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RESEARCH ARTICLE

TO COMARE THE EFFICACY OF DORZOLAMIDE 2% TIMOLOL 0.5%FIXED COMBINATION VERSUS BRINZOLAMIDE 1% BRIMONIDINE 0.2% FIXED COMBINATION THERAY IN PATIENTS OF PRIMARY OPEN ANGLE GLAUCOMA

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ABSTRACT

A study was done to compare the efficacy of dorzolamide 2% timolol 0.5%fixed combination versus brinzolamide 1% brimonidine 0.2% fixed combination therapy in patients of primary open angle glaucoma. A randomized, open label, comparative, parallel group study was conducted on 40 patients of POAG attending the Outpatient Department of Ophthalmology, Government Medical College, Patiala. Patients selected were then randomised into two groups of 20 each. Baseline IOP was recorded at 9 am and 11 am on day 0 of the study.Group A: Fixed drug combination of Dorzolamide2%/ Timolol 0.5% (DTFC) dosed twice daily at 9 am and 9 pm .This group instilled 1 drop of DTFC ophthalmic solution into study eye twice daily at 9.00 a.m. and 9.00 p.m. for 6 weeks. Group B: Fixed drug combination of Brinzolamide 1%/ Brimonidine 0.2% (BBFC) dosed twice daily at 9 am and 9 pm. This group instilled 1 drop of BBFC ophthalmic solution into study eye twice daily at 9.00 a.m. and 9.00 p.m. for 6 weeks. Patients were then called for follow up at 2nd week, 4th week and 6th week during the study period and IOP recorded at 9 am and 11 am in the OPD. In Group A (DTFC), mean IOP at visit 1 (baseline) at 9:00 AM was 27.00 ± 1.78 mm Hg, at 11:00 AM was 27.50 ± 1.91 mm Hg and mean IOP at all time points was 27.25 ± 1.81 mm Hg. There was no statistically significant variation in the mean IOP at any of the follow up visit in group A ($p > 0.05$). In Group B (BBFC), mean IOP at visit 1 (baseline) at 9:00 AM was 26.85 ± 1.98 mm Hg, at 11:00 AM was 27.10 ± 2.17 mm Hg and mean IOP at all time points was 26.98 ± 2.04 mm Hg.There was no statistically significant variation in the mean IOP at any of the follow up visit in group A ($p > 0.05$).The reduction in mean IOP at visit 6 weeks in group A (DTFC) was 10.32 mm Hg (37.87%) and in group B (BBFC) was 9.50 mm Hg (35.21%). The reduction in mean IOP was comparable between the two groups. The difference was statistically non significant ($p > 0.05$).

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INTRODUCTION

The glaucomas are a group of optic neuropathies characterized by progressive degeneration of retinal ganglion cells. Glaucoma affects more than 70 million people worldwide with approximately 10% being bilaterally blind, making it the leading cause of irreversible blindness in the world. Glaucom as can be classified into 2 broad categories: open-angle glaucoma and angle-closure glaucoma. In the United States, more than 80% of cases are open-angle glaucoma; however, angle-closure glaucoma is responsible for a disproportionate number of patients with severe vision loss (Weinreb, 2014). The normal value of IOP ranges from 10-21mmHg. In glaucoma, sustained increase in IOP may be due to an increase in the formation of the aqueous humour or difficulty in its outflow or raised pressure in the episcleral veins (Shields, 1998). Treatment that reduces intraocular pressure has been shown to improve outcomes in randomized clinical trialsandit is one of the most important modifiable parameter in the treatment of glaucoma. Topical β-blockers such as timolol have been widely used since 1970s and they

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reduce IOP by decreasing aqueous humor secretion. The precise mechanism of action is presumed to be mediated via blockade of the β2 adrenergic receptors found in the ciliary body. Since then, newer treatments have become available, including carbonic anhydrase inhibitors such as dorzolamide and brinzolamide (Lester, 2008), prostaglandins such as latanoprost and travoprost, and α2 adrenergic agonists such as brimonidine (Greenfield, 1997). As these drugs reduce IOP through different pathways, they are often given as combinations, for example, the combination of dorzolamide 2% and timolol 0.5%, which is available in a fixed single-dose preparation, which is more effective at reducing IOP than either of its components given alone (Jocson, 1971). Pharmacological therapy is the most common first-line approach for patients with glaucoma requiring intraocular pressure (IOP) reduction. More than one medication is necessary in many cases, with one study reporting that a 20% reduction in IOP to ≤24 mm Hg required two medications in 30% of patients and ≥3 medications in an additional 9%. Patients requiring two medications can either concomitantly administer two separate medications or use a single fixed-combination medication. Fixed-combination therapy may be preferred due to reduced exposure to ocular preservatives, avoidance of the potential for washout of the first medication by administration of the second, and increased patient convenience resulting from having only one bottle of medication, which could increase the likelihood of adherence to glaucoma therapy and potentially lower cost from fewer copays (Frampton, 2006). The purpose of this study was to compare the efficiency of the new brinzolamide/brimonidine fixed combination vs the dorzolamide/timolol fixed combination.

