Efficacy of the latanoprost versus timolol/dorzolamide combination therapy in patients with primary open angle glaucoma

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ABSTRACT

الأهداف: لنقيم في هذه الدراسة كفاءة عقار لاتانوبروست واتحاد عقار دورزولاميد وتيمولول على مدى ستة أشهر.

الطريقة: تم تصميم هذه الدراسة كدراسة عشوائية لمدة ستة أشهر.شملت الدراسة 120 مريضاً يعانون من الماء الأسود الأولي (جلوكوما) بزاوية مفتوحة بمستشفى فيبز في الفترة ما بين 2006م الى 2007م. تم توزيع المرضى عشوائياً (عقار لاتانوبروست n = 60، دورزولاميد/تيمولول n = 60) للعلاج إما بعقار لاتانوبروست، 0.005% مرة واحدة يومياً او باتحاد عقار تيمولول 0.5% مرتين يومياً وعقار دورزولاميد 2% ثلاث مرات في اليوم. تمت مقارنة متوسط الضغط داخل مقلة العين (IOP) بعد3 و6 أشهر من العلاج بواسطة الخط القاعدي في كلتي المجموعتين.

النتائج: تم تقسيم كامل عدد المرضى 120 الى مجموعات متساوية للعلاج. كان متوسط الخط القاعدي للضغط داخل مقلة العين (IOP) متشابهاً بين كلتا المجموعتين. بلغ متوسط الأرجاعات داخل العين عند 1.3 شهر و6 أشهر 7.2 (0.4)، 7.3 (0.4) و 7.1 (0.3) ملليتر زئبقي في مجموعة لاتانوبروست و7.5 (0.3) و 7.8 (0.3) و7.4 (0.3) ملليتر زئبقي لمجموعة دورزولاميد/تيمولول على التوالي. كانت كلتا المجموعتين متشابهتين في الكفاءة في إنقاص الضغط داخل العين ولم يكن هنالك اختلافا إحصائيا ملحوظاً بينهما.

خاتمة: كان عقار لاتانوبروست وعقار دورزولاميد/تيمولول متساويين في الكفاءة في إنقاص الضغط داخل مقلة العين مقارنة مع الخط القاعدي.

Objective: To evaluate the efficacy of latanoprost and combination of dorzolamide and timolol over 6 months.

Methods: The study was designed as a 6 months randomized, observer-masked study comprising 120 patients with primary open-angle glaucoma in Feiz Hospital, Isfahan, Iran, from 2006 to 2007. The patients were randomized (latanoprost, n = 60; dorzolamide/timolol, n = 60) to treatment with either latanoprost, 0.005% once daily, or the combination of timolol 0.5% twice daily, and dorzolamide 2% 3 times daily. The mean intraocular pressure (IOP) after one, 3, and 6 months of treatment was compared with baseline in the 2 groups

Results: A total of 120 patients were randomized to 2 equal treatment groups. The mean baseline IOP values were similar between the 2 groups. The mean (standard error of mean [SE]) IOP reductions at months one was 7.2 (0.4), at month 3 was 7.3 (0.4), and at month 6 was 7.1 (0.3) mm Hg for the latanoprost group and 7.5 (0.3), 7.8 (0.3), and 7.4 (0.3) mm Hg for the dorzolamide/timolol group. The 2 therapies were similarly effective

Conclusion: The latanoprost and dorzolamide/timolol combination were equally effective at lowering IOP compared to untreated baseline.

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The only medical treatment for open-angle glaucoma and ocular hypertension is reducing intraocular pressure (IOP). Topical ß-blockers such as timolol have been used to reduce IOP by decreasing aqueous humor secretion. The presumed mechanism of action is the blockage of the $ß_2$ adrenergic receptors found in the ciliary body.[1,2] However, in many patients, topical ß-adrenergic antagonists alone do not sufficiently lower IOP, and additional medications have to be prescribed.[3] Carbonic anhydrase inhibitors, such as dorzolamide,

