

A 4-year retrospective study of add-on therapy to the fixed combination of dorzolamide/timolol for the treatment of POAG

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Abstract

• **AIM:** To evaluate the long-term response to the fixed combination of dorzolamide/timolol in patients with primary open angle glaucoma (POAG) and the addition of other intraocular pressure (IOP) lowering medications such as prostaglandin analogs and brimonidine.

• **METHODS:** A retrospective, non-randomized, and descriptive clinical study was performed with 182 eyes diagnosed with POAG. Patients were divided into three groups: a group with fixed combination of dorzolamide/timolol only, a second group with prostaglandin analogs plus fixed combination of dorzolamide/timolol, and a third group with the addition of brimonidine to the same fixed combination. IOP data were gathered retrospectively and the differences between groups were calculated.

• **RESULTS:** IOP was reduced satisfactorily in all three groups; however, a progressive IOP reduction was noted in the group with the fixed combination plus prostaglandin analogs. In this group, a progressive, significant and more homogeneous response of the reduction was noted in comparison with the other groups.

• **CONCLUSION:** IOP reduction was efficacious in all three groups. The addition of prostaglandin analogs showed progressive IOP reduction, progressive response

and absence of long-term drift. Brimonidine did not show a significant additive effect.

• **KEYWORDS:** fixed combination; Cosopt®; dorzolamide/timolol; prostaglandin analogs; brimonidine; glaucoma
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INTRODUCTION

Glaucoma is one of the principal causes of blindness worldwide. According to the World Health Organization (WHO), glaucoma is the second cause of blindness in developed countries and affects more than sixty million people worldwide. It is estimated that more than 50% of the glaucoma cases have not been diagnosed yet^[1].

The principal type of glaucoma is primary open angle glaucoma (POAG). The causes of intraocular pressure (IOP) damage to the optic nerve are still unknown, but elevated IOP is considered to be one of the principal risk factors for this damage^[2]. The standard of treatment in glaucoma consists of IOP reduction^[3,4]. Initial treatment consists typically of topical IOP reducing agents, preferably as monotherapy. When monotherapy does not control IOP adequately, fixed combinations are used as a second line of treatment, since they are more effective in IOP reduction, reduce secondary effects and increase patient compliance^[5]. Another positive aspect of combined treatment is the reduced quantity of preservatives, which have been shown to increase irritation of the conjunctiva and dryness of eye, among other side effects^[6]. The fixed combination of 2% dorzolamide/0.5% timolol (Cosopt®) is frequently used as a single drop for glaucoma IOP control. However, it is sometimes necessary to add extra IOP lowering medications such as prostaglandin analogs or brimonidine. At this moment, we have little information about the addition of fixed combinations for the long-term treatment of glaucoma.

The goal of this analysis was to evaluate the long-term efficacy (4y) of Cosopt® and also the addition of prostaglandin analogs or brimonidine in patients with POAG.

SUBJECTS AND METHODS

Subjects This is a descriptive, retrospective, non-randomized and comparative study. Data were obtained from the Glaucoma Service of the Instituto de Oftalmología Fundación Conde de Valenciana in Mexico City. Patients were seen between January 2004 and January 2009, and had full case histories for POAG. We found 122 patients with glaucoma OU (*oculus utro*, both eyes), and 36 patients with the unilateral illness. One hundred and eighty-two eyes filled inclusion criteria. At follow-up, compliance was routinely questioned to ensure adequate treatment. Experienced glaucoma specialists and fellows, using a Goldmann applanation tonometry, routinely did IOP measurements between 8h and 12h. Since it was a retrospective study, informed consent was not needed, and the authors confirm the strict adherence to the tenets of the Helsinki Declaration.

Methods

Data acquisition An instrument for data acquisition was designed, including patient demographics and their follow-up for data analysis.

Group selection All patients were diagnosed with POAG, and were divided into three groups: 1) patients treated with Cosopt® as primary therapy (Cosopt® group); 2) patients using prostaglandin analogs such as latanoprost, travoprost or bimatoprost who did not achieve IOP control with the subsequent addition of Cosopt® (Cosopt® +PG) and, 3) patients using brimonidine without IOP control, with subsequent addition of the fixed combination (Cosopt®+B). Latanoprost, travoprost or bimatoprost were considered as a group of prostaglandin analogs because there are no differences in the mechanisms of action between these drugs. Eyes with no light perception were excluded, as were patients with previous ocular surgery.

