ORIGINAL ARTICLE

Efficacy and Cardiovascular Safety of Topical Timolol, Brimonidine & Latanoprost in Newly Diagnosed Patients of Open Angle Glaucoma

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Abstract

The present study was conducted in chronic open angle glaucoma patients to evaluate their efficacy in reducing IOP and their cardiovascular safety. 48 newly diagnosed patients of glaucoma completed the trial. Patients were divided into three groups and received medications in form of topical instillations. Group I (Timolol 0.5% twice a day), Group II (Brimonidine Tatrate 0.2% twice a day) & Group III (Latanoprost 0.005% once a day) for 12 weeks. All the three medications, significantly decreased IOP ($P<0.05$), however, Latanoprost caused maximum decrease in IOP, followed by Brimonidine and Timolol. Visual Acquity was not affected by any of the medication. Pulse Rate and PR Interval were decreased in Timolol group significantly ($P < 0.001$) while Brimonidine and Latanoprost did not alter Pulse Rate. Blood Pressure was not affected by either of medication except Brimonidine which caused reduction in systolic Blood Pressure at 12 weeks. The results of present study demonstrates superiority of Latanoprost over Timolol and Brimonidine as it lacked effect on Pulse Rate, Blood Pressure and HR, besides being more efficacious.

Key Words

Glaucoma, Latanoprost, Brimonidine, Timolol, IOP, Pulse Rate, HR, PR-Interval

Introduction

Glaucoma in developing country like India is the 3rd leading cause of blindness after cataract and refractory errors (1). The strategies to reduce the raised IOP are numerous. Till recent past miotics, epinephrine, beta-blockers and carbonic anhydrase inhibitors, Prostaglandins and Prostamides, beta-adrenergic agonist were frequently used. Since the glaucoma patients are to be treated on long term basis safety profile of the drug is a deciding factor amongst the numerous anti-glaucoma drugs.

Timolol a beta-blocker introduced in 1977 was the first beta-blockers approved by FDA for glaucoma therapy which reduce IOP , but even its topical application has potential to cause systemic beta-blockade effects (2-6). Brimonidine, more selective beta2-adrenergic agonists cause decrease in IOP. This drug is well tolerated and has minimal ocular adverse effects like mydriasis, chemosis and systemic effects like fatigue, sedation, headache and dry mouth (7-11). Latanoprost (PG F2alpha analog) is currently the frontline drug in the treatment of glaucoma, and has been shown to have better safety profile (5, 12-14).There are number of studies comparing ocular efficacy of these drugs but there is paucity of the research evaluating their systemic effects after topical application so the present study was undertaken to compare the ocular efficacy and safety of Timolol, Brimonidine and Latanoprost and to study their cardiovascular effects after the topical application.

Materials & Methods

The present one year randomised open label controlled trial approved by Institutional ethical committee was undertaken.Patients of either sex in the age group of 20 or above suffering from open angle glaucoma diagnosed on gonioscopy with IOP more than 21mm Hg in one or both eyes without parametric evidence of glaucomatous visual defects were included in study, while patients with history of hypersensitivity to either of the drug, cardiovascular disease, Diabetes mellitus, Hypertension, Corneal abnormalities, contact lens users, laser treated, concurrent lridocyclitis, Keratitis, closed angle glaucoma and pregnant women were excluded.Study Design: 54

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newly diagnosed patients of glaucoma were included in the study who fulfilled inclusion criteria and baseline parameters were recorded. 6 patients dropped during the study because the IOP was not controlled with single medication and needed change in the therapy. Remaining 48 patients were randomised to three different groups of 16 patients each and received following medical regimen instilled in eye as drops for 12 weeks.

Group 1 received Timolol (0.5%) twice a day, while Group 2 received Brimonidine tartrate (0.2 %) twice a day whereas Group 3 received Latanoprost (0.005%) once a day. Ocular Parameters recorded were IOP with non contact tonometer and Visual acquity for distant and near vision. Cardiovascular Parameters recorded were Pulse Rate, Blood Pressure & E.C.G. Effect of each drug on these parameters were analyzed by using paired t-test and inter group comparison between two groups was done using unpaired t-test and ANOVA.

Results

IOP:- All the three medications reduced IOP significantly. The reduction in IOP followed similar pattern with all three groups, it started at two weeks with maximum effect at 12 weeks. Timolol significantly reduced IOP with maximum reduction of 5.6 mm Hg while Brimonidine significantly declined IOP with maximum reduction of 6.4 mm Hg whereas Latanoprost significantly decreased IOP with maximum reduction of 7.3 mm Hg observed at twelve weeks ($P<0.001$) (*Table 1*). When Timolol, Brimonidine and Latanoprost were compared between each other no difference was observed. There was no significant change in VA with the use of either medication in any group during the 12 weeks period of trial .