have an additive IOP-lowering effect in patients that used timolol. As these drugs reduce IOP through different pathways than ß-blockers, they are often given as adjunctive therapy to ß-blockers. The combination of dorzolamide 2% and timolol 0.5%, is more effective at reducing IOP than either of its components.[1] Combined therapy, however, often requires more complex, sometimes inconvenient treatment regimens, involving an increased frequency of instillations of eye drops. As such regimens can reduce medication compliance, long-term management of glaucoma with monotherapy could be advantageous for patients. Latanoprost 0.005% reduces IOP by increasing uveoscleral outflow.[4,5] In addition, latanoprost provides a smooth diurnal and nocturnal IOP curve without peaks and a consistent IOP reduction over 24 hours.[6] Long-term studies (1-2 years) have shown that latanoprost maintains IOP reductions without serious systemic adverse effects.[7-9] Previous studies that compared the IOP lowering effects of the dorzolamide/timolol combination versus latanoprost have found similar effects,[10] or a small advantage for latanoprost.[1] The present study was designed to further compare the efficacy of latanoprost instilled daily with dorzolamide administered 3 times daily and timolol administered twice daily in patients with glaucoma.

Methods. Patients 18 years of age or older with unilateral or bilateral primary open-angle glaucoma that were newly diagnosed and never treated were included in this study. The study was performed in Feiz Hospital, Isfahan, Iran from 2006 to 2007. Glaucoma was defined as either visual field defect or glaucomatous changes of the optic nerve head in association with elevated IOP. At the pre-study examination the IOP had to be at least 22 mm Hg in patients with glaucoma. Patients with a history of acute angle closure and closed anterior chamber angle, were excluded from the study. Ocular filtering surgery (the unfiltered eye might be eligible), argon laser trabeculoplasty, any condition in which treatment with a beta-blocker is contraindicated, such as histories of asthma or chronic obstructive pulmonary disease, cardiac failure, sinus bradycardia, or second and third degree atrioventricular block were considered criteria for exclusion, as were severe renal impairment and hyperchloremic acidosis. Women who were pregnant or breast-feeding, and patients with a history of noncompliance or any hypersensitivity to the component of the study medications were also excluded. Use of systemic medications known to affect IOP prevented the patient from entering the study. Prior to inclusion in the study, investigators provided patients with full and adequate verbal and written information regarding the objectives and procedures of the trial and the possible risks involved, and all patients provided written informed consent (in accordance with the declarations of Helsinki) to participate. The study was also approved by the Isfahan University of Medical Science and Health Services ethics committee. At the screening visit, we reviewed the patient's medical and ocular histories, demographic data and concomitant diseases. Best-corrected visual acuity, refraction, visual field testing, ophthalmoscopy, IOP and slit-lamp examination were obtained. The IOP was measured by Goldmann applanation tonometer. Patients underwent 4 study visits: at baseline (randomization) and after one, 3, and 6 months of therapy. At each study visit, the same masked examiner measured the IOP by the same Goldmann applanation tonometer, and the IOP was measured before pupil dilatation. At the baseline visit (another day different from pre-study visit), patients were randomly were assigned in a 1:1 ratio to receive either latanoprost 0.005%, or the combination of dorzolamide 2% and timolol 0.5%. Patients in the latanoprost group received one drop in the affected eye daily, and patients in the dorzolamide/timolol group received timolol one drop in the affected eye twice daily, and dorzolamide one drop in the affected eye 3 times daily beginning on the baseline day. Patients requiring bilateral IOP-reducing therapy were treated in both eyes, but only the eye that had all inclusion and no exclusion criteria was included in the study. If both eyes qualified, the worse eye was designated as the study eye.

The statistical significance of within and between group IOP changes from baseline was tested using the paired t-test and the t test. The data collected was analyzed using the Statistical Package for Social Sciences (SPSS). Data were also described as mean ± 2 standard error (2SE), and differences were considered significant if p-value < 0.05.