Intraocular pressure data Basal IOP was established as the IOP before the use of any medication. Target IOP was established as a 30% reduction of basal IOP. If target pressure was not achieved, prostaglandin analogs or brimonidine had been added. For the purposes of this study, a minimum of 4 IOP measurements per year were registered and averaged. In case of not reaching a 30% reduction with add-on medication, surgery was indicated and these cases were excluded from the study.

Statistical Analysis Given the non-parametric characteristics of data, we analyzed differences between groups with the ANOVA test, with an alpha of 0.05 considered as significant.

RESULTS

Group Characteristics A total of 182 eyes with POAG were analyzed. Of these, 38 eyes (20.88%) were treated exclusively with Cosopt®; 103 eyes (56.6%) were treated with the fixed combination and a prostaglandin analog (Cosopt®+PG), and 41 eyes (22.52%) were treated with the

Table 1 Demographic and baseline characteristics of the study population (n=182)

Variable	Value
Age, a	
Mean (SD)	63.8 (9.4)
95%CI	62.4-65.13
Race	
Mestizo	182 (100%)
Sex, n (%)	
M	133 (73.08%)
F	49 (26.92%)

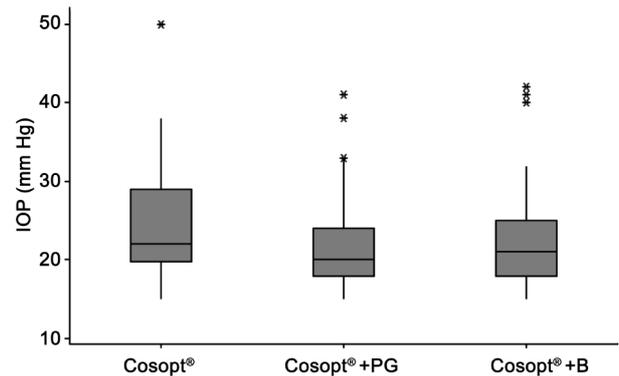


Figure 1 Boxplot of baseline IOP in all groups of analysis A significant statistical difference between groups was found ($P=0.023$). Cosopt®: 2% dorzolamide/0.5% timolol; Cosopt®+PG: Cosopt®+prostaglandin analogs; Cosopt®+B: Cosopt®+brimonidine. *Outlier data.

fixed combination and Brimonidine (Cosopt®+B). These groups were analyzed to detect long-term efficacy and to compare the IOP reduction with the different treatments. Patient demographics are shown in Table 1.

Baseline Intraocular Pressure Showed Differences Between Assignments of Treatment Our data show that the group receiving Cosopt® showed an initial mean higher IOP than the other two groups, which was statistically significant ($P=0.023$) (Figure 1).

Because there were statistically significant differences between the groups (Figure 1), data were adjusted to compare differences in therapeutic effect. However, we focused our analysis on the differences between the mean values of IOP during the years of follow-up. Further, we evaluated the differences in IOP reduction for each group at each time of follow-up.

All Treatments Reduced Intraocular Pressure Apparently in a Similar Fashion At first glance, the three treatment modalities showed a similar and significant IOP lowering tendency during the first year of treatment, and this response continued during follow-up until the fourth year (Figure 2).

As mentioned previously, data were adjusted to avoid the differences observed in baseline. Interestingly, we observed differences in the clinical behavior of IOP from the first year

Table 2 Mean and standard deviation of IOP at baseline and follow-up in patients with POAG

Groups	Mean IOP (SD)				
	Baseline	1 st year	2 nd year	3 rd year	4 th year
Cosopt [®]	24.24 (7.51)	16.7 (6.22)	16.4 (6.1)	13.6 (2.65)	14.6 (2.97)
Cosopt [®] +PG	21.57 (4.78)	13.83 (2.3)	13.83 (2.8)	13.041 (2.07)	12.95 (1.32)
Cosopt [®] +B	22.48 (6.67)	14.72 (3.4)	14.72 (3.39)	14.85 (2.07)	14.06 (1.48)
<i>P</i>	0.059	0.004	0.01	0.002	0.004

Cosopt[®]: 2% dorzolamide/0.5% timolol; Cosopt[®]+PG: Cosopt[®]+prostaglandin analogs; Cosopt[®]+B: Cosopt[®]+brimonidine.

