The Effect of Dorzolamide on Intraocular Pressure and Ocular Pulse Amplitude: Adjunctive Therapy to Beta-Blockers as a Substitite for Pilocarpine or as a Second-Line Therapeutic Agent in Patients with Open-Angle Glaucoma

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Objective: **To evaluate the effect of dorzolamide on the intraocular pressure (IOP), ocular pulse amplitude (OPA), systemic blood pressure and pulse rate in open-angle glaucoma patients using a beta-blocker and 2% pilocarpine combination and beta-blocker monotherapy. The secondary aim was to find out the effect of dorzolamide on IOP and OPA in patients using selective versus nonselective beta-blocker.**

Methods: **Thirteen patients who had beta-blocker and pilocarpine combination (Group 1) and 15 patients who had beta-blocker monotherapy (Group 2) were enrollled. A randomly selected eye of bilaterally affected patients was included in the observer-blinded and parallel-group study. Baseline data consisted of 4 day-time IOP, OPA, systemic blood pressure and pulse rate measurements. Patients in Group 1 discontinued pilocarpine and used beta-blocker-dorzolamide combination and patients in Group 2 used dorzolamide as a second-line therapeutic agent with a beta-blocker. The same measurements were performed after 4 weeks and after 6 months in both groups.**

Results: **In Group 1 the baseline IOP was 18.9±2.2 mmHg; after 4 weeks and 6 months no statistically significant change was observed (17.6±2.3 and 17.8±3.2 mmHg respectively, p>0.05). However in Group 2, a statistically significant IOP decrease from 22.5 ± 3.3 mmHg to 18.0 ± 2.0 mmHg after 4 weeks (p<0.05) and to 18.4 ± 1.8 mmHg after 6 months (p<0.05) occurred. There were no changes in OPA, systemic blood pressure and pulse rate in either groups during the follow-up period. The additive effect of dorzolamide with selective and nonselective beta-blockers was analyzed using a cross-sectional study design of the data obtained from 28 eyes. Twelve patients who used selective beta-blocker and dorzolamide showed an increase in IOP (from 18.4±2.3 to 19.3±1.9 mmHg, p>0.05) and a decrease in OPA (from 3.7±1.2 to 3.2±0.9 mmHg, p>0.05) after 5 months, although these changes were not statistically significant. The IOP was stable during the same period (17.3±2.0 and 17.2±2.6 mmHg, p>0.05) but the OPA showed a slight, but not significant increase (2.7±1.1 and 3.1± 1.5 mmHg, p>0.05) in sixteen patients using nonselective beta-blocker and dorzolamide.**

Conclusion: **Dorzolamide is safe and effective when used with beta-blockers but its interaction with selective and nonselective beta-blockers needs further investigation.**

Key Words: *Intraocular pressure, ocular pulse amplitude, medical therapy, beta-blocker, dorzolamide, pilocarpine*

Open-angle glaucoma is characterized by progressive optic disc damage and visual field defects in presence of elevated intraocular pressure (IOP) in majority of the cases. Lowering IOP may stop or slow down the progression of the disease (1). Beta-blockers are widely used as monotherapy or in combination with other drugs for glaucoma therapy. Pilocarpine, a parasympathomimetic drug, is a very potent adjunct to beta-blockers, but its side effects such as spasm of accomodation in young patients, visual acuity decrease in patients with lens opacities, tonic and myotic pupil which complicates the cataract surgery, formation and progression of cataract and poor compliance of patients have limited its use in the presence of new ocular hypotensive drugs (2). Dorzolamide is an inhibitor of carbonic anhydrase isoenzymes II, which is the major carbonic anhydrase enzyme in the human ciliary body and IV (3).