Results. Of the 120 patients included in the study, 60 were randomized to latanoprost and 60 to the combination of timolol and dorzolamide. **Table 1** presents the characteristics of the 2 treatment groups. All patients had primary open-angle glaucoma. At baseline, the mean IOP was 29.6±1.5 mm Hg (mean ± 2SE) for patients randomized to treatment with latanoprost (group one) and 30.4 ± 1.7 mm Hg for patients randomized to timolol/dorzolamide (group 2). Mean IOP values were similar between groups at baseline and there was no statistically significant different (p=0.501). After one month of treatment, the mean IOP were 22.3±1.4 mm Hg in group one and 22.8±1.5 mm Hg in group 2. The mean change from baseline was -7.2±0.8 mm Hg (mean±2SE) for the patients treated with latanoprost and -7.5±0.7 mm Hg for the patients treated

Table 1 - Patient characteristics in the 2 parallel treatment groups.

Characteristics		Latanoprost	Dorzolamide/ Timolol	Total
Age (years)	Mean±2SE	52.7±2.8	54.8±4	53.7±2.4
	Range	35-80	21-80	21-80
Gender	Woman	28	32	60
	Man	32	28	60
Cup/Disc Ratio (Mean±2SE)		0.61±0.02	0.60±0.04	0.61±0.02

with timolol+dorzolamide, representing reductions of 24% and 25%. The 95% confidence interval for the difference in mean IOP reduction between treatment groups was -0.8-1.4 mm Hg. There is no statistically significant difference in treatment effect (p=0.664). After 3 months of treatment, the mean IOP was 22.2±1.3 mm Hg in group one, and 22.5±1.4 mm Hg in group 2. The mean change from baseline was -7.3±0.8 mm Hg (mean±2SE) for the patients treated with latanoprost and -7.7±0.6 mm Hg for the patients treated with timolol+ dorzolamide, representing reductions of 24% and 25%. The 95% confidence interval for the difference in mean IOP reduction between treatment groups was -0.5-1.5 mm Hg. There was no statistically significant difference in treatment effect (p=0.777). After 6 months of treatment, the mean IOP was 22.4±1.4 mm Hg in group one and 22.9±1.5 mm Hg in group 2. The mean change from baseline was -7.1±0.7 mm Hg (mean±2SE) for the patients treated with latanoprost and -7.4±0.6 mm Hg for the patients treated with timolol+dorzolamide, representing reductions of 24% in both groups. The 95% confidence interval for the difference in mean IOP reduction between treatment groups was -0.7-1.3 mm Hg. There was no statistically significant difference in treatment effect (p=0.647). Compared with baseline measurements, IOP reduction at months one, 3, and 6 was statistically significant in both treatment groups (p<0.0001). The finding shows that the 2 treatments were equally effective at reducing IOP in this study.

Discussion. In this randomized, observer-masked study that directly compared the dorzolamide/timolol combination with latanoprost in 120 patients with open angle glaucoma, both treatments were equally effective at reducing mean IOP over one, 3, and 6 months. Compared with baseline, reductions in mean IOP levels were 24% in both groups over 6 months. Latanoprost is considered to provide 24-hour efficacy with once daily dosing.[1] Combined therapy can affect quality of life in glaucoma patients. An increased number of medications negatively impact these patient's daily lives.[11] Monotherapy may maximize patient compliance. Therefore, the goal of medical treatment is to select the simplest treatment regimen that achieves the most effective IOP reduction in order to prevent or at least slow disease progression.[12,13] Switching to another drug rather than combining therapies is one way of achieving a simple treatment schedule.[14] The short duration of the present study did not allow comparison of disease progression between treatment groups. By design, the present study excluded patients in whom treatment with a beta-blocker was contraindicated, such as patients with a history or evidence of bradycardia and/or asthma. This exclusion criterion and others may have resulted in a patient population somewhat healthier than might be expected in a general ophthalmic clinic population. No serious side effects were observed. Mild conjunctival hyperemia and ocular irritation was observed in some patients of both groups. Although fewer adverse effects might be expected when administering one rather than 2 ocular hypotensive agents, long-term effects sometimes associated with latanoprost use, such as hyperpigmentation,[15] hypertrichosis,[16] uveitis, recurrent corneal herpes keratitis, and cystoid macular edema,[17] might not have developed because of the short duration (6 months) of the study.

In conclusion, the results of this study indicate that the convenient regimen of one drop of latanoprost daily provided IOP control equivalent to that from 2 drops of timolol and 3 drops of dorzolamide.

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