Table 3 IOP reduction by treatment

Groups	Absolute change (mm Hg)		Relative change (%)		<i>P</i>
	Mean difference from baseline	95%CI for mean	Mean difference from baseline	95%CI for mean	
1 st year					
Cosopt [®]	-8.57	(-5.48 to -11.65)	-32.25%	(-0.24 to -0.41)	0.696
Cosopt [®] +PG	-7.88	(-6.9 to -8.78)	-34.51%	(-0.32 to -0.37)	
Cosopt [®] +B	-8.71	(-6.24 to -11.17)	-34.16%	(-0.27 to -0.4)	
2 nd year					
Cosopt [®]	-8.87	(-5.78 to -11.96)	-33.47%	(-0.25 to -0.41)	0.63
Cosopt [®] +PG	-7.88	(-6.99 to -8.78)	-34.51%	(-0.32 to -0.37)	
Cosopt [®] +B	-8.7	(-6.24 to -11.17)	-34.16%	(-0.27 to -0.4)	
3 rd year					
Cosopt [®] t	-7.9	(-5.46 to -10.34)	-35.60%	(-0.27 to -0.44)	0.893
Cosopt [®] +PG	-8.7	(-7.6 to -9.79)	-37.73%	(-0.35 to -0.41)	
Cosopt [®] +B	-8.5	(-5.34 to -11.68)	-32.00%	(-0.25 to -0.39)	
4 th year					
Cosopt [®]	-7.92	(-4.93 to -10.91)	-34.91%	(-0.2 to -0.47)	0.657
Cosopt [®] +PG	-8.9	(-7.6 to -10.25)	-38.35%	(-0.35 to -0.42)	
Cosopt [®] +B	-7.87	(-6.04 to -9.7)	-34.30%	(-0.27 to -0.41)	

Statistical differences between groups are shown. Cosopt[®]: 2% dorzolamide/0.5% timolol; Cosopt[®]+PG: Cosopt[®]+prostaglandin analogs; Cosopt[®]+B: Cosopt[®]+brimonidine.

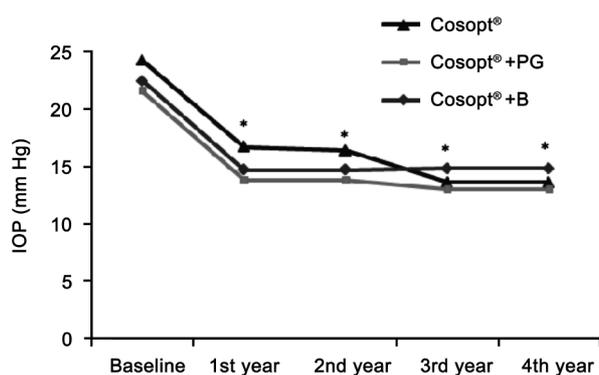


Figure 2 Mean IOP at baseline and follow-up in patients with POAG (adjusted) *: Statistically significant difference between groups.

of treatment and during the course of analysis (4y), with statistical significance between groups (Table 2).

The Cosopt[®] group showed a mean reduction of 32.25% of IOP from baseline (24.24-16.7 mm Hg) for the first year. The Cosopt[®]+PG group showed a mean reduction of 34.51% (from 21.57-13.83 mm Hg) for the same period. The Cosopt[®]+B group showed a 34.16% reduction of IOP (22.48-14.72 mm Hg). During the second year, there was a

33.47% reduction for the Cosopt[®] group, 34.51% for the Cosopt[®]+PG and 34.16% for the Cosopt[®]+B groups, compared to baseline. For the third year, there was an IOP reduction of 35.6% for the Cosopt[®] group, 37.73% for the Cosopt[®]+PG and 32% for the Cosopt[®]+B group. For the fourth year, there was an IOP reduction of 34.91% for the Cosopt[®] group, 38.35% for the Cosopt[®]+PG and 34.3% for the Cosopt[®]+B group. We did not observe statistically significant difference among the three groups for the percentage of IOP reduction in any year of analysis (Table 3).

