Efficacy and safety of timolol-dorzolamide fixed-combination three times a day versus two times a day in newly diagnosed open angle glaucoma

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Abstract:

Purpose: To compare the therapeutic efficacy and safety of dorzolamide/timolol fixed-combination in newly diagnosed primary open angle glaucoma patients.

Methods: In this prospective, interventional case series, newly diagnosed primary open angle glaucoma (POAG) patients that had not been treated for glaucoma were included. Patients were started on Cosopt twice a day (BID) for 1 month and then switched to three times a day (TDS) for additional 1 month. Patients underwent comprehensive ophthalmic examination, diurnal intraocular pressure (IOP), blood pressure (BP) and 24-hours heart rate (HR) measurements at baseline, month 1 (BID), and month 2 (TDS). IOP, systolic and diastolic pressures were measured at 8:00 AM, 12:00 AM, 4:00 PM, 8:00 PM and 12:00 PM.

Throughout the study, all adverse events were recorded and monitored by the investigators.

Results: In 31 POAG patients that completed the study, mean baseline IOP was 23.1±3.15 mmHg. IOP was decreased significantly 16.5 ± 2.21 at 1 month (P<0.0001) and 13.9 ± 2.23 mmHg at 1 and 2 month follow up. (P<0.0001) IOP was significantly lower in month 2 compared to month 1. (P= 0.0004)

While Cosopt BID significantly reduced the mean 24-hour systolic BP and mean 24-hour HR from baseline (P< 0.0001), the mean 24-hour systolic BP and HR remained unchanged with Cosopt TDS compared to BID. (P= 0.62)

Conclusions: Cosopt TDS has a superior IOP-lowering effect than Cosopt BID in POAG patients with comparable safety profile.

Key words: Primary open angle glaucoma, Dorzolamide/timolol fixed combination, drug efficacy, safety
Glaucoma is a major public health issue as it is a leading cause of blindness and affects more than 60 million people worldwide. Lowering intraocular pressure is the only established treatment for glaucoma. While the pendulum is swinging from medical treatment to minimally invasive glaucoma surgeries for mild to moderate glaucoma, medications are still first line therapy in the most practice settings.

The ideal medication regimen should address both peak and fluctuation characteristics of intraocular pressure profile. Typically, first line treatment involves monotherapy with prostaglandin analogues as they are more efficacious than any other single agent and yield flatter IOP-controlling pattern. Meanwhile, fixed combination (FC) glaucoma medications are introduced to improve the outcome of medical therapy by boosting the compliance as well as efficacy. As such several ophthalmologists opted to use them as first line treatment to avoid ocular side effects of prostaglandin analogues.

Fixed combination of timolol 0.5% - dorzolamide 2.0% is the most frequently prescribed FC medication and perhaps the most studied one. It is well established that it reduces IOP more than monotherapy of each agent alone and is as safe and effective as concomitant use of timolol and dorzolamide.

In the lights of the results of Early Manifest Glaucoma Trial that showed more IOP reduction in early glaucoma results in less disease progression as well as concerns regarding the diurnal IOP-controlling effects of fixed combination medications, some ophthalmologists started to schedule three-times a day Cosopt administration instead of advocated twice daily dosage.

Although increasing the dosage of timolol from twice to three times a day resulted in more IOP reduction in one study, concern remains regarding the systemic side effects, especially cardiovascular, of more frequent exposure to non-selective beta-blocker activity of timolol.

The purpose of this study is to compare the efficacy and cardiovascular safety of two times and three times a day administration of Cosopt eye drop in treatment naive primary open angle glaucoma eyes.
Method:

This study was conducted at the glaucoma clinic of the Labbafinejad Medical Center from September 2014 to March 2015. The study was approved by the ethics committee and the institutional review board at the Ophthalmic Research Center and followed the tenets of the Declaration of Helsinki. Informed written consent was obtained from each participant. Patients with newly diagnosed primary open angle glaucoma who had not received any glaucoma medication were included. Exclusion criteria were: age ≤ 30, history of using glaucoma medication, past history of glaucoma surgery, any ocular or systemic condition that prohibit using timolol or dorzolamide, severe glaucoma that needed more aggressive initial IOP control, and using systemic beta blockers.

