Original Article

TRANSLATIONAL&PRACTICAL MEDICINE

DOI: 10.51271/JTPM-0031

J Transl Pract Med. 2023;2(1):1-5

Evaluation of treatment response with color Doppler ultrasonography in cases with primary open-angle glaucoma

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Cite this article as: Ertürk H, Sarpkaya A. Evaluation of treatment response with color Doppler ultrasonography in cases with primary open-angle glaucoma. *J Transl Pract Med.* 2023;2(1):1-5.

Received: 20/02/2023 ◆ **Accepted**: 19/03/2023 ◆ **Published**: 29/04/2023

ABSTRACT

Aims: Beta-blockers, the most frequently preferred drug group in glaucoma. With color Doppler ultrasonography (CDU), the localization of retrobulbar vascular structures, their flow rates and directions, and the effects of the drugs used on the ocular circulation can be examined in a dynamic, reliable, and noninvasive way in less time than other techniques. The aim of our study was to compare the effects of beta-blockers, widely used in glaucoma treatment, and the additional neuroprotectant flunarizine on ocular hemodynamics using CDU.

Methods: Between November 1998 and August 1999, 30 cases diagnosed with POAG in the Glaucoma Unit of the 2nd Eye Clinic of our center were included in the study. Patients were divided into 3 groups according to their beta-blocker treatment. Patients' CDU examinations were then examined by an experienced radiologist, and peak systolic flow velocity (PSFV) and end-diastolic flow velocity (EDFV) of the ophthalmic artery (OA), central retinal artery (CRA), and lateral (temporal) posterior ciliary arteries (LPCA) in the right or left eye were detected.

Results: Of the 30 patients who participated in the study, 14 were male and 16 were female. Nine patients had hypertension (HT), 3 patients had diabetes (DM), and 6 patients had migraine. The mean age was similar in all three groups. There was a significant reduction in IOP in all three patient groups in whom IOP was measured after the use of topical beta-blockers ($P<0.01$). The use of flunarizine had no effect on IOP in all three groups ($P>0.05$). There was no statistically significant difference between groups in OA PSFVs and EDFVs at the first, second, and third measurements using the three beta-blockers ($P>0.05$). No statistically significant difference existed between all three groups in the measurements of CRA PSFVs and EDFVs ($P>0.05$). There were also no significant differences between groups in measurements of LPCA, PSFVs, and EDFVs at baseline and follow-up ($P>0.05$).

Conclusion: We found that the changes in hemodynamic parameters and reduction in IOP with all three beta-blockers were similar on color Doppler USG in patients using beta-blockers for the treatment of glaucoma. We observed that flunarizine had no effect on systemic hemodynamic parameters, did not affect IOP, and had no adverse effects on retrobulbar hemodynamic parameters when combined with beta-blockers. Local beta-blockers remain the mainstay of medical treatment for POAG because of their low systemic side effects and beneficial effects on the eye.

Keywords: Glaucoma, color Doppler USG, beta-blockers

INTRODUCTION

Glaucoma comprises a group of diseases characterized by optic nerve head cupping and visual field loss. These functional and structural disorders are associated with elevated intraocular pressure (IOP). If not diagnosed and treated, it is one of the most common causes of irreversible blindness. Primary open-angle glaucoma (POAG) is a bilateral, chronic, progressive, anterior optic neuropathy in which there is resistance to anterior chamber fluid drainage independent of ocular disease. It accounts for 60-70% of all diseases grouped under the term glaucoma. The main goal of glaucoma treatment is to lower IOP. In modern glaucoma treatment, the important thing is not the extent to which the drugs lower IOP, but the extent to which they reduce visual field loss, stop atrophy of the optic nerve head, and change blood flow in the eye. Beta-blockers, the most commonly preferred group of drugs for treating glaucoma, are used as the first topical drugs for almost all types of the disease. Timolol, a nonselective beta-blocker, betaxolol, a selective beta-blocker, and carteolol, a nonselective but intrinsically sympathomimetic beta-blocker, are commonly used drugs. Flunarizine, a calcium channel blocker long used

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as an adjunctive medication in the prophylactic treatment of migraine, vertigo, and treatment-resistant epilepsy, is thought to have neuroprotective effects because of its ability to block calcium and sodium channels together. There are studies on the use of flunarizine in the treatment of glaucoma. In the treatment of glaucoma, medications used for both pressure reduction and neuroprotection should not adversely affect blood flow in the eye.

