

Intraocular pressure reduction of fixed combination timolol maleate 0.5% and dorzolamide 2% (Cosopt) administered three times a day

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Purpose: To evaluate the safety and efficacy in intraocular pressure (IOP) reduction of increasing Cosopt dosage from twice to three times a day.

Methods: The study included patients with primary open-angle glaucoma or ocular hypertension. After a washout period, IOP was measured at baseline, after 4 weeks of treatment with Cosopt twice a day, and after another 4 weeks of treatment with Cosopt three times a day. Blood pressure, heart rate, and oxygen saturation levels were also recorded.

Results: Twenty-nine eyes of 29 patients were included. Increasing Cosopt dosage resulted in a statistically significant ($P < 0.001$) additional reduction in IOP of 2.2 ± 1.58 mmHg ($10.69\% \pm 7.49\%$ of the baseline IOP values). There were no local or systemic adverse effects.

Conclusion: Treatment with Cosopt three times a day was more effective in reducing IOP than twice a day, with no effect on safety.

Keywords: Cosopt, timolol, dorzolamide, glaucoma, intraocular pressure, dosage

Introduction

Primary open-angle glaucoma (POAG) is a chronic progressive disease, characterized by painless intraocular pressure (IOP) elevation, optic nerve damage, and visual field loss.¹ POAG is the most common adult-onset type of glaucoma in the western world, and incidence increases with age.² It is one of the most common causes of chronic visual impairment³ and the second leading cause of blindness in the world.⁴

Large scale clinical studies have demonstrated the importance of early IOP reduction in order to prevent optic nerve damage and visual loss.^{5–8} Specifically, the Early Manifest Glaucoma Trial has shown that every 1 mmHg reduction in IOP is important, and is associated with approximately 10% reduction in the risk of disease progression.⁸

First-line treatment typically consists of monotherapy with a single agent, and if the IOP reduction is insufficient treatment is switched to an alternative monotherapy or combination with a second agent.⁹ In patients requiring treatment with more than one agent, combination therapy is usually preferred since it is associated with increased compliance.^{10,11} However, it has been shown that in reality, combination therapy is often administered as first-line therapy for patients diagnosed with POAG or ocular hypertension (OHT).^{11,12}

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A common combination treatment for glaucoma is Cosopt® (Merck & Co, Inc, Whitehouse Station, NJ), which is a fixed single dose combination of maleate timolol 0.5% (a nonselective beta-blocker) and dorzolamide 2.0% (a carbonic anhydrase inhibitor). Combination therapy with Cosopt has been consistently proven to be more effective in IOP reduction than monotherapy with either timolol or dorzolamide.^{13–15} It has also been demonstrated that treatment with Cosopt is as safe and effective as concomitant treatment with timolol and dorzolamide.^{16–18} Treatment with Cosopt has been shown in various studies to decrease IOP by 10.6%–40%, with an average of 25%–30% reduction of IOP.^{11,13,14,16,19–24}

All studies involving Cosopt included twice-daily administration. The recommended administration of its components is twice a day for timolol and three times a day for dorzolamide.^{16,17} A review of the literature revealed no study in which Cosopt was administered three times a day. The purpose of this study was to assess the safety and efficacy in IOP reduction of increasing Cosopt dosage from twice to three times a day.

Methods

Twenty-nine patients with POAG or OHT were included in this study. All patients were 18 years or older, and were diagnosed with POAG or OHT by a glaucoma specialist after undergoing detailed ophthalmologic examination including evaluation of glaucomatous optic disc damage and gonioscopy, IOP measurements by applanation tonometry, and automated perimetry. Patients with advanced glaucoma (mean deviation lower than –12 dB or presence of central scotoma) were not included.

Exclusion criteria included closed-angle glaucoma or secondary open-angle glaucoma, such as pseudoexfoliation or pigment-dispersion syndrome. Also excluded were patients receiving systemic treatment with beta-blockers or carbonic anhydrase inhibitors for any reason, and patients with systemic conditions that may be adversely affected by timolol or dorzolamide, such as asthma, hypotension, bradycardia, cardiac arrhythmia, impaired kidney function, or impaired hepatic function. Patients who had previously undergone surgery or laser treatment to reduce IOP were also excluded. All patients had visual acuity of 20/80 or better. Only one eye of each patient was included in the study. If both eyes of a patient met the inclusion criteria, the left eye was routinely chosen arbitrarily.

