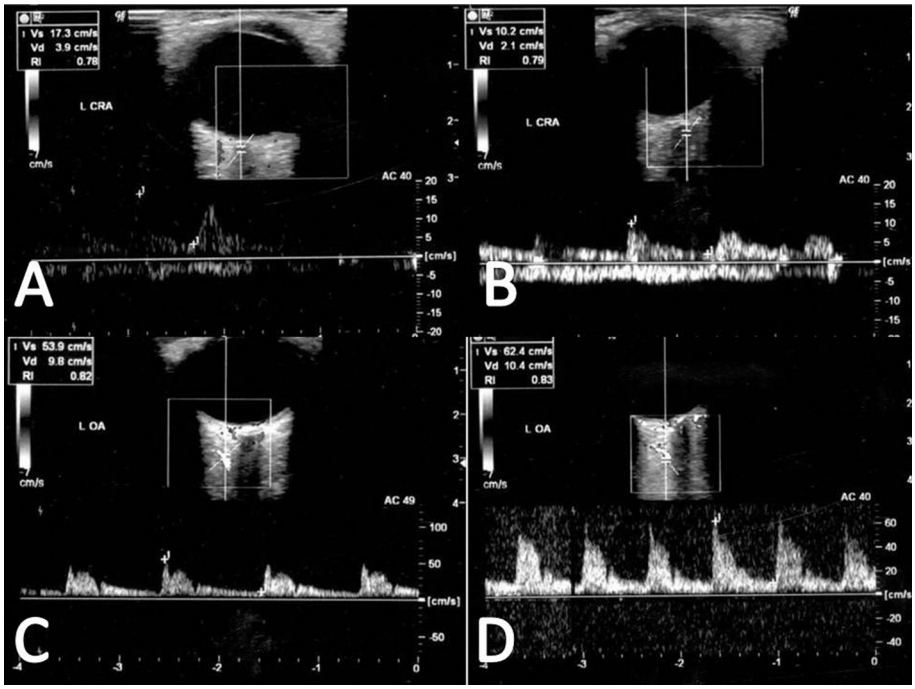

Figure 1. Peak systolic velocity, end diastolic velocity, and resistive index values of the central retinal artery (A, B) and ophthalmic artery (C, D) in patients with pseudoexfoliative glaucoma, at the two time points.

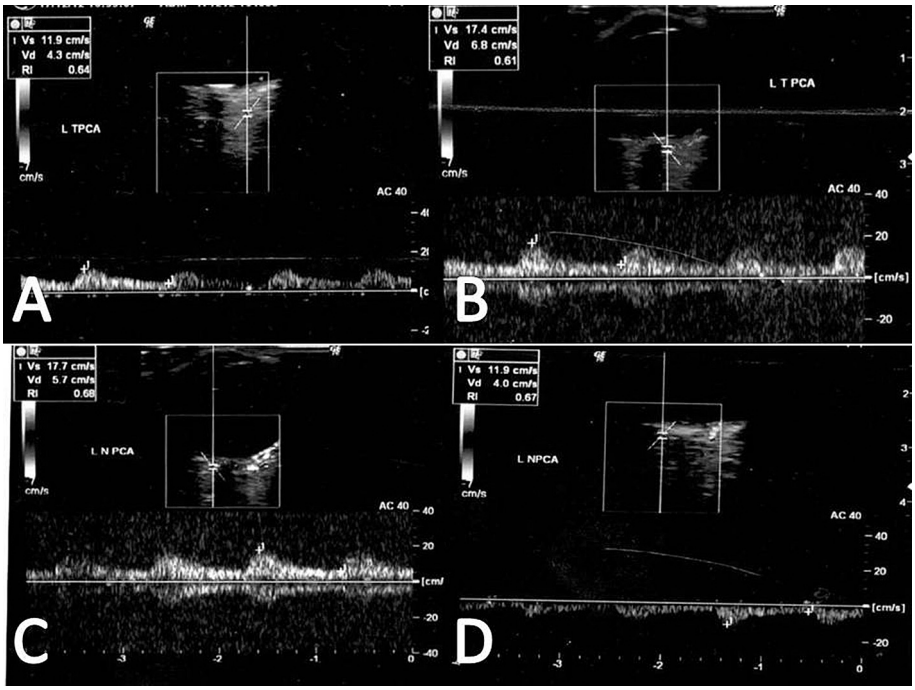

Figure 2. Peak systolic velocity, end diastolic velocity, and resistive index values of the temporal short posterior ciliary arteries (A, B) and nasal short posterior ciliary arteries (C, D) in patients with pseudoexfoliative glaucoma, at the two time points.