All Treatment Groups Showed Absence of Long-term Drift (Tachyphylaxis) All combined medications containing Timolol could present tachyphylaxis [7]. In this study, we found progressive IOP reduction in all the treatment groups, which was more evident in the fixed combination group+PG during the first year (34.51%). In the subsequent years, we also found a greater IOP reduction in the last two years in the Cosopt[®]+PG group (37.73% in the third year, and 38.35% in the fourth year) (Figure 3).

PG Addition was Associated with Progressive Reduction in Mean IOP We also found that the Cosopt[®]+PG group showed statistically significant differences during different

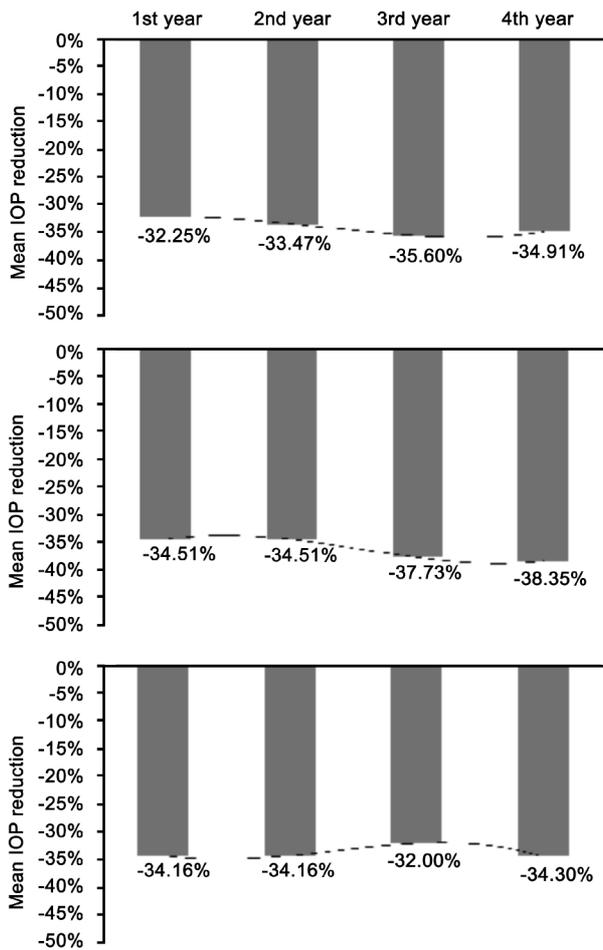


Figure 3 Percentage of IOP reduction on each group A: Cosopt[®]; B: Cosopt[®]+P; C: Cosopt[®]+B. Cosopt[®]: 2% dorzolamide/0.5% timolol; Cosopt[®]+PG: Cosopt[®]+prostaglandin analogs; Cosopt[®]+B: Cosopt[®]+brimonidine.

periods of evaluation: at the first year IOP differences were statistically significant in basal vs first year comparison ($P=0.00001$); between the first and 4th year ($P=0.00001$), and between the second and fourth year ($P=0.004$) (Figure 4). The other groups (Cosopt[®] and Cosopt[®]+B) did not show statistically significant differences in the periods evaluated.

DISCUSSION

Although the long term effects of the fixed combination of dorzolamide/timolol are well known [8], there are few reports of the efficacy of treatment with a fixed combination such as Cosopt[®] with prostaglandin analogs or brimonidine, over a long term (4y) and with a large number of eyes[9]. This study confirms the fixed combination of dorzolamide/timolol as an efficacious treatment to reduce IOPs, and also the additional benefits of adding other drugs, such as prostaglandin analogs. Although we observed a difference in the basal IOPs in the three groups, with the mean initial IOPs being lower for the Cosopt[®]+PG group, we focused our analysis using comparisons of IOP reduction year by year among the three groups, and avoided comparing mean IOPs during the follow-up periods, which showed statistical differences between groups in adjusted analysis (Figure 2).