MATERIALS AND METHODS

This randomized, open label, comparative, parallel group study was conducted on 40 patients of POAG attending the Outpatient Department of Ophthalmology, Government Medical College, Patiala.

Inclusion Criteria: Patients having minimum age of 18 years with unilateral/bilateral primary open angle glaucoma, untreated IOP > 21 mm Hg and </= 30 mm Hg after washout period were included in the study. Cases of established POAG were enrolled for the study if the IOP was >21 mm Hg after discontinuation of all ocular hypotensive medication and after a wash out period. The wash out period was as followed
Cholinergics and carbonic anhydrase Inhibitors:1 week

Alpha and beta adrenergic agonists:2 weeks

Beta blockers, prostaglandin analogues and :4 weeks
combination drugs

Exclusion Criteria: Patients with any history of surgery within 6 months of the study, pregnancy,Cup-to-disc ratio >0.8 and severe central visual field loss were not included in the study. Patients with history of chronic, recurrent, or current severe inflammatory eye disease, ocular infections were also excluded from study. Any known sensitivity or contraindication to study drugs or Chronic use of ocular medication other than the glaucoma medications. Patients having any contraindication to the use of beta blockers and carbonic anhydrase inhibitors.

Study Sequence

A written informed consent was obtained**.** Patients selected were then randomised into two groups of 20 each. Baseline IOP was recorded at 9 am and 11 am on day 0 of the study.

Study Drugs

- Fixed drug combination of Dorzolamide2%/ Timolol 0.5% (DTFC) dosed twice daily at 9 am and 9 pm.
- Fixed drug combination of Brinzolamide 1%/ Brimonidine 0.2% (BBFC) dosed twice daily at 9 am and 9 pm.

Group A: This group instilled 1 drop of DTFC ophthalmic solution into study eye twice daily at 9.00 a.m. and 9.00 p.m. for 6 weeks.

Group B: This group instilled 1 drop of BBFC ophthalmic solution into study eye twice daily at 9.00 a.m. and 9.00 p.m. for 6 weeks.

Patients were then called for follow up at 2nd week, 4th week and 6th week during the study period and IOP recorded at 9 am and 11 am in the OPD. Patients having bilateral POAG were treated for both eyes, but only the one eye fulfilling the inclusion criteria was taken as the study eye.

IOP Measurement

IOP readings were taken from the study eye with the Goldmannapplanation tonometer (GAT) at each visit.

1.IOP was measured on day 0 at 9.00 a.m. and 11.00 a.m before administration of the study drugs to get the baseline IOP.
2.Patients were asked to self-administer the study drug twice daily (at 9 am and 9 pm) for 6 week.
3.Patients followed up at 2nd week, 4th week and 6th week during the study period and IOP was recorded at 9 am and 11 am in OPD.

RESULTS

The mean IOP between the two groups at baseline at 9:00 AM and 11:00 AM was comparable with the difference being statistically insignificant (p>0.05). In Group A (DTFC), mean IOP at visit 1 (baseline) at 9:00 AM was 27.00 ± 1.78 mm Hg, at 11:00 AM was 27.50 ± 1.91 mm Hg and mean IOP at all time points was 27.25 ± 1.81 mm Hg. There was no statistically significant variation in the mean IOP at any of the follow up visit in group A (p > 0.05).

In Group B (BBFC), mean IOP at visit 1 (baseline) at 9:00 AM was 26.85 ± 1.98 mm Hg, at 11:00 AM was 27.10 ± 2.17 mm Hg and mean IOP at all time points was 26.98 ± 2.04 mm Hg. There was no statistically significant variation in the mean IOP at any of the follow up visit in group A (p > 0.05). The reduction in mean IOP at visit 6 weeks in group A (DTFC) was 10.32 mm Hg (37.87%) and in group B (BBFC) was 9.50 mm Hg (35.21%). The reduction in mean IOP was comparable between the two groups. The difference was statistically non significant (p > 0.05).

Table 1. age distribution in both groups

Age (Years)	Group A (DTFC)		Group B (BBFC)	
	No. of Patients	Percentage	No. of Patients	Percentage
56-60	5	25%	3	15%
61-65	1	5%	5	25%
66-70	8	40%	6	30%
71-75	6	30%	6	30%
Total	20	100%	20	100%
Mean Age	67.15±5.55		67.00±5.35	
Median	67.00		70.00	
Range	58-75		58-76	

Table 2. Comparison of mean iop of both groups at baseline at various time points

(Baseline IOP)	Group	Mean ± SD	Std. Error Mean	t-test	Sign.
9:00 AM	Group A	27.00 ± 1.78	0.40	0.252	NS
	Group B	26.85 ± 1.98	0.44		
11:00 AM	Group A	27.50± 1.91	0.43	0.619	NS
	Group B	27.10 ± 2.17	0.49		

Table 3. Mean of IOP at Both Visits in Group A

Visits	Mean IOP 9:00 AM	Mean IOP 11:00 AM	Mean IOP	t-test	p value	Sign
Baseline	27.00±1.78	27.50±1.91	27.25±1.81	0.858	0.396	NS
2 Weeks	18.15±1.14	18.45±1.19	18.30±1.13	0.815	0.420	NS
4 Weeks	17.50±1.24	17.70±1.13	17.60±1.14	0.535	0.596	NS
6 Weeks	16.85±0.93	17.00±0.97	16.92±0.92	0.497	0.622	NS

Table 4. Mean iop at various visits in group b

Visits	Mean IOP 9:00 AM	Mean IOP 11:00 AM	Mean IOP	t-test	p value	Sign
Baseline	26.85±1.98	27.10±2.17	26.98±2.04	0.380	0.706	NS
2 Weeks	17.90±1.25	18.10±1.45	18.00±1.30	0.467	0.643	NS
4 Weeks	17.75±1.12	17.75±1.29	17.75±1.14	0.000	1.000	NS
6 Weeks	17.55±1.23	17.40±1.23	17.47±1.21	0.385	0.703	NS

Table 5. Reduction of mean iop at various visit in the two groups

Visits	Group A (DTFC)			Group B (BBFC)			t-test	p value	Sign.
	Mean IOP	Reduction of Mean IOP From Baseline		Mean IOP	Reduction of Mean IOP From Baseline				
		Difference	%age		Difference	%age			
Baseline 1	27.25±1.81	---	---	26.98±2.04	---	---	0.451	0.654	NS
2 Weeks	18.30±1.13	-8.95	32.84%	18.00±1.30	-8.98	33.28%	0.780	0.440	NS
4 Weeks	17.60±1.14	-9.65	35.41%	17.75±1.14	-9.23	34.21%	0.415	0.680	NS
6 Weeks	16.93±0.92	-10.32	37.87%	17.48±1.21	-9.50	35.21%	1.619	0.114	NS

DISCUSSION

In present study, the mean IOP reduction at the end of 6 weeks was similar between DTFC and BBFC. Mean IOP reduction with DTFC and BBFC after 6 weeks was 10.32 mmHg (37.87 %) and 9.50 mmHg (35.21 %) respectively. Comparison between the two groups showed that across all time points and visits during the 6 week treatment period IOP reduction produced with DTFC was comparable with BBFC. The difference in IOP lowering in the two groups was statistically non significant. In the present study, most common side effect with DTFC was taste perversion seen in 20% of patients that is 4 patients at the end of 6 weeks. Most common side effect with BBFC was conjunctival hyperemia seen in 8(40%) patients, followed by eye irritation seen in 4(20%) patients at the end of 6 weeks. In our study, we compared 2 fixed combinations of carbonic anhydrase inhibitor (CAI) with a β-blocker and an α adrenergic agonist. Both of these drugs have the same hypotensive effect.

The presence of brimonidine instead of timolol[7] in the fixed combination does not affect its efficacy. This can be explained by the dual mode of action of brimonidine, which acts on both aqueous production and the facilitation of uveoscleral out flow. BBFC has a low concentration of benzalkonium chloride so it has fewer ocular side effects without affecting the efficacy of the drug. Advantage of BBFC is the absence of side effects that can be caused by β-blocker and it is the only fixed combination which does not contain a β-blocker. β-blocker can exacerbate previous pulmonary and heart disorders. Moreover benefits of combinations include reduced exposure to preservatives, reduced frequency of ocular surface symptom and fewer drop instillations. There is no wash out effect as seen in two medications administered separately. The limitations of study was that this was a single centre study with limited number of patients. The study was limited by its short time frame and fact that IOP was measured at 2 specific time points and we did not perform a 24 hours phasing. However, the preliminary results of our study shows that BBFC seems to

be an effective and safe alternative β-blocker free fixed combination.

Summary and Conclusion

The management of glaucoma is first and foremost through medical means before resorting to surgical options. With the introduction of innovative and newer medications, treatment of glaucoma has become more complex. The newer glaucoma medications in combination have advantages like increased efficacy, reduced dosing frequency, and improved side effect profile.

From the results of the present study, following conclusions were drawn:

- The IOP reductions of both DTFC and BBFC were clinically significant at 6 weeks at all time points.
- The mean decrease in IOP at 6 weeks by fixed combination of DTFC and fixed combination of BBFC in our study was 10.32 mmHg (37.87%) and 9.50 mmHg (35.21%) respectively.
- The most frequently reported side effect was taste perversion with DTFC seen in 4(20%) patients and conjunctival hyperemia with BBFC seen in 8(40%) patients.

Henceforth from the study we concluded that IOP lowering efficacy of DTFC and BBFC was similar in 6 week follow up period. Both DTFC and BBFC were well tolerated.

Though both drugs have equal efficacy as far as IOP lowering is concerned, BBFC has advantage of beta blocker free fixed drug combination.

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