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

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% ± 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
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. It has also been demonstrated that treating in IOP reduction than monotherapy with either timolol or dorzolamide. It has also been demonstrated that treating in IOP reduction than monotherapy with either timolol or dorzolamide. It has also been demonstrated that treating in IOP reduction than monotherapy with either timolol or dorzolamide. It has also been demonstrated that treating in IOP reduction than monotherapy with either timolol or dorzolamide. It has also been demonstrated that treating in IOP reduction than monotherapy with either timolol or dorzolamide. 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After another 4 weeks of treatment with Cosopt three times a day, mean IOP levels were $13.17 \pm 1.81$ mmHg (range 9–17 mmHg). Mean systolic and diastolic blood pressure values were $145.51 \pm 15.75$ mmHg and $74.93 \pm 12.46$ mmHg, respectively. Mean heart rate was $71.20 \pm 12.16$ 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 $5.71 \pm 2.57$ 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 $2.2 \pm 1.58$ 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 $2.2 \pm 1.58$ 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
1 mmHg reduction in IOP is associated with approximately 10% reduction in the risk of glaucoma progression. Since dorzolamide by itself is usually administered three times a day, 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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