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To Compare the IOP lowering efficacy and side effect profile of fixed combination Brinzolamide 1% / timolol 0.5% and fixed combination Dorzolamide 2% / timolol 0.5% in patients with Primary Open Angle Glaucoma

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Abstract
Aim*: To compare the IOP lowering efficacy and side effect profile of Brinzolamide 1% / Timolol 0.5% Fixed combination (BTFC) versus Dorzolamide 2% / Timolol 0.5% Fixed combination (DTFC) in patients with POAG.*
Methods: *A prospective, randomized, comparative, open labeled, cross over study was conducted in patients coming to the Department of Ophthalmology, Rajindra Hospital attached to Government Medical College, Patiala. In this study, 40 patients of POAG were selected fulfilling the inclusion criteria. Patients were then randomized into 2 groups (group 1 and 2) with 20 patients in each group. On day 0, baseline IOP was recorded before starting the treatment. Group 1 patients were given fixed drug combination of Brinzolamide 1% / Timolol 0.5% (BTFC) twice daily and group 2 patients were given a fixed drug combination of Dorzolamide 2% / Timolol 0.5% (DTFC) twice daily for 14 days and IOP was recorded in OPD on 15th day of the study at 9am, 11am and 4pm after instillation of the study drug. From 17th – 30th day of the study, Group 1 received DTFC and Group 2 received BTFC. IOP was again recorded in OPD on 31st day of the study at 9am, 11am and 4pm after instillation of the study drug. Effectiveness of the drugs was calculated in terms of mm Hg fall in mean intraocular pressure and side effect profile was monitored. All the observations thus made were compiled on a proforma and subjected to statistical analysis using appropriate tests.*
Results: *BTFC produced mean IOP reductions ranging from 8.27 to 10.01 mmHg (30.32-35.55%) whereas DTFC produced mean IOP reductions ranging from 9.01 to 10.60 mmHg (32.76-37.68%) (p<0.001).The difference in the IOP reduction of BTFC and DTFC was similar in both the groups and statistically non significant (p>0.05). BTFC being a suspension was associated with blurring of vision whereas DTFC being prepared in acidic pH was associated with stinging and abnormal taste sensation.*
Conclusion: *BTFC provided similar reduction in IOP as DTFC in patients of POAG.*
Keywords: *Brinzolamide 1% / Timolol 0.5% Fixed combination, Dorzolamide 2% / Timolol 0.5% Fixed combination, POAG*

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I. Introduction

Glaucoma is a chronic, progressive optic neuropathy caused by a group of ocular disorders that lead to damage of the optic nerve with loss of function.[1] It is a neurodegenerative disease involving the loss of Retinal Ganglion Cells (RGC) and raised Intraocular Pressure (IOP) is the leading and only mutable risk factor for glaucoma.[2] The vast majority of glaucomatous patients are older than 60 years and due to longer life expectancy, the prevalence of glaucoma is increasing worldwide.[3]In 2013, the number of people with glaucoma worldwide was estimated to be 64.3 million and is projected to increase to 76.0 million by 2020 and 111.8 million by 2040.[4]

POAG is the most common type of glaucoma constituting about two-third of the cases. The main aetiology of POAG is obstruction to aqueous outflow leading to increased intra ocular pressure (IOP) which ultimately lead to optic nerve ischaemia.[5,6] . After loss of more than 40 percent of the nerve fibers, patients may

notice a gradual loss of peripheral vision, or "tunnel vision".[7] Open-angle glaucoma usually is an incidental finding during an adult eye evaluation performed for other indications.[8]