Pulse Rate: Timolol caused decrease in pulse rate, which was statistically significant in the entire duration of study ($P < 0.001$), while Pulse Rate in Brimonidine group and Latanoprost remained unaffected. When the pulse rate of Timolol group was compared with Brimonidine and Latanoprost groups, it was observed Timolol caused significant pulse rate decrease over the other two groups at 6 weeks and at 12 weeks ($P < 0.0001$) (*Table 2*).

*P-R Interval:*The mean P-R Interval in Timolol group at 0 weeks was 0.12 + 0.04 sec which changed to 0.14 + 0.004 sec at 2 weeks and remained same at 6 and 12 weeks. This decrease in P-R Interval was statistically significant ($P<0.001$) while in Brimonidine and Latanoprost group PR Interval remained unaffected. When Timolol group was compared with Brimonidine and Latanoprost significant difference was observed in Timolol group at 12 weeks. (*Table 3*)

Blood Pressure:The BP both systolic as well as diastolic were not affected by either of the medication except Brimonidine which caused significant reduction in systolic BP at 12 weeks ($P < 0.05$). Mean baseline systolic BP in Brimonidine was 126.37 + 2.62 mm Hg and it decreased to 125.62 + 2.56 mm Hg at 2 weeks, 125.12 + 2.05 mm Hg at 6 weeks and 124.62 + 2.49 mm Hg at 12 weeks while Latanoprost and Timolol did not alter the Blood Pressure (*Table 4*). All the medications were well tolerated in Timolol group, one patient had burning sensation in eye and another complained of irritation. One patient from Brimonidine group had conjunctival hyperaemia. No ocular side effect was reported from the Latanoprost group. Oral dryness, fatigue was reported in one patient of Brimonidine group and was self limiting.

Discussion

In the present study we compared the ocular and systemic safety of commonly used drugs Timolol, Brimonidine and Latanoprost besides monitoring their efficacy in lowering IOP.In the present study Timolol caused significant reduction in IOP during entire phase of study ($P < 0.05$). This is in agreement with previous studies (15, 16).Brimonidine selective beta 2 adrenergic agonist with better corneal penetration because of its lipophilicity reduce IOP, Brimonidine reduce aqueous humor production and enhance uveoscleral outflow. It binds to presynaptic beta 2 receptors and reduce release of neurotransmitter of sympathetic nerves. It also decreases aqueous humor production by attaching to postsynaptic beta 2 receptors and stimulating G1 pathway reducing cAMP production (17). Brimonidine has neuroprotective role and increases retinal blood flow and have the potential to improve visual acuity which was not seen in present trial which could be because of shorter duration of the trial. While Brimonidine caused reduction in IOP which was observed from 2 weeks with maximum effect at 12 weeks. Such present observation are in accordance with previous study (18). Latanoprost PG F2 alpha-analog increases uveoscleral outflow because of relaxation of ciliary body muscles bundles and also alter the metabolism of extra cellular matrix that surround the cillary muscles cells. In the present study Latanoprost, topically lead to decrease in IOP 26.2 + 0.50 mm Hg to 18.9 + 0.26 mm Hg ($P < 0.05$) with maximum effect at 12 weeks.All the drugs produced reduction in IOP in similar magnitude though the Latanoprost caused numerically more reduction. Previous reports have also shown similar results (19). However, few studies have shown Brimonidine more effective than Timolol (20) and Latanoprost more effective than Brimonidine (21).

Table. 1 Effect of Timolol, Brimonidine and Latanoprost on IOP

Drug	Timolol (n = 32) (Mean + SEM)	Brimonidine (n = 32) (Mean + SEM)	Latanoprost (n = 32) (Mean + SEM)	F - Ratio	df	(P – value)
0 Weeks	24.7 + 0.78	25.4 + 0.08	26.2 + 0.50	1.21	2,93	(> 0.05)
2 Weeks	23.2 ± 0.76*	22.7 ± 0.75*	24.0 ± 0.47*	0.88	2,93	(> 0.05)
6 Weeks	21.6 + 0.59*	20.2 + 0.48*	20.8 + 0.26*	2.27	2,93	(> 0.05)
12 Weeks	19.1 ± 0.45*	18.9 ± 0.41*	18.9 ± 0.26*	0.83	2,93	(> 0.05)

**P value < 0.001 as compared to baseline values. No significant difference was seen between the three groups after applying Anova.*

Table. 2 Effect of Timolol, Brimonidine and Latanopost on Pulse rate

Drug	Timolol (n = 16) (Mean ± SEM)	Brimonidine (n = 16) (Mean ± SEM)	Latanoprost (n = 16) (Mean ± SEM)	F - Ratio	df	(P – value)
0 Weeks	77.2 + 0.92	78.7 + 1.63	79.3 + 0.78	0.86	2,45	0.42
2 Weeks	72.5 ± 1.04*	78.1 ± 1.46	78.3 ± 0.75	1.99	2,45	0.14
6 Weeks	72.2 + 1.09*	78.0 + 1.42	79.1 + 0.65	11.14	2,45	0.0001**
12 Weeks	70.0 ± 1.18*	78.2 ± 1.40	78.7 ± 0.79	18.14	2,45	< 0.0001**

Table. 3 Effect of Timolol, Brimonidine and Latanoprost on E.C.G (Heart Rate beats/minutes)

Drug	Timolol (n = 16) (Mean ± SEM)	Brimonidine (n = 16) (Mean ± SEM)	Latanoprost (n = 16) (Mean + SEM)	F - Ratio	df	(P – value)
0 Weeks	77.25 + 0.92	78.75 + 1.63	79.37 + 0.78	0.86	2,45	0.42
2 Weeks	75.5 ± 1.04*	78.12 ± 1.46	78.37 ± 0.75	1.99	2,45	0.14
6 Weeks	72.25 + 1.09*	78.0 + 1.42	79.12 + 0.65	11.14	2,45	0.0001**
12 Weeks	70.0 ± 1.18*	78.25 ± 1.40	78.75 ± 0.79	18.14	2,45	<0.0001**

Table. 4 Effect of Timolol, Brimonidine and Latanoprost on Systolic & Diastolic B.P (mmHg)

Drug		Timolol (n = 16) (Mean ± SEM)	Brimonidine (n = 16) (Mean ± SEM)	Latanoprost (n = 16) (Mean ± SEM)	F - Ratio	df	(P – value)
0 Weeks	Systolic	124.75 + 1.77	126.37 + 2.62	127.12 + 0.70	0.41	2,45	0.65
	Diastolic	81.75 + 1.53	80.25 + 1.51	81.25 + 0.60	0.34	2,45	0.70
2 Weeks	Systolic	124.87 + 1.71	125.62 + 2.56	126.75 + 0.81	0.65	2,45	0.52
	Diastolic	82.37 + 1.46	80.5 + 1.32	81.0 + 0.36	0.70	2,45	0.50
6 Weeks	Systolic	124.75 ± 1.70	125.12 ± 2.65	127.75 ± 0.87	0.74	2,45	0.47
	Diastolic	81.25 + 1.42	78.37 + 1.38	82.0 + 0.44	2.65	2,45	0.08
12 Weeks	Systolic	124.25 ± 1.61	124.62 ± 2.49*	127.75 ± 0.94	1.114	2,45	0.32
	Diastolic	79.75 + 1.74	80.12 + 1.16	80.87 + 0.54	0.21	2,45	0.81

However these patients were already on systemic beta-blockers and could explain pre-existing ciliary beta-blockade and beta-adrenegic receptor desensitization due to chronic beta-blockade, whereas in the present study fresh diagnosed patients were evaluated who had not received any previous medication . Latanoprost has been shown to be more effective than Brimonidine and Timolol but authors included different types of glaucomas in their inclusion criteria where as only primary open angle glaucoma patients were assessed in our study (21).

Topically administered drugs have potential to produce systemic side effects because of their absorption through nasolacrimal duct. Since conjuctival sac has capacity of 10µl and each eye drop is 2.5 to 5 mls, so 60 to 80 percent eye drops over flows and reaches systemic circulation (22).Timolol produced significant reduction in Pulse Rate at all time intervals (2, 6,12 weeks) . Bradycardia because of beta-blockers is known response due to beta 1-blockade in the heart, such a blockade can cause life threatening bradyarrythmias in patients with partial or complete AV block (23). Brimonidine and Latanoprost had no effect on Pulse Rate and various authors also have documented no alteration in Pulse Rate (15, 24, 25). There was no statistically significant reduction in Blood Pressure in all the three groups except with Brimonidine where significant reduction in mean systolic Blood Pressure was observed at 12 weeks. Similarly earlier studies reported no significant effect of Timolol, Brimonidine and Latanoprost on Blood Pressure (8, 15, 24). However, reduction in systolic Blood Pressure with

Brimonidine is in accordance with previous published reports (15, 24-26). beta-blockers are known to produce reduction in BP in hypertensive patients due to inhibition of rennin secretion, inhibition of presynaptic beta-blockade, central beta-blockade and negative inotropic and chronotropic effects on heart (17). However, since hypertensive patients were excluded , no such effect was observed . No serious side effects were observed in any medication group except few transitory ones. These disappeared on their continuous use. None of the side effects were severe in nature and disappeared with continuous use of medication. Our study demonstrates superiority of Latanoprost over Timolol and Brimonidine as it lacked side effects on pulse rate, heart rate and blood pressure and should be preferred. Recent study has also shown that Latanoprost 0.005% is very effective and safe in primary open angle glaucoma patients (27). The study have some limitations also as the it has been done in open angle glaucoma patients without any chronic risk factors & is shorter in duration.

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