Thirty-three subjects with bilateral primary open angle glaucoma were included. At baseline, all patients underwent a comprehensive ophthalmic examination including best corrected visual acuity (BCVA), biomicroscopic slit lamp examination, Goldmann applanation tonometry, gonioscopy, fundus examination, and perimetry (Humphrey visual field analyzer; model 750; Carl Zeiss Meditec, Dublin, California, USA).

Diurnal IOP was measured every 4 hours from 8 AM to 12 PM.

Standard exercise test and a 24-hours ECG recording was carried out at the baseline using an Oxford Holter system (Oxford Instruments, Abingdon, UK), and blood pressure (BP) was measured by a cardiologist using a Baumanometer mercury sphygmomanometer (W.A. Baum Co. Inc., Copiague, New York, USA), the patient having been comfortably seated for at least 5 min. Blood pressure was also checked at the time of diurnal IOP measurements.

Patients were started on Cosopt eye drop twice a day for one month and upon their return all the baseline measurements were repeated again by the same examiners. After filling the questionnaires and recording 24 hours heart rate and BP, patients were instructed to increase from twice a day to three times a day schedule.

After one month of higher dosage therapy, all the previous examinations were performed in the same manner and data were recorded. All measurements were taken between 9-11 am, before instillation of the morning drop of Cosopt.
The primary outcome measure was IOP and secondary measures were changes in heart rate and blood pressure.

All analyses were performed using SPSS software (SPSS Statistics for Windows, Version 25, Armonk, NY, IBM Corporation). Frequency, percent, mean±SD, median, and range were used to describe the data. The student’s t test was used to measure changes in IOP, heart rate, and BP at different time points. Statistical significance was set at p< 0.05.

Results:

A total of 33 patients were enrolled in this study but only 31 patients were included in final analysis. One patient was lost to follow-up and one patient quitted the study due to bradycardia. Both cases were excluded during the first month of treatment. Only the eye with higher baseline IOP was included for final analysis.

Patients were instructed to use one drop of Cosopt in their study eye every 12 hours during the first month, and every 8 hours during the second month. The patients were scheduled to instill the drops between 10 am and noon and between 10 pm and midnight during the first month, and then between 6 am and 8 am, 2 pm and 4 pm, and 10 pm and midnight during the second month. Mean 24-hour IOP at baseline was 23.1±3.15 mmHg (95%CI 20.0 to 29). IOP was decreased significantly to 16.5 ± 2.21 mmHg (95%CI 14. to 20) after 1 month of treatment with Cosopt BID and, mean change from baseline was -6.6 mmHg (P<0.0001). The average IOP reduction at the end of one month was 28.5%.

After 1 month of treatment with Cosopt TDS, mean 24-hour IOP level was 13.9 ± 2.23 mmHg (range 10–17 mmHg), mean change from baseline was -8.9 mmHg, and the average IOP reduction was 39.8%. (P <0.0001)

The higher dosage of Cosopt resulted in additional 2.7 ± 1.35 mmHg IOP reduction, corresponding to 11.7% change. (P= 0.0004)
The IOP at each time points of the diurnal IOP with Cosopt TDS was significantly lower than the corresponding time points at baseline and Cosopt BID. (Figure 1)

Figure 1. diurnal curve of mean intraocular pressure (IOP) at baseline and during dorzolamide-timolol fixed combination treatment.

Mean 24-hour HR at baseline was 76.6 beats per minute (bpm) (95%CI 65 to 90) and after one month of treatment with Cosopt BD, it was significantly reduced to 74.4 bpm, (95%CI 65 to 87;P=0000). After another month of treatment with Cosopt TDS, mean 24h HR was 74.06 bpm (range 64-88) , which was comparable to Cosopt BID. (P= 0.62) (Figure 2).
Figure 2. Diurnal curve of mean heart rate at baseline and during dorzolamide-timolol fixed combination treatment.
Mean 24h systolic blood pressure was 131±14.9 mmHg at baseline and was decreased to 128.5±15.7 after 1 month of treatment with Cosopt BID (P = 0.03). The 2-month measurement was comparable with 1-month BP reading. (Figure 3).

Figure 3. diurnal curve of mean systolic at baseline and during dorzolamide-timolol fixed combination treatment.

Mean 24h diastolic blood pressure at baseline, month 1, and month 2 was 82.6±12, 81.3±12.1, and 81.3±14.1 mmHg (Ps = 0.16 and 0.13, respectively). (Figure 4)
One case developed bradycardia 3 weeks after starting Cosopt and medication was immediately discontinued, which led to normalization of heart rate. No ocular discomfort was reported by the patients during the course of the study.