At present, the only effective treatment for glaucoma is to lower the IOP and topical hypotensive drops remain the standard form of therapy for glaucoma. Some of the fixed combinations that are currently available for lowering the IOP contain timolol and either CAI dorzolamide or alpha agonist brimonidine or prostaglandin analog.[9] Combining two medications reduce the time required to administer drops, the frequency of use, and the total number of bottles hence improving the compliance.[10,11] They also offer a reduced time for drop instillation and potentially a greater efficacy by eliminating the washout effect. Instilling two medications in a single drop reduces the amount of preservatives, which may improve the tolerability and eventual surgical outcomes in patients who require filtering procedures.[10] Also, the complementary mechanisms of action of a prostaglandin analogue and a β-blocker are likely to show additive IOP-lowering effect in combination when compared with effects of either single agent.[12] The major limitation of a fixed combination therapy is that dosing of the concomitant medication cannot be alerted within the concomitant product. Fixed combination medications may cause problems if a patient is allergic to any constituent of the fixed combination and make difficulties in finding which constituent causes allergy.[13,14]

The brinzolamide/timolol fixed combination is comprised of the CAI brinzolamide and the beta-blocker timolol and is recommended to be dosed twice daily (bid). It is delivered as a suspension with a pH of 7.2 and is preserved with benzalkonium chloride 0.01%.[15] The concentration of brinzolamide is 1% (10 mg/mL), equal to that of brinzolamide ophthalmic suspension [16] and the timolol concentration is 0.5% (5 mg/mL), equal to that of single-agent timolol.[17-19]Contraindications of topical carbonic anhydrase inhibitors are renal failure and sulfonamide allergy. Caution should be taken in patients with a compromised corneal endothelium.[20] The activity of timolol is subject to circadian changes, showing less efficacy at night. Contraindications for the use of timolol are asthma, obstructive pulmonary disease, sinus bradycardia and heart block.[21]

II. Material and Methods:

This was a prospective, randomized, open labeled cross over study to be conducted on 40 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.

Study sequence: In this study, 40 patients diagnosed with POAG were selected fulfilling the inclusion criteria. Patients already on antiglaucoma therapy had completed a wash out period of 6 weeks for prostaglandins analogues, 4 weeks for topical beta blockers and 2 weeks for adrenergic agents or carbonic anhydrase inhibitors before entering into study. A written informed consent was obtained. Patients were then randomised into 2 groups (group 1 and 2) with 20 patients in each group. On day 0, baseline IOP was recorded in OPD before starting the treatment. Group 1 patients were then given fixed drug combination of Brinzolamide 1% / Timolol 0.5% twice daily and group 2 patients were given a fixed drug combination of Dorzolamide 2% / Timolol 0.5% to be administered twice daily for 14 days and IOP was recorded in OPD on 15th day of the study at 9am, 11am and 4pm after instillation of the study drug. From 17th- 30th day of the study, Group 1 received DTFC and Group 2 received BTFC twice daily. IOP was again recorded in OPD on 31st day of the study at 9am, 11am and 4pm after instillation of the study drug. Effectiveness of the drugs was calculated in terms of mm Hg fall in mean intraocular pressure and side effect profile was monitored. All the observations thus made were compiled on a proforma and subjected to statistical analysis using appropriate tests.

Inclusion criteria:

1. Age of >18 yrs
2. Diagnosed cases of unilateral/bilateral primary open angle glaucoma.
3. IOP < 32 mmHg in one or both eye without treatment or after wash out period.
4. Patient who were willing to discontinue use of all other ocular hypotensive agents at screening and throughout the study.
5. Patients who were willing to get enrolled in study.

Exclusion criteria:

1. Hypersensitivity or contraindication to the study medication.
2. Any abnormality preventing reliable applanation tonometry or examination of the ocular fundus or anterior chamber.
3. Corneal dystrophy or degeneration
4. Any intraocular inflammation like Conjunctivitis, Keratitis or uveitis .
5. Intraocular surgery < 6 months before screening.

6. Cardiopulmonary conditions like asthma, heart block that preclude safe administration of a topical beta blocker.
7. Use of corticosteroids < 30 days before screening.
8. Risk of visual field or visual acuity worsening as a consequence of participation in the study.
9. Pregnant and breast feeding females.
10. Progressive retinal/optic nerve damage other than glaucoma.

Study eye: In both the groups, one eye (the affected eye) fulfilling the inclusion criteria was considered as the study eye. If both eyes were having glaucoma then both eyes were treated but only one eