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Research Article

Efficacy and Safety of Brinzolamide 1% vs Timolol 0.5% as an Adjunctive Medication to Latanoprost 0.005% in Medically Uncontrolled Primary Open Angle Glaucoma

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Abstract

Aim: The aim of the study was to compare Intraocular pressure (IOP) lowering efficacy of Brinzolamide 1% versus Timolol 0.5% as an adjunctive medication to Latanoprost 0.005% in medically uncontrolled primary open angle glaucoma.

Materials and Methods: A prospective, open-label, comparative, transition trial was conducted on 30 patients of POAG attending the Outpatient Department of Ophthalmology, Government Medical College, Patiala. Patients fulfilling the inclusion criteria and having none of the exclusion criteria were enrolled in the study after obtaining written informed consent. Patients who were already on Latanoprost 0.005% monotherapy for more than 8 weeks were included in the study. IOP readings were recorded at the baseline before starting the study, at 8:00 am, 10:00 am and 4:00 pm. Timolol 0.5% twice daily was then added to Latanoprost 0.005% monotherapy for 8 weeks and IOP was recorded at 8:00 am, 10:00 am and 4:00 pm at 4 weeks and 8 weeks. Timolol 0.5% was then substituted with Brinzolamide 1% twice daily as an add on for another 8 weeks to Latanoprost 0.005%. IOP was again recorded at 8:00 am, 10:00 am and 4:00 pm at 12 weeks and 16 weeks of starting the study. Side effects were recorded at each follow up visit.

Results: The mean age of presentation was 64.60 years with 20 (66.67%) males and 10 (33.33%) females. Baseline mean IOP was 20.87 mmHg. Both Timolol 0.5% and Brinzolamide 1% showed comparable additional IOP reduction at both 8 and 16 weeks. The mean decrease in IOP with Timolol 0.5% and Brinzolamide 1% as an adjunct to Latanoprost 0.005% was 3.49 ± 0.97 mmHg (16.93%) and 3.46 ± 0.97 mmHg (16.77%) respectively. The difference in mean diurnal IOP reduction between the two groups at all follow up visits was statistically insignificant (p value = 0.946).

Conclusion: Both Brinzolamide 1% and Timolol 0.5% showed similar IOP lowering efficacy when used as an adjunct to Latanoprost 0.005% but Timolol being cheaper may be preferred as an adjunctive of first choice.

Keywords: Primary Open Angle Glaucoma; Timolol; Latanoprost; Brinzolamide

Introduction

Glaucoma describes a heterogeneous group of progressive optic neuropathies causing a slow progressive degeneration of retinal ganglion cells and their axons, resulting in a characteristic structural damage to the optic disc and a concomitant pattern of visual field loss if untreated [1]. It is one of the potentially blinding and debilitating disease requiring lifelong treatment and constitutes amongst the greatest problems in ophthalmologic care worldwide [2]. Glaucoma is the second most common cause of blindness worldwide after cataract [3]. According to W.H.O. statistics published in 1995, glaucoma accounts for 5.1 million persons or 13.5% of global blindness [4].

The main aetiology of primary open angle glaucoma (POAG) is obstruction to aqueous outflow and increase in IOP that ultimately leads to vascular sclerosis and optic nerve ischemia [5]. Primary open angle glaucoma is defined by 3 criteria which are an IOP consistently above 21 mmHg in at least on eye, an open, normal appearing anterior chamber angle with no apparent ocular or systemic abnormality that might account for elevated IOP, and typical glaucomatous visual field and/or optic nerve head damage [6].

Raised IOP is currently the most important risk factor for the development of POAG. The mainstay of POAG treatment is lowering of intraocular pressure either by means of medication, laser or surgery. Despite advances in laser and surgical treatments, topical hypotensive drops remain the first line of therapy for glaucoma which, as a chronic disease, requires long-term treatment often with multiple ophthalmic medications [7]. Currently, there are five major classes of drugs used for the treatment of glaucoma which are cholinergic agonists, alpha adrenergic- receptor agonist, beta adrenergic- receptor antagonists, topical and systemic carbonic anhydrase inhibitors and hypotensive lipids i.e. prostaglandin analogues and prostamides [8]. Initiating glaucoma treatment usually begins with the use of a single topical drug to lower the IOP, most often a prostaglandin analogue. When a single topical drug fails to lower IOP, an additional topical drug is added as an adjunctive therapy. Brinzolamide1%, a CAI, and Timolol 0.5%, a beta blocker, are among the options used as an adjunctive therapy [9]. Timolol 0.5% is a non-selective β1 and β2 adrenergic antagonist, reduce IOP by decreasing aqueous humour formation without changing the outflow pathway. Timolol 0.5% may cause adverse reactions in the cardiovascular and respiratory systems [10]. Brinzolamide 1% is a more recently developed CAI. It is highly specific, non-competitive reversible inhibitor of carbonic anhydrase. Brinzolamide lowers IOP by suppressing production of aqueous humour [9].

Materials and Methods

In this prospective, open label, non-randomized, comparative single arm transition study, 30 patients of POAG attending the Outpatient Department of Ophthalmology, Government Medical College, Patiala were included. The patients fulfilling the inclusion criteria and having none of the exclusion criteria were enrolled in the study after obtaining written informed consent in accordance with declaration of Helsinki. All patients were given an option to opt out of the study without having to give any reason for the same at any time point. Patients who were already on Latanoprost 0.005% (Latina RT, Zydus Cadila, Ahmedabad, India) monotherapy for more than 8 weeks were included in the study. Baseline IOP readings on Latanoprost monotherapy were recorded and was considered as baseline. After additional topical Timolol (Glucomol, Allergan, Bengaluru, India) or Brinzolamide (Brinolar, Sun Pharma, Goregaon, Mumbai, India) therapy IOP recordings were done at 8:00 am, 10:00 am and 4:00 pm. Timolol 0.5% twice daily was then added to Latanoprost 0.005% monotherapy for 8 weeks. Timolol 0.5% was then substituted with Brinzolamide 1% twice daily as an add on for another 8 weeks to Latanoprost 0.005%. IOP was recorded at 8:00 am, 10:00 am and 4:00 pm at 4 weeks, 8 weeks, 12 weeks and at 16 weeks from initial commencement of the study. Effectiveness of the drugs was calculated in terms of mmHg fall in mean IOP. Side effect profile was monitored and cost analysis was additionally done. All the observations thus made were compiled on a excel sheet proforma and subjected to statistical analysis using paired t tests via SPSS software (version 22.0 Chicago, Illinois, USA).

Results

Population characteristics

The mean age of the patients included in the study was 64.60 +- 9.15yrs. Age of most patients ranged between 60 to 70 years (Table 1). Gender distribution showed that 20 (66.67%) were males and 10 (33.33%) were females (Table 2).

IOP lowering

Mean starting IOP on Latanoprost monotherapy was 20.62 ± 1.98 mm Hg (baseline, V1). Considering the disease status of patient this IOP was still deemed higher and additional medical

Age (Years)	Patients	Percentage
31 - 40	1	3.33%
41 - 50	2	6.67%
51 - 60	10	33.33%
61 - 70	12	40%
71 - 80	5	16.67%
Total	30	100%
Mean	64.60 years	
Range	39-79 years	

Table 1: Age wise distribution of cases.

Gender	Patients	Percentage
Female	10	33.33%
Male	20	66.67%
Total	30	100%

Table 2: Gender wise distribution of cases.

therapy with Timolol or Brinzolamide was initiated. On Timolol additional therapy, at week 4, the mean diurnal IOP was 17.38 ± 2.01 mmHg. At 8 weeks of Timolol therapy, mean diurnal IOP was 17.13 ± 2.00 mmHg. The mean reduction in diurnal IOP from baseline with addition of Timolol 0.5% to Latanoprost 0.005% was 3.25 ± 0.97 (15.74%) and 3.49 ± 0.97 (16.93%) mm Hg at 4 weeks and 8 weeks respectively which was statistically significant (Table 3). After 8 weeks patients were transitioned from Timolol to Brinzolamide and Latanoprost was continued. At week 12, on Brinzolamide add-on therapy, the mean diurnal IOP was 17.20 ± 1.92 mmHg. At week 16 mean diurnal IOP was 17.17 ± 1.85 mmHg. The mean reduction in diurnal IOP from baseline with addition of Brinzolamide 1% to Latanoprost 0.005% was 3.42 ± 1.11 (16.60%) mm and 3.46 ± 0.97 (16.77%) mm Hg at 12 weeks and 16 weeks respectively which was statistically significant (Table 4). There was no statistically significant difference between mean IOP on first two visits (with addition of Timolol, V2, V3) and next 2 visits (with transition to Brinzolamide, V4, V5) at all points of time (Table 5 and figure 1).

Time Interval	N	Mean + SD (mm Hg)	Reduction in IOP	%age Reduction	t-test	p value (vs baseline)
Baseline IOP (V1)	30	20.62 + 1.98	---	---	---	---
4 Weeks IOP (V2)	30	17.38 ± 2.00	3.25 ± 0.97	15.74	12.639	< 0.001
8 Weeks IOP (V3)	30	17.13 ± 2.00	3.49 ± 0.97	16.93	14.191	< 0.001

Table 3: Comparison of mean diurnal IOP on subsequent visits with addition of Timolol 0.5% to Latanoprost 0.005%.

Time Interval	N	Mean	Reduction in IOP	%age Reduction	t-test	p value (vs Baseline)
Baseline IOP (V1)	30	20.62 + 1.98	---	---	---	---
12 Weeks IOP (V4)	30	17.20 + 1.92	3.42 ± 1.11	16.60	12.139	< 0.001
16 Weeks IOP (V5)	30	17.17 + 1.85	3.46 ± 0.97	16.77	14.392	< 0.001

Table 4: Comparison of mean diurnal IOP on transition from Timolol to Brinzolamide 1% as add-on to Latanoprost 0.005%.

Side effect profile

When Timolol 0.5% was used as an adjunct with Latanoprost 0.005% for a period of 8 weeks, most common side effect observed in the patients was conjunctival hyperemia in 2 patients (6.67%) followed by foreign body sensation in 1 patient (3.33%) and stinging sensation in 1 patient (3.33%).

After 8 weeks of adjunctive therapy with Brinzolamide 1% and Latanoprost 0.005% the most common side effect was taste perversion seen in 2 patients (6.66%) followed by conjunctival hyperemia in 1 patient (3.33%), and blurred vision in 1 patient (3.33%). The adverse effects were mild in severity and did not lead to discontinuation of therapy in any of the study patients (Figure 2).

Time Interval	Groups	Mean	Reduction in IOP	%age Reduction	t-test	p value
8 AM	Latanoprost + Timolol	17.17 ± 2.10	0.03 ± 0.81	0.19	0.062	0.951
	Latanoprost + Brinzolamide	17.20 ± 2.04				
10 AM	Latanoprost + Timolol	17.13 ± 1.98	0.03 ± 0.93	0.19	0.068	0.946
	Latanoprost + Brinzolamide	17.17 ± 1.80				
4 PM	Latanoprost + Timolol	17.10 ± 2.01	0.03 ± 0.96	0.19	0.068	0.946
	Latanoprost + Brinzolamide	17.13 ± 1.78				
AVG	Latanoprost + Timolol	17.13 ± 2.00	0.03 ± 0.79	0.20	0.067	0.946
	Latanoprost + Brinzolamide	17.17 ± 1.85				

Table 5: Comparison of mean diurnal IOP at 8 am, 10 am, 4 pm and avg on visits 3 and 5 i.e. weeks 8 and 16 (comparison of add-on Timolol vs add-on Brinzolamide to Latanoprost).

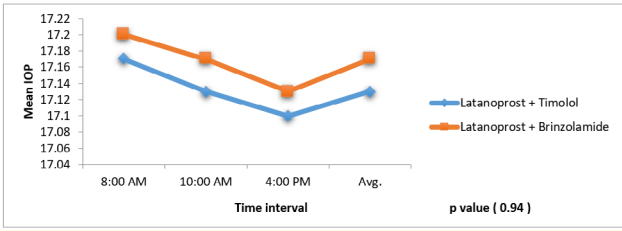

Figure 1: Comparison of mean diurnal IOP at 8 am, 10 am, 4 pm & avg on visits 3 (Timolol as add on) & 5 (Brinzolamide as add on) i.e. weeks 8 and 16.

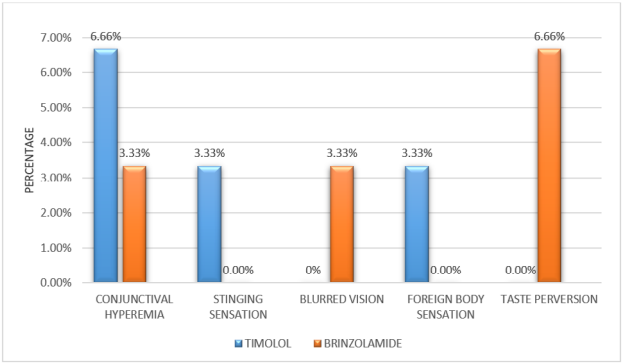

Figure 2: Side effect profile after 8 and 16 weeks.

Cost analysis

The volume of Timolol 0.5% and Brinzolamide 1% per bottle was 5.08 ± 0.08 and 5.06 ± 0.05 ml respectively. It was found that Timolol 0.5% had 90.4 ± 1.14 drops/bottle and Brinzolamide 1% had 94.6 ± 1.52 drops/bottle. Number of drops per ml was 20.36 ± 0.39 and 22.26 ± 0.41 for Timolol 0.5% and Brinzolamide 1% respectively. The drop size in ml of Timolol 0.5% and Brinzolamide 1% was 0.042 ± 0.0004 and 0.035 ± 0.0004 ml respectively (Table 6). The INR exchange rate for US Dollar was Rs 72.72 therefore, the 8-weekly cost for Brinzolamide 1% was found to be Rs. 515.88 ± 2.73 ($ 7.09) while for Timolol 0.5% was Rs. 95.33 ± 0.93 ($ 1.31) (Table 7). As percentage reduction of IOP from the baseline was equivalent in both the groups ($p > 0.05$), applying the cost minimisation analysis by directly comparing the cost incurred with both the drugs for a period of 8 weeks, we observed that the Brinzolamide 1% as an adjunctive to Latanoprost 0.005% costs Rs.420.50 ± 2.75 ($ 5.78) more than Timolol 0.5% to attain similar IOP lowering (Table 8).

Discussion

IOP-lowering has been proven to reduce the risk of glaucomatous progression in patients with glaucoma. In cases of advanced glaucoma large IOP reduction is required and low target IOP should be maintained [11].

When a single topical drug becomes ineffective in lowering the IOP, an additional topical drug may be added as an adjunctive

Drug	Volume (ml)	Drops/ bottle	Drops/ ml	Drop size (ml)
Timolol 0.5%	5.08 ± 0.08	90.4 ± 1.14	20.36 ± 0.39	0.042 ± 0.0004
Brinzolamide 1%	5.06 ± 0.05	94.6 ± 1.52	22.26 ± 0.41	0.035 ± 0.0004

Table 6: Volumetric analysis.

Drug	MRP (Rs)	Cost per day per eye (Rs)	Cost per 8 weeks per eye (Rs)
Timolol	65.31	1.85 ± 0.016	95.33 ± 0.93
Brinzolamide	430.50	8.03 ± 0.048	515.88 ± 2.73

Table 7: Daily and 8-weekly costs of therapy per eye.

Drugs	Additional IOP Lowering	8 weeks cost	Cost Minimisation Analysis
Latanoprost + Timolol	16.93%	95.33 ± 0.93	420.50 ± 2.75
Latanoprost + Brinzolamide	16.77%	515.88 ± 2.73	

Table 8: Cost minimization analysis.

therapy. More than 50% of glaucoma patients need more than one drug to reach their target IOP. Brinzolamide 1%, a CAI and Timolol 0.5%, a beta blocker are among various options used as adjunctive therapy [12].

In the present study diurnal mean IOP lowering from the baseline with Timolol 0.5% as an add on to Latanoprost 0.005% at the end of 8 weeks was 3.49 ± 0.97 mmHg (16.93%). The percentage reduction of this study is almost similar to values found in a study by Alexender H Rulo., *et al*. (1994) and Cengaver Tamer and Huseyin Oksuz where IOP reduction with Timolol 0.5% was found to be 13% and 10.3% respectively [12,13].