Dorzolamide is frequently used as an adjuntive drug to beta-blockers either as a substitute for pilocarpine to eliminate its side effects or to achieve further IOP decrease in patients with progressive glaucoma using beta-blocker monotherapy. It has been reported that in both circumstances dorzolamide can substitute the effect of pilocarpine (4-8) or can result in an additional decrease in IOP (9,10). In almost all studies on the additive effect of dorzolamide to beta-blockers, the beta-blocker studied was timolol maleate. There is only one study so far which has investigated the additive effect of dorzolamide to selective and nonselective beta-blockers but it is a retrospective study (11).

Ocular pulse amplitude (OPA) reflects the pulsability of the globe, ie, filling of the choroid during the systolic and diastolic phases of the heart. Vascular supply of the optic disc is dependent mainly on posterior ciliary arteries which also supply the choroid. Therefore OPA could be an indirect indicator of the vascular condition of the optic disc. It has been reported that dorzolamide bid monotherapy for two days (12) and 0.5% timolol - dorzolamide combination therapy for 4 weeks (13) increase the OPA in primary open-angle glaucoma patients.

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The primary aim of this study is to evaluate the substitution effect of dorzolamide with pilocarpine in patients using beta-blocker and pilocarpin combination and the additive effect of dorzolamide to beta-blocker monotherapy using a parallel-group, observer-blinded study design. OPA changes during follow-up have also been investigated. The second goal is to find out the difference in interaction of dorzolamide with selective and nonselective beta-blockers by means of IOP and OPA using a cross-sectional study design.

Material and Method

Twenty-eight patients with open-angle glaucoma (either primary open-angle or pseudoexfoliation glaucoma) were enrolled. None of the patients had previous laser therapy or surgery.

Thirteen patients were using beta-blocker bid and 2% pilocarpin qid in combination (Group 1). Diurnal IOP follow-up, measurements of systolic and diastolic blood pressure, pulse rate and OPA was carried out as baseline examination in the specified order. The patients were asked to discontinue 2% pilocarpin and dorzolamide (bid) was added to the beta-blocker therapy (bid) that they used previously. After 4 weeks and 6 months, the same procedure was repeated for all patients.

Fifteen patients were receiving beta-blocker monotherapy bid (Group 2) and their diurnal IOP follow-up showed a peak IOP over the target pressure. After measuring the systolic and diastolic blood pressures, pulse rate and OPA as baseline examination they were asked to use the same beta-blocker and 2% dorzolamide combination twice daily. After 4 weeks and 6 months the same measurements were also repeated for these patients.

All patients used at least for one year either selective (Betaxolol 0.5%) or nonselective beta-blocker (0.5% Timolol maleate or Levobunolol HCl) at 8:00 and 20:00 hours. Pilocarpine users in Group 1 instilled it at 8.30, 13.30, 18.30 and at bed-time. During follow-up, all patients used the beta-blocker and dorzolamide at 8.00-20.00 and 8.30-20.30 hours respectively. IOP was measured with Goldmann applanation tonometer at 9, 11, 13 and 15 hours (± 30 minutes). Systemic blood pressure was measured with a manometer after 5 minutes of rest. Ocular Blood Flow Tonograph (OBF Labs, UK) was used for OPA measurements.

One randomly selected eye of patients with bilateral disease was included in the study. The observer was blinded about the prescribed agents. The individual and mean of four IOP measurements in a day were used for statistical analysis. IOP, OPA, systemic blood pressure and pulse rate changes were compared after 4 weeks and 6 months with baseline values.

The other aim of the study was to find out the difference of dorzolamide interaction from selective and nonselective beta-blockers. For this purpose data from 28 patients at the 4th week was pooled and a cross-section of the data was obtained. Eyes in which selective and nonselective beta-blockers have been used were compared to see whether there were changes in IOP and OPA during the follow-up period.

One way Anova and Wilcoxon signed ranks tests were used for statistical analysis of the data and significance was set at $p<0.05$.