Color Doppler ultrasonography (CDU) has gained importance in ophthalmology in recent years. The localizations, flow rates, and directions of retrobulbar vascular structures, as well as the effects of the drugs used on the ocular circulation, can be examined dynamically, reliably, and noninvasively in less time than with other techniques. Since injection of contrast media and application of mydriatic drops are not required, this is less uncomfortable for the patient.

The aim of our study was to compare the effects of beta-blockers, which are widely used in glaucoma treatment, and the additional neuroprotectant flunarizine on ocular hemodynamics using CDU.

METHODS

This study was carried out as a specialist thesis with the approval of the institutional board. Ethical approval was not obtained for that period. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between November 1998 and August 1999, 30 cases diagnosed with POAG in the Glaucoma Unit of the 2nd Eye Clinic of Ulucanlar Eye Training and Research Hospital were included in the study. Patients with a history of ocular or laser surgery, patients with cataracts impairing visual acuity, patients with progressive eye disease, patients with a history of unregulated DM, patients with hypertension or heart disease taking systemic calcium channel blockers or beta blockers, patients with POAG in the normotensive glaucoma group regardless of cause, and patients whose vision was dependent on one eye were excluded from the study.

The topical beta-blockers taken by the patients were discontinued for approximately three weeks (21.56±3.87 days) (wash-out times), and ophthalmological examination of the newly diagnosed patients was performed in detail by an ophthalmologist. Subsequently, a CDU examination was performed by an experienced radiologist, and the peak systolic flow velocity (PSFV) and end-diastolic flow velocity (EDFV) of the ophthalmic artery (OA), central retinal artery (CRA), and lateral (temporal) posterior ciliary arteries (LPCA) in the right or left eye were determined. Ocular blood flow measurements of the patients were made in the Ultrasound Unit of the Radiology Department of Yüksek İhtisas Hospital, Turkey, using the Toshiba Sonolayer SSA-270 A CDU device.

Patients in whom the initial examination and Doppler measurements were completed were divided into 10 groups, and one of the three topical beta-blockers was randomly started (timolol maleate 0.5%, betaxolol 0.5%, carteolol 2%). In addition to the topical beta-blockers used, flunarizine was administered at the dose recommended by the neurological clinic to patients whose second measurements were completed. After approximately two months, all examinations and Doppler measurements were repeated. All patients enrolled in the study completed the study.

Statistical Analysis

To determine the statistical significance of the data obtained in our study, "nonparametric tests" were performed using the program "SPSS for Windows Release 6.0." The "Wilcoxon Matched-Pairs Signed-Ranks" test was used to evaluate differences within groups, and the "Kruskal-Wallis 1-way ANOVA" test was used to evaluate differences between groups.

RESULTS

Of the 30 patients who participated in the study, 14 were male and 16 were female. Patients were divided into 3 groups according to the use of topical beta-blockers (timolol maleate 0.5%, betaxolol 0.5%, carteolol 2%). Nine patients suffered from hypertension (HT), 3 patients from DM, and 6 patients from migraine, and their diseases were under control with the treatment they received. The mean age was similar in all three groups.

For each group, age, gender, initial visual acuity (VA), cup-to-disk ratio (C/D), history of hypertension (HT), diabetes mellitus (DM), and history of migraine, as well as wash-out times of the patients, were recorded. Statistical analysis revealed no statistically significant difference between groups in age, gender, initial visual acuity, C/D ratios, and wash-out times for patients using topical drugs.

At the second measurements after starting the use of topical drops, local side effects were inquired about. It was determined that there was no need to discontinue drugs or use additional drugs. There was no significant difference between the three groups in systolic blood pressure measurements at baseline and follow-up ($p > 0.05$). All measurements were within the normotensive range in all patients. The mean corrected visual acuity of the patients remained constant at baseline and follow-up (mean±SD=0.92±0.16). No significant change in the C/D ratio was observed during fundus examination (mean±SD=0.52±0.08).

Intraocular pressure measurements showed a significant reduction in IOP in all three patient groups after the use of topical beta-blockers (p<0.01). The use of flunarizine had no effect on IOP in all three groups (p>0.05). There was no statistically significant difference between groups in OA PSFVs and EDFVs at the first, second, and third measurements when three beta-blockers were used (p4,5,6>0.05). No statistically significant changes were observed after the use of flunarizine (p>0.05) (**Table 1**).