**Discussion:**

In the current study, Cosopt BD reduced the IOP by almost 28% from the baseline which is comparable to previous reports on its efficacy.\(^9\,5,9,11,12\) Increasing the dose of the medication to three times a day provided further IOP reduction by 12% and delivered 40% reduction from the baseline that agrees with significant efficacy of Cosopt TDS observed in previous study.\(^9\)
additional IOP lowering effect was not associated with any major systemic adverse effect or any change in heart rate and blood pressure.

Introduction of several classes of glaucoma medications since 1979 has rendered medical therapy as the mainstay treatment for early glaucoma cases. Unfortunately, no new class of glaucoma medication has been developed since early 2000 and recent endeavors revolved around combining already existing medications to increase the efficacy and improve the compliance.

Fixed combination drugs are attractive alternative for glaucoma patients as it is shown that more than 50% of glaucoma cases need more than one drop, and there is direct correlation between the number of the medication and the compliance. Fixed combination drugs have at least the same efficacy as concomitant administration and they increase patient persistence and reduce the cost. The problem though is to sync the different dosage schedule of each of agents in combination. While timolol is recommended to be administered twice daily, dorzolamide needs three-times a day doses to build up to steady state levels of drug concentration in the ciliary body. Cosopt is recommended to be used twice daily to trade off higher dorzolamide efficacy for less timolol side effect.

The result of our study showed that increasing the dosage result in significant IOP reduction unparalleled to any other single or combined medication. Furthermore, IOP controlling pattern of more frequent usage tended to have a plateau profile, which by blunting IOP fluctuations prevents further optic nerve head damage caused by undetected IOP peaks. The dynamic behaviour of intraocular pressure is thoroughly studied. It is demonstrated that two-third of IOP peaks occur outside office hours and rise of IOP during the nocturnal period is documented in both glaucoma and normal eyes. These undetected high IOPs are considered a reason for progressing glaucomatous optic neuropathy despite apparently well
controlled IOP. In fact, 24-hours IOP reading led to a modification of clinical management in almost 80% of reviewed glaucoma patients. 27

Our findings shows that timolol significantly decreases heart beat and blood pressure at all visit points during a day. This finding is in agreement with previous reports on systemic effects of topical timolol administration 28–30 and corroborates with high bioavailability of timolol drop through conjunctival and nasal mucosa. 31–33

Also, our results confirmed findings of Moisseiev et al. and showed that higher dosage has no additional systemic beta-blockade effect. 9

Although undoubtedly higher dosage of medication expose patients to higher systemic concentration of timolol, careful patient selection and thorough review system as well as punctal occlusion and eyelid closure help to avoid undesired systemic side effects. 30

The strength of current study is its prospective nature and using 24 hours heart rate and blood pressure monitoring.

But there are limitation to this study. We did baseline comprehensive cardiology exam and would have excluded the patient if there was unusual finding, but in real practice systemic evaluation is rarely done for healthy individual and higher exposure may affect susceptible patients. Also, respiratory function test was not performed in this study, so we cannot comment on the possible respiratory side effect of higher dosage. Further, the effect of higher dosage schedule on lipid profile, central nervous system, exercise intolerance, and endocrine system was not evaluated in our study. One potential disadvantage of higher dosage schedule is the late night dosing of timolol as it may reduce ocular perfusion pressure, which is linked to progressive glaucomatous damage by some studies. 34,35 Although we did not observe any change in blood pressure by increasing the dose of timolol, aggravated nocturnal hypotension remains a concern for administering Cosopt three times a day.
Moreover, we only followed our patients for 2 months and it is possible that by longer follow up and more exposure to timolol inadvertent cardiac and respiratory side effects devole.

In conclusion, our study showed that Cosopt administered three times a day has significantly higher IOP reduction than 2-times a day schedule.

References:


9. Moisseiev E, Shemesh, Lazar, Kurtz. Intraocular pressure reduction of fixed combination timolol maleate 0.5% and dorzolamide 2% (Cosopt) administered three times a day. OPTh. 2012: 283.


31. Chang SC, Lee V. ... to the systemic absorption of topical timolol in the pigmented rabbit: implications in the design of strategies to maximize the ratio of ocular to systemic absorption. J.