Results

In Group 1 (6 male, 7 female) 10 patients had primary open-angle glaucoma and 3 patients had pseudoexfoliation glaucoma. Mean age of the patients was 60.7 ± 6.7 years. Mean baseline IOP was 18.9 ± 2.2 mmHg. Following the discontinuation of pilocarpin and beginning of dorzolamide as adjunct to the beta-blocker therapy, the mean IOP was 17.6 ± 2.3 after 4 weeks and 17.8 ± 3.2 mmHg after 6 months and the IOP change was not statistically significant ($p>0.05$) (Table I, Fig 1). The four individual IOP measurements after 4 weeks and 6 months were not statistically different from their corresponding baseline values ($p>0.05$) (Table I).

There was no statistically significant change in mean values of OPA ($p>0.05$), systolic ($p>0.05$) and diastolic ($p>0.05$) blood pressures and pulse rate ($p>0.05$) during the follow-up period in Group 1 (Table II).

Eleven patients had primary open-angle glaucoma and 4 patients pseudoexfoliation glaucoma in Group 2 (9 male, 6 female). Mean age of the patients was 61.5 ± 9.2 years.

Table I. The IOP response of Group 1 and 2 during the follow-up period

	Group 1				
	9 hour	11 hour	13 hour	15 hour	Mean IOP
Baseline	18.6 ± 2.7	19.8 ± 2.6	19.0 ± 3.1	18.2 ± 2.3	18.9 ± 2.2
4 weeks	17.3 ± 3.2	17.9 ± 2.7	18.1 ± 2.5	17.2 ± 2.3	17.6 ± 2.3
6 months	18.3 ± 3.9	17.9 ± 1.9	17.5 ± 4.3	17.3 ± 3.8	17.8 ± 3.2
			Group 2		
Baseline	22.8 ± 3.5	23.5 ± 3.3	21.5 ± 3.8	22.0 ± 4.1	22.5 ± 3.3
4 weeks	17.0 ± 3.3 †	18.3 ± 1.5 †	17.9 ± 2.9 †	18.6 ± 2.3 †	18.0 ± 2.0 †
6 months	18.8 ± 2.3 †	18.6 ± 2.8 †	18.2 ± 2.0 †	18.0 ± 2.1 †	18.4 ± 1.8 †

†: Statistically significant difference from baseline ($p<0.001$)

Table II. The OPA and systemic parameters of Group 1 and 2 during the follow-up period

	Baseline	4 weeks	6 months
Group 1			
OPA	3.83 ± 1.25	3.71 ± 1.31	3.85 ± 1.18
SBP	140.0 ± 16.3	139.2 ± 13.8	133.1 ± 14.4
DBP	81.1 ± 7.9	83.5 ± 7.7	77.7 ± 6.0
PR	69.1 ± 10.8	64.7 ± 8.4	64.5 ± 7.2
Group 2			
OPA	2.67 ± 1.01	2.61 ± 1.01	2.55 ± 0.97
SBP	122.9 ± 8.8	121.3 ± 8.3	121.3 ± 7.4
DBP	79.3 ± 10.3	78.7 ± 9.1	76.7 ± 6.2
PR	78.3 ± 17.7	83.3 ± 13.9	77.8 ± 11.2

Table III. The responses of IOP and OPA in eyes using selective and nonselective beta-blocker

		Selective beta-blocker (n=12)		Nonselective beta-blocker (n=16)
IOP	4 weeks	18.4 ± 2.3	p>0.05	17.3 ± 2.0
		p>0.05		p>0.05
	6 months	19.3 ± 1.9	p<0.05	17.2 ± 2.6
OPA	4 weeks	3.7 ± 1.2	p<0.05	2.7 ± 1.1
		p>0.05		p>0.05
	6 months	3.2 ± 0.9	p>0.05	3.1 ± 1.5

IOP decreased from 22.5 ± 3.3 mmHg to 18.0 ± 2.0 mmHg after 4 weeks ($p<0.05$) and to 18.4 ± 1.8 mmHg after 6 months ($p<0.05$) (Table I, Fig 1). The four day-time IOP measurements at the 4th week and the 6th month were significantly lower than the corresponding baseline values ($p<0.05$) (Table I).