In our study, IOP lowering from the baseline with Brinzolamide 1% as an add on to Latanoprost 0.005% at the end of 16 weeks was 3.46 ± 0.97 mmHg (16.77%). Similarly, Thomas E Bournias., *et al*. (2009) in their study found that the mean IOP reduction from baseline was 3.4 mmHg (16%) [14]. Yoshimi Nakamura., *et al*. (2009) in their study concluded that percent reduction of IOP from baseline with Brinzolamide 1% was 17.8 ± 8.8%, which corresponds to 3.6 mm Hg fall in IOP [15].

In present study, it was found that Timolol 0.5% and Brinzolamide 1% as an adjunct to Latanoprost 0.005% monotherapy significantly reduced the IOP at all study time points. The diurnal mean IOP lowering with Timolol 0.5% was 3.49 ± 0.97 mmHg (16.93%) in comparison to 3.46 ± 0.97 mmHg (16.77%) reduction with Brinzolamide 1%. Difference in mean additional IOP reduction between the two drugs was statistically insignificant. Similarly Katsuya Miura., *et al*. (2008), found that Brinzolamide 1% and Timolol 0.5% significantly decreased IOP, by a mean of 2.1 mm Hg and 2.7 mm Hg, respectively [16]. The difference was statistical insignificant and both the drugs were equally effective. Similarly, a study by John HK Liu., *et al*. (2009) found that the mean IOP with Brinzolamide 1% or Timolol 0.5% as an add-on treatment to Latanoprost 0.005% was reduced by 1.9 mmHg and 1.5 mmHg respectively. There was no statistical difference between the 2 add-on treatments [17]. Thus, the results of our present study were in concordance with the previous reported studies.

In present study, the most common side effect associated with Timolol 0.5% and Brinzolamide 1% administration were conjunctival hyperaemia and taste perversion respectively. Both Timolol 0.5% and Brinzolamide 1% were well tolerated and safe and most of the adverse events were mild. None of the patients discontinued the treatment because of occurrence of adverse events.

In our study, we also did volumetric analysis of both the drugs and cost of both the drugs for 8 weeks was calculated. Cost of Timolol 0.5% for 8 weeks was Rs. 95.33 ± 0.93 (USD 1.31) and for Brinzolamide 1% was Rs. 515.88 ± 2.73 (USD 7.09). As both the drugs were found to be similar in efficacy ($p > 0.05$), applying cost minimization analysis by comparing the cost of both the treatments, we noted that Timolol 0.5% as an add on was Rs. 420.50 + 2.75 (USD 5.78) cheaper than Brinzolamide 1%.

The limitation of this study was that it was a single arm, open-labelled non randomised study with limited number of patients. The duration of the study was short (16 weeks), so data about long term efficacy of the drugs could not be evaluated. Also, considering the small number of patients enrolled, the study was not adequately powered to statistically analyse the occurrence of side

effects. Our study, however, did have an advantage that the patients enrolled were same whether for add on Timolol or add on Brinzolamide which reduces the chance of bias in IOP measurements.

Future studies should continue to enrol more patients in multi centric trials to form further robust opinion on which category of drug should be employed as first choice add on therapy to Latanoprost monotherapy.

Conclusion

From our study it was concluded that in patients already receiving the Latanoprost 0.005% monotherapy, adding Timolol 0.5% or Brinzolamide 1% can further reduce the IOP significantly during the study period. Both Timolol 0.5% and Brinzolamide 1% showed similar IOP lowering efficacy when used as an adjunct to Latanoprost 0.005%. Additionally, Timolol 0.5% as an adjunctive to Latanoprost 0.005% is cheaper than adjunct Brinzolamide 1%, hence, considering the low socio-economic status of patients in country like India, Timolol 0.5% should be preferred as an adjunctive of first choice to Latanoprost 0.005% in medical management of moderate to advance POAG who do not achieve their target IOPs with Latanoprost monotherapy.

Conflicts of Interest

Nil declared.

Financial Disclosure

None of the authors have any financial interest in any of the products used during the study period.

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