All patients were previously treated only by either dorzolamide or timolol, and treatment was switched to Cosopt

twice a day for a washout period of 4 weeks. Patients were then followed for another 4 weeks and then the dosage was increased to three times a day for another 4 weeks.

IOP was measured in all patients at baseline, after 4 weeks of treatment with Cosopt twice a day, and after another 4 weeks of treatment with Cosopt three times a day. Baseline measurements were made after a 4 week washout period with Cosopt twice a day, to eliminate any effect of previous treatment. All measurements were made by Goldmann applanation tonometry, and were performed by a single ophthalmologist. All measurements were taken between 8–10 am, prior to instillation of the morning drop of Cosopt.

At each time point heart rate, blood pressure, and blood oxygen saturation levels were measured. Heart rate and blood pressure were measured by an automatic device and oxygen saturation was measured by a pulse oxymeter. All measurements were made by the same physician at the time of IOP measurement.

The study protocol was reviewed and approved by the Institutional Review Board, and a written informed consent was obtained from all participants.

Descriptive statistics including the mean and standard deviation (SD) were produced for all continuous study variables. The statistical significance of the changes in IOP, systolic and diastolic blood pressure, heart rate, and oxygen saturation levels between time points was assessed by Student's *t*-test for paired observations. The statistical significance level was set at 0.05. Data were analyzed using SPSS for Windows (version 17.0; SPSS Inc, Chicago, IL).

Results

Twenty-nine eyes of 29 patients were included in the study. Patients included 17 men (58.7%) and 12 women (41.3%), with a mean age of 71.1 years \pm 7.9 (SD) (range 59–85 years).

At baseline, mean IOP levels were 21.11 ± 3.14 mmHg (range 13–27 mmHg). Mean systolic and diastolic blood pressure values were 146.31 ± 14.45 mmHg and 76.55 ± 10.87 mmHg, respectively. Mean heart rate was 75.06 ± 10.95 bpm, and mean oxygen saturation levels were $98.17\% \pm 1.31\%$.

After 4 weeks of treatment with Cosopt twice a day, mean IOP levels were 15.34 ± 2.27 mmHg (range 10–20 mmHg). Mean systolic and diastolic blood pressure values were 142.96 ± 12.07 mmHg and 72.82 ± 10.44 mmHg, respectively. Mean heart rate was 71.62 ± 12.86 bpm, and mean oxygen saturation levels were $97.96\% \pm 1.20\%$.

Table 1 Mean and standard deviation of IOP, systolic and diastolic blood pressure, heart rate, and oxygen saturation levels at baseline, after 4 weeks of treatment with Cosopt twice a day, and after 4 weeks of treatment with Cosopt 3 times a day

Time point	IOP (mmHg)		Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)		Heart rate (bpm)		Oxygen saturation levels (%)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	21.11	3.14	146.31	14.45	76.55	10.87	75.06	10.95	98.17	1.31
After 4 weeks of Cosopt \times 2/day	15.34	2.27	142.96	12.07	72.82	10.44	71.62	12.86	97.96	1.20
After 4 weeks of Cosopt \times 3/day	13.17	1.81	145.51	15.75	74.93	12.46	71.20	12.16	98.06	0.96

Note: Only the differences in IOP were of statistical significance (**Bold**).

Abbreviations: IOP, intraocular pressure; SD, standard deviation.

After another 4 weeks of treatment with Cosopt three times a day, mean IOP levels were 13.17 ± 1.81 mmHg (range 9–17 mmHg). Mean systolic and diastolic blood pressure values were 145.51 ± 15.75 mmHg and 74.93 ± 12.46 mmHg, respectively. Mean heart rate was 71.20 ± 12.16 bpm, and mean oxygen saturation levels were $98.06\% \pm 0.96\%$. Data are presented in Table 1.

Treatment with Cosopt twice a day for 4 weeks resulted in a mean reduction of 5.71 ± 2.57 mmHg in IOP. This corresponds to a mean reduction of $25.90\% \pm 10.37\%$ compared with the baseline IOP values, which was statistically significant ($P < 0.001$).