The OPA ($p>0.05$), systolic ($p>0.05$) and diastolic blood pressures ($p>0.05$) and pulse rate ($p>0.05$) values in Group 2 did not differ significantly from baseline values in Group 2 (Table II).

Data from 28 patients (15 males, 13 females) was pooled while all patients were using beta-blocker bid for at least one year and dorzolamide bid for 1 month during the follow-up at the 4th week. Twelve patients (6 male, 6 female) used a selective beta-blocker (0.5% Betaxolol HCl) and 16 patients (9 male, 7 female) a nonselective (0.5% Timolol maleate or Levobunolol HCl) beta-blocker in the pooled group. Nine patients had primary open-angle glaucoma and 3 patients had pseudoexfoliation glaucoma in the selective beta-blocker group, whereas 12 patients had primary open-angle glaucoma and 4 patients had pseudoexfoliation glaucoma in the nonselective beta-blocker group. Mean age was 59.7 ± 8.7 and 62.8 ± 7.9 years in selective and nonselective beta-blocker groups respectively ($p>0.05$). Mean systolic and diastolic blood pressure and mean pulse rate of the selective and nonselective groups were not significantly different at the examinations at the 4th week and 6th month ($p>0.05$); which suggests that both groups were comparable by means of IOP and OPA.

We compared the IOP values of selective (18.4 ± 2.3 mmHg) and nonselective beta-blocker groups (17.3 ± 2.0) at the 4th week and observed that there was not any statistically significant difference ($p>0.05$). Mean IOP increased to 19.3 ± 1.9 mmHg ($p>0.05$) in the selective beta-blocker group and was stable in the nonselective beta-blocker group (17.2 ± 2.6 mmHg $p>0.05$). On the other hand, at follow-up, the mean IOP of the selective beta-blocker group was significantly higher than that of nonselective group ($p<0.05$) (Table III, Fig 2).

Mean OPA at the 4th week was significantly higher in the selective beta-blocker group than that of nonselective beta-blocker group (3.7 ± 1.2 mmHg and 2.7 ± 1.1 mmHg respectively, $p<0.05$). OPA decreased in selective beta-

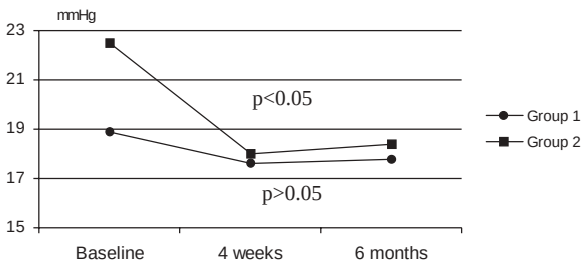

Figure 1. The IOP in Groups 1 and 2

blocker group (3.2 ± 0.9 mmHg) and increased in the nonselective group (3.1 ± 1.5 mmHg) during the follow-up period but the differences were not statistically significant (p>0.05). Mean OPA of the selective beta-blocker group versus nonselective beta-blocker group at 6th month was not statistically significant (p>0.05) (Table III, Figure 3).