vasodilating and IOP lowering effect. Martinez et al [22] indicate that dorzolamide/timolol fixed combination has been shown to be effective and generally well tolerated. Their study was carried out on patients diagnosed as having primary open-angle glaucoma or pseudoexfoliation glaucoma. The results of this retrospective study indicate that dorzolamide/timolol fixed combination is effective in reducing IOP in glaucoma patients (even though with pseudoexfoliation) who did not respond to prostaglandin analogs/prostamides [22]. Based on previous studies with dorzolamide, most of the color Doppler imaging parameters, except in the ophthalmic artery, have clearly improved [9,16,17]. This is highly interesting, and it remains unclear why essentially similar medications, such as brinzolamide, demonstrates such differences in their vasoactive pharmacological effects. Martinez et al [3] point to differences between dorzolamide and brinzolamide in their impact on ocular blood flow outcomes in glaucomatous eyes over 5 years. According to their findings lower diastolic blood pressure, lower mean arterial pressure, antihypertensive medication, lower end diastolic velocity in the ophthalmic artery and short posterior ciliary arteries, and higher resistive index in the ophthalmic artery and short posterior ciliary arteries lead to progression in glaucoma. Also they showed dorzolamide/timolol fixed combination treatment reduced the risk for progression compared with brinzolamide/timolol fixed combination treatment half-and-half. These results are compatible with those previously reported by Galassi et al [16], Satilmis et al [23], and Zeitz et al [24,25]. They concluded that there is a straight relation between reduced ocular blood flow and visual field loss, and enhanced blood flow can influence the visual function of glaucoma patients. By contrast to these findings Siesky et al [26] found that brinzolamide and dorzolamide may provide an increase in retinal oxygen saturation in patients with primary open angle glaucoma without any influence on the retrobulbar blood supply. In another published study Siesky et al [19] also compared the effects of dorzolamide/timolol and brimonidine/timolol combinations on ocular blood flow in a 1-month period and found the same results with their previous study. Both studies included 15 primary open angle glaucoma patients. One of the most important limitations of these studies is number of patients. A small number of cases cast doubts on vasodilatator effects of dorzolamide. Yüksel et al found significant decreases in all orbital blood flow velocities, and increases in the resistive index values in patients with PXG, as compared with controls. In their study, patients with PXG showed statistically significant decreases in the mean peak systolic and end-diastolic velocities and increased mean resistive indices in all vessels except for the ophthalmic artery mean peak systolic velocity compared with the control individuals. Patients with primary open angle glaucoma, when compared with the control individuals, showed statistically significant decreases in the mean end-diastolic velocities and increased mean resistive indices in all vessels measured. They also indicate that no statistically significant differences were found in the mean blood flow parameters between primary open angle glaucoma and PXG. Although no significant difference in the mean blood flow parameters was found between primary open angle glaucoma and PXG, alterations of retrobulbar vessels might be associated with different pathogenic mechanisms of PXG [27,28].

In the current investigation, we examined the effects of dorzolamide on retrobulbar blood flow in newly diagnosed PXG patients. To the best of our knowledge, there has been no prior published study that has reported on the ocular

blood flow effects of dorzolamide/timolol fixed combination in primary open angle glaucoma patients with pseudoexfoliation.

A major limitation of our study is there is no control or comparative groups such as primary open angle glaucoma patients. Further studies including these groups would be more informative.

Previous studies, investigating the vaso-relaxing effect of CAI, pointed out that dorzolamide depended on its vasodilator effect on carbonic anhydrases in the perivascular tissue, involving different membrane-bound isoenzymes IV and XIV found in the retinal astrocytes and Muller cell. However, we think that accumulation of pseudoexfoliation material in the cells such as vascular endothelial cells, smooth muscle cells, and pericytes, which regulate local microcirculation, could achieve this result in patients with PXG.

Most of the previous studies supported the positive effect of dorzolamide on retrobulbar hemodynamics. The results of this study showed that the retrobulbar hemodynamics might be affected less than expected by dorzolamide/timolol fixed combination in patients with PXG, although the reduction of IOP was statistically significant. This finding raises some questions regarding the effects of pseudoexfoliation on retrobulbar vascular structures; such as vascular endothelial cells, smooth muscle cells, and pericytes. Further investigations with other types of antiglaucoma drugs are needed to confirm our results.

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