In the CRA PSFV measurements, no statistically significant difference was found between the groups in all three measurements of the three patient groups (p>0.05). In the within-group evaluations, regular increases in mean flow velocities were observed at the first, second, and third measurements in all three groups. These increases were not significant between the first two measurements (p>0.05). Statistically significant increases were observed between the second and third measurements in the carteolol group (p:0.018). When comparing the first and last measurements, the differences in the betaxolol and timolol groups were not statistically significant (p>0.05), whereas they were significant in the carteolol group (p:0.012) (**Table 2**).

In the CRA EDFV measurements (**Table 2**), there was no statistical difference between the three groups at all measurement time points (p>0.05). In the within-group evaluations, increases in flow velocities were detected in all groups during the follow-up measurements compared with the first measurements. The increases in flow velocity observed between the first two measurements were not statistically significant (p>0.05). In the third measurement, performed after flunarizine administration, a greater increase in flow velocity was observed in the carteolol group than in the other two groups (p:0.043). When the differences between the first and last measurements were evaluated, a significant increase in flow velocity was observed in the betaxolol and timolol groups, falling within the range of p<0.1-P>0.05, whereas the change was more significant in the carteolol group (p:0.007). There were no significant differences between groups in measurements of LPCA, PSFVs, and EDFVs at baseline and follow-up (p>0.05). The within-group analyses revealed no difference in flow velocities after the use of topical beta-blockers or flunarizine in all three groups (p>0.05) (**Table 3**).

DISCUSSION

Our study examined the effects of the beta-blockers timolol, betaxolol, and carteolol, which are widely used in the treatment of glaucoma, on ocular hemodynamics and the effects of flunarizine, administered as a neuroprotectant in combination with beta-blocker therapy, on ocular hemodynamics with CDU. Many studies have shown that there are some retrobulbar hemodynamic disorders in glaucoma detected with

Table 1. OA PSFV and OA EDFV measurements (cm/s)

Group	Flow velocity (cm/s)	First measurement Ort.±ss	Second measurement Ort.±ss	Third measurement Ort.±ss	P1	P2	P3
Betaxolol	OA TSAH	37.2 ±4.1	35.5 ±5.3	34.8 ±4.7	0.063	0.610	0.154
	OA DSAH	7.9 ±0.9	7.7±1.2	8.4±1.1	0.463	0.063	0.161
Carteolol	OA TSAH	37.3 ±4.1	36.9 ±5.1	34.9 ±4.7	0.959	0.093	0.236
	OA DSAH	7.9±1.1	7.6 ±0.9	7.5±1.1	0.398	0.689	0.294
Timolol	OA TSAH	38.3 ±6.2	36.5 ±3.8	37.4 ±3.0.	0.260	0.575	0.624
	OA DSAH	7.8±1.6	7.3±0.9	7.8 ±0.9	0.249	0.208	0.933

Table 2. CRA PSFV ve CRA EDFV measurements (cm/s)

Group	Flow velocity (cm/s)	First measurement Mean±SD	Second measurement Mean±SD	Third measurement Mean±SD	P1	P2	P3
Betaxolol	CRA PSFV	10.7 ±2.4	11.2 ±2.3	12.1 ±2.2	0.483	0.173	0.103
	CRA EDFV	2.8 ±0.7	3.0 ±0.6	3.4±0.7	0.361	0.142	0.058
Carteolol	CRA PSFV	10.1 ±2.1	10.6 ±2.7	11.6±1.4	0.447	0.018	0.012
	CRA EDFV	2.6 ±0.8	3.0 ±0.9	3.5 ±0.8	0.142	0.043	0.0077
Timolol	CRA PSFV	10.2 ±2.2	10.6 ±2.6	11.0 ±2.2	0.441	0.575	0.294
	CRA EDFV	2.6 ±0.6	2.8±0.7	3.0 ±0.6	0.361	0.361	0.679

Table 3. LPCA PSFV and LPCA EDFV measurements (cm/s)

Group	Flow velocity (cm/s))	First measurement Mean±SD	Second measurement Mean±SD	Third measurement Mean±SD	P1	P2	P3
Betaxolol	LPCA PSFV	11.6±2.7	11.9±2.3	11.7±1.9	0.735	0.834	0.000
	LPCA EDFV	3.1 ±1.1	3.1 ±0.7	3.3 ±0.8	1.000	0.463	0.463
Carteolol	LPCA PSFV	11.0± 1.6	11.9± 1.7	11.6±1.4	0.236	0.673	0.363
	LPCA EDFV	2.9 ±0.7	3.3 ±0.6	3.2 ±0.7	0.177	0.686	0.447
Timolol	LPCA PSFV	11.1 ±2.1	10.5±1.5	11.8±2.3	0.575	0.213	0.173
	LPCA EDFV	2.9 ±0.7	2.7 ±0.4	3.2 ±0.6	0.500	0.116	0.109