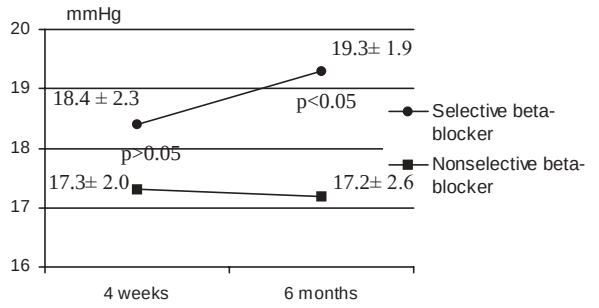

Figure 2. The IOP in selective and nonselective beta-blocker groups

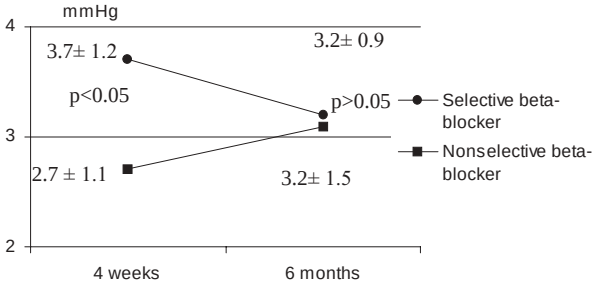

Figure 3. The OPA in selective and nonselective beta-blocker groups

Discussion

The IOP lowering effect of 2% pilocarpine qid and dorzolamide bid used as adjunctive therapy to beta-blockers was found to be not significant in previous parallel-group and cross-over designed studies (4-8). We have also found that the IOP control with dorzolamide as adjunct to beta-blockers was as good as pilocarpine during our 6-month follow-up period. The mean IOP decrease from baseline (1.3 and 1.1 mmHg at the 4th week and 6th month respectively) after switching from pilocarpine to dorzolamide was not statistically significant.

Wayman et al. (9) reported that dorzolamide used as adjunctive to beta-blockers could suppress aqueus humor production to the same extent as monotherapy; meaning that the aqueous suppression mechanisms of either drug was different. Adamsons (10) reported that 2% dorzolamide used as adjunct to 0.5 % timolol gel-form has the same IOP lowering effect when used bid or tid. In our second study group, patients with IOP higher than the target pressure on beta-blocker monotherapy showed statistically significant IOP decrease after addition of dorzolamide bid to the therapy protocol during 6-month follow-up.

There is only one retrospective study evaluating the interaction of dorzolamide with selective and nonselective beta-blockers by means of IOP. Domingo et al. (11) reported 5.23 mmHg IOP decrease after addition of 2% dorzolamide to 0.5% timolol maleate monotherapy, whereas 3.75 mmHg IOP decrease occurred in patients using betaxolol monotherapy. Although this was not among the primary goals in our study, we observed that dorzolamide had a better additive effect to nonselective rather than selective beta-blockers in our cross-sectional study design. This subject needs to be clarified by further randomized, double-blind and placebo-controlled studies.

The systemic perfusion parameters (systolic and diastolic blood pressures, pulse rate) were unaffected during the follow-up period. Our results showed that 2% dorzolamide is an effective adjunct to beta-blockers by means of IOP; it is also safe with respect to systemic side effects.

Schmidt (12) reported OPA increase in patients with primary open-angle glaucoma and in the control group using 2% dorzolamide for two days. In another study it was reported that 0.5% timolol significantly decreased IOP after 4 weeks in patients with primary open-angle glaucoma, but did not affect the OPA. The addition of dorzolamide to timolol caused a further decrease of IOP after 4 weeks and it was observed a statistically significant OPA increase; which suggests that OPA increase is an IOP independent effect of dorzolamide (13).

We did not observe such an effect in Groups 1 and 2; the OPA was stable during the follow-up period. On the other hand in the second part of the study we found that OPA decreased in patients using selective beta-blocker and dorzolamide combination and increased in patients using nonselective beta-blocker and dorzolamide combination, although these differences were not statistically significant. From these results it can be concluded that selective and nonselective beta-blockers may have other interaction mechanisms with dorzolamide which might be responsible for different OPA responses.

In conclusion; dorzolamide is an effective and safe alternative for pilocarpine in patients using a beta-blocker and pilocarpine combination. It is also an effective and safe adjunct in patients using beta-blocker monotherapy. Dorzolamide may have different effect on IOP and OPA when used in combination with selective and nonselective beta-blockers. The elucidation of the related mechanisms responsible for this effect needs further investigation.

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