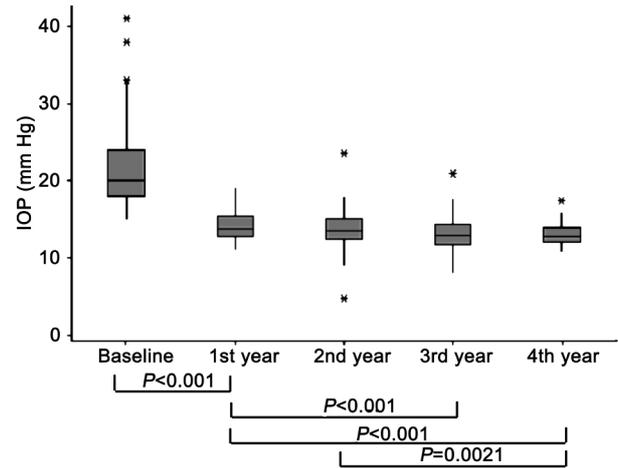


Figure 4 IOP in Cosopt[®]+PG group at 4y of analysis Statistical significant differences between periods of treatment are shown. Cosopt[®]+PG: Cosopt[®]+prostaglandin analogs. *Outlier data.

IOP was successfully reduced in all treatment modalities (Cosopt[®], Cosopt[®]+PGs, and Cosopt[®]+B), and mean IOP lowering was always over 30% of initial IOPs. Interestingly, the Cosopt[®]+PG group showed the highest IOP reduction during the first year of treatment (34.51%). Cosopt[®] group probably represents a group of patients who are high responders to Cosopt[®]; if IOPs had increased, they would have had a PG added. Previously, the use of Cosopt[®] has shown IOP reductions even higher than we observed, over 50%[10].

On the other hand, we found that the addition of Cosopt[®]+PGs presents additional benefits, such as a more homogenous and relatively more predictable response of IOPs (Table 2). Prostaglandin analogs are known to be potent medications, for which reason they have become part of the primary therapy for glaucoma [11]. The addition of a third or fourth medication to glaucoma therapy can even reduce IOP by up to 40%, but most authors have questioned the use of such additional therapy because frequently, there is no additional IOP lowering effect [12]. Other sources have suggested the addition of a prostaglandin analog to a fixed combination if an important IOP reduction is required or if one medication by itself is not efficacious in reducing IOP [6]. Our results suggest that the addition of a prostaglandin analog to the fixed combination of Cosopt[®], has important supplementary long-term benefits.

In this study we have observed that even though the IOP reduction can be very similar in the different groups, even without statistical differences in absolute IOP values, we found that the addition of PG analogs to the fixed combination can have subtle additional impact such as a progressive efficacy and more homogenous responses among patients treated with this combination of medications. To our knowledge, this is the first time this response has been described long term for the use of combined treatment for

glaucoma. However, these results could be influenced by different sample sizes between groups, because the Cosopt®+PG group ($n=103$) was by far the biggest group in our study (Cosopt®, $n=38$; Cosopt®+B, $n=38$).

Other randomized clinical studies, which evaluated the addition of brimonidine to the fixed combination of dorzolamide/timolol, have found a higher IOP reduction, but these studies have been mostly short term (6mo), which might explain the differences with our findings^[13-15].

Some of the strengths of this study are the long-term evaluation of patients, the high number of patients analyzed and the combinations of treatments evaluated. Since this study is a retrospective clinical study, it lacks the strength and objectiveness of a prospective randomized controlled clinical trial, so the impact of our conclusions must necessarily be limited.

In conclusion, in this descriptive, retrospective study, we showed that treatment with the fixed combination of dorzolamide/timolol (Cosopt®) using an large number of patients (182 eyes), was effective in reducing IOP during the four years of follow-up. We also found a lack of long-term drift in every group, and that the addition of prostaglandin analogs shows additional effects such as a more homogenous response and a better, cumulative effect. To our knowledge, this study shows new and interesting results about the combination of treatments that could be beneficial in such a chronic and incapacitating disease. Based on these findings, we consider it is important to do long term, prospective, randomized treatment studies on previously untreated patients with these combinations.

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Conflicts of Interest: Hartleben–Matkin C, None; Prada D, None; Mancilla–Vences R, None.

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