the CDU method, in which ocular blood flow can be measured noninvasively.[1-3] Yamazaki and Drance found that retrobulbar hemodynamic parameters in patients whose visual fields progressively deteriorated were statistically significantly different from those with stable visual fields.[4] The positive or negative effects of beta-blockers, commonly used to treat glaucoma, on ocular blood flow are controversial.[5] Martin and Rabineau compared retinal artery diameters in 12 healthy subjects after one week of timolol treatment with baseline images and found a 4.1% narrowing.[6]

Carenini et al.[7,8] pointed out timolol decreased pulsatile ocular blood flow in a 12-month study using the Langham pulsatile ocular blood flow (POBF) system, whereas betaxolol had no effect. Yoshida et al.[9] showed that timolol decreased pulsatile ocular blood flow by 12% using the same method. Langham compared timolol, betaxolol, and clonidine by the same method and found that betaxolol increased blood flow, whereas timolol decreased it.[10] Betaxolol is thought to cause vasodilation in the choroidal circulation and increase blood flow in the eye, especially at the end of diastole. Measurement of pulsatile ocular blood flow is a test that shows wide variation in the population and is dependent on scleral rigidity.[11]

A study by Schmetterer et al.[12] concluded that befinolol, metoprolol, timolol, and clonidine decreased fundus pulsation in the macula and optic disc after a single dose, whereas betaxolol, levobunolol, and pilocarpine produced no change. They observed that OA and CRA flow velocities did not change on the CDU examinations they performed in patients.

Harris et al.[13] compared the retrobulbar hemodynamic effects of betaxolol and timolol in a study. They used timolol 0.5% for one month followed by betaxolol 0.5% for one month in 13 patients with normal blood pressure, three weeks after discontinuation of medication. Peak systolic flow velocities (PTSFV) in retrobulbar arteries (OA, PCA, CRA) did not change in CDU examinations before and after medication use with either medication. While no difference was observed in end-diastolic flow velocities (EDFV) in the group using timolol, an increase in EDFV was observed in the group using betaxolol. This effect of betaxolol was attributed to the direct vasodilator effect of the drug.

When we examined the systemic and ocular effects of the topical beta-blockers used in the first part of our study, similar systemic hemodynamic changes were detected in all three patient groups. Systolic and diastolic blood pressure and pulse rate decreased slightly in all three patient groups after beta-blocker use. No statistically significant differences were found in the initial and follow-up measurements. All three beta-blockers significantly lower systolic blood pressure and pulse rate, but diastolic blood pressure less so. These results suggest that the topical beta-blockers used are largely absorbed into the systemic circulation.[14,15] According to Zimmermam, serious side effects of topical beta-blockers are not observed in young patient groups who do not have serious cardiovascular problems or whose vasoregulatory potential is preserved, as in our study group.[16]

In our study, we did not find that timolol caused retrobulbar vasospasm, as claimed by Yoshida et al.[9] Martin et al.[6] Carenini et al.[7,8] and Langham et al.[10] All three topical drugs we used had some effect on retrobulbar flow. Our results are also in agreement with the study by Schmetterer et al.[12] Our results are in complete agreement with the studies of Haris et al.[13] which compared the efficacy of timolol and betaxolol.

We observed that patients were evenly distributed between groups in almost all parameters in our study. We also found that systemic hemodynamic parameters changed to a similar degree in all three groups, with generally more marked decreases in systolic blood pressure and pulse measurements. We hypothesize that the potential for perfusion vasoregulation is preserved because our patients belong relatively to the group of moderately damaged, stable glaucoma patients in the young population. In larger and longer continuous studies, betaxolol and carteolol have been shown to have less effect on systemic parameters.[16,17] It is recommended to use this group of drugs especially in cardiovascular and bronchopulmonary unstable patients.[17] Our study did not reveal significant differences between the groups ($P>0.05$). When we compared the reductions in IOP, we determined that the efficacy was similar in all three patient groups.

In our study, we evaluated treatment with flunarizine and its results in addition to treatment with beta-blockers. Our evaluation showed that flunarizine did not affect IOP in all three groups.