Comparing IOP values after 4 weeks of treatment with Cosopt twice a day and after another 4 weeks of Cosopt three times a day revealed an additional reduction of IOP that varied between 0–6 mmHg. The higher dosage resulted in a mean additional reduction of 2.2 ± 1.58 mmHg in IOP, which corresponded with a change of $10.69\% \pm 7.49\%$ of the baseline IOP values. This reduction was statistically significant ($P < 0.001$). Data are presented in Figure 1.

Changes in systolic and diastolic blood pressure, heart rate, and oxygen saturation levels between all three time

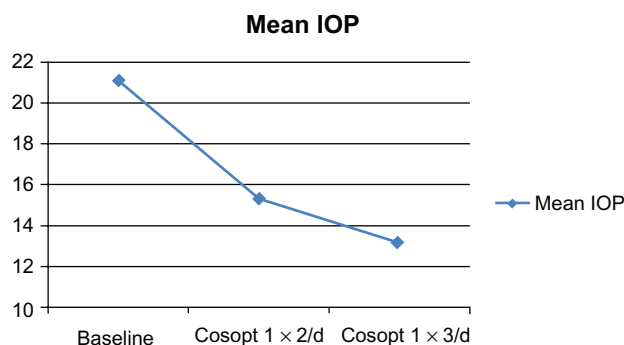
points were minimal and of no statistical significance. No patient complained of ocular surface irritation, and no patient suffered any systemic or local adverse effect that required cessation of Cosopt therapy.

Discussion

In this study, treatment with Cosopt twice a day caused a mean IOP reduction of $25.90\% \pm 10.37\%$, comparable to the results of previous studies of its efficacy.^{11,13,14,16,17,19–25} This effect on IOP was expected, as most patients included in this study did not receive previous treatment. After another 4 weeks of treatment with an increased dosage of Cosopt three times a day, IOP had decreased by another 2.2 ± 1.58 mmHg, corresponding to an additional reduction of $10.69\% \pm 7.49\%$ of the baseline IOP value. The increased dosage was not associated with any significant systemic adverse effect or any change in blood pressure, heart rate, or oxygen saturation. It was also not associated with any local adverse effects or intolerability.

The strengths of this study include its prospective nature, exclusion of patients with any glaucoma other than POAG/OHT, and its open label design emulating the real life clinical setting. Potential limitations of this study include its relatively small cohort size and short treatment duration. However, the purpose of the study was to assess the effect on IOP of increasing Cosopt dosage from twice to three times a day, and the study was designed for this comparison, which revealed statistically significant results.

This study is the first to evaluate Cosopt administered three times a day. Our results indicate that increasing Cosopt dosage from twice to three times a day is associated with increased efficacy in IOP reduction, with no change in its safety profile. The additional reduction in IOP was considerable and statistically significant. This new finding is of clinical importance, as it has been demonstrated that every

**Figure 1** Mean IOP values at baseline, after 4 weeks of treatment with Cosopt twice a day, and after another 4 weeks of treatment with Cosopt three times a day.

Note: Differences between time points were statistically significant.

Abbreviation: IOP, intraocular pressure.

1 mmHg reduction in IOP is associated with approximately 10% reduction in the risk of glaucoma progression.⁸ Since dorzolamide by itself is usually administered three times a day,^{16–17} it may be possible that it does not exert its full effect when given only twice a day as a component of Cosopt.

In conclusion, we found that Cosopt administered three times a day is more effective and as safe as when administered twice a day. Based on our results, we suggest that increasing Cosopt dosage to three times a day may be useful clinically in POAG/OHT patients in which a small yet significant additional reduction in IOP is required. Instead of changing or adding other antiglaucoma agents, this treatment may be a safe and simple way to achieve the target IOP. We also believe that increasing the dosage will not adversely affect patients' compliance. It is possible that in POAG/OHT patients treated with Cosopt in which further IOP reduction is required, increasing the dosage to three times a day may be considered before other medications or surgery. Further large scale studies are required to corroborate our findings and establish their place in clinical practice.

Disclosure

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