CONCLUSION

We found that the changes in hemodynamic parameters and reduction in IOP with all three beta-blockers were similar on CDU examination in patients using beta-blockers for the treatment of glaucoma. We observed that flunarizine had no effect on systemic hemodynamic parameters, did not affect IOP, and had no adverse effects on retrobulbar hemodynamic parameters when combined with beta-blockers. Local beta-blockers remain the mainstay of medical treatment for POAG because of their low systemic side effects and beneficial effects on the eye.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out as a specialist thesis with the approval of the institutional board. Ethical approval was not obtained for that period (year: 1998-1999).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Giovagnorio F, Quaranta L, Bucci MG. Color Doppler assessment of normal ocular blood flow. *J Ultrasound Med.* 1993;12(8):473-477. doi:10.7863/jum.1993.12.8.473
2. Lieb WE, Cohen SM, Merton DA, Shields JA, Mitchell DG, Goldberg BB. Color Doppler imaging of the eye and orbit. Technique and normal vascular anatomy. *Arch Ophthalmol.* 1991;109(4):527-531. doi:10.1001/archopht.1991.01080040095036
3. Sergott RC, Aburn NS, Trible JR, Costa VP, Lieb WE Jr, Flaharty PM. Color Doppler imaging: methodology and preliminary results in glaucoma. *Surv Ophthalmol.* 1994;38 Suppl:S65-S71. doi:10.1016/0039-6257(94)90048-5
4. Yamazaki Y, Hayamizu F. Effect of trabeculectomy on retrobulbar circulation and visual field progression in patients with primary open-angle glaucoma. *Clin Ophthalmol.* 2012;6:1539-1545. doi:10.2147/OPTH.S36331
5. Graf-Grauwiller T, Stümpfig D, Flammer J. Do beta-blockers cause vasospasm?. *Ophthalmologica.* 1993;206(1):45-50. doi:10.1159/000310362
6. Martin XD, Rabineau PA. Vasoconstrictive effect of topical timolol on human retinal arteries. *Graefes Arch Clin Exp Ophthalmol.* 1989;227(6):526-530. doi:10.1007/BF02169445
7. Carerini BB, Brogliati B, Carerini AB. Pulsatile blood flow and antiglaucomatous drugs. International glaucoma symposium, Jerusalam, Israel, 1991:526-30.
8. Carenini AB, Sibour G, Boles Carenini B. Differences in the longterm effect of timolol and betaxolol on the pulsatile ocular blood flow. *Surv Ophthalmol.* 1994;38 Suppl:S118-S124. doi:10.1016/0039-6257(94)90055-8
9. Yoshida A, Feke GT, Ogasawara H, Goger DG, Murray DL, McMeel JW. Effect of timolol on human retinal, choroidal and optic nerve head circulation. *Ophthalmic Res.* 1991;23(3):162-170. doi:10.1159/000267116
10. Langham ME, Romejko WJ. The unfavorable action of timolol on ocular blood-flow and vision in glaucomatous eyes. in investigative ophthalmology and visual science 1992: 33(4), 1046
11. Silver DM, Farrell RA, Langham ME, O'Brien V, Schilder P. Estimation of pulsatile ocular blood flow from intraocular pressure. *Acta Ophthalmol Suppl (1985).* 1989;191:25-29. doi:10.1111/j.1755-3768.1989.tb07083.x
12. Schmetterer L, Strenn K, Findl O, et al. Effects of antiglaucoma drugs on ocular hemodynamics in healthy volunteers. *Clin Pharmacol Ther.* 1997;61(5):583-595. doi:10.1016/S0009-9236(97)90138-7
13. Harris A, Spaeth GL, Sergott RC, Katz LJ, Cantor LB, Martin BJ. Retrobulbar arterial hemodynamic effects of betaxolol and timolol in normal-tension glaucoma. *Am J Ophthalmol.* 1995;120(2):168-175. doi:10.1016/s0002-9394(14)72604-2
14. Cioffi GA, Wang L. 1999 Optic nerve blood flow in glaucoma. In Seminars in Ophthalmology. Taylor and Francis 1999;14(3):164-170.
15. Saudin W. Beta blockers and ocular blood flow. International symposium on glaucoma, Williams and Wilkins, 1992:107-16.
16. Zimmerman TJ. Topical ophthalmic beta blockers: a comparative review. *J Ocul Pharmacol.* 1993;9(4):373-384. doi:10.1089/jop.1993.9.373
17. Scoville B, Mueller B, White BG, Krieglstein GK. A double-masked comparison of carteolol and timolol in ocular hypertension. *Am J Ophthalmol.* 1988;105(2):150-154. doi:10.1016/0002-9394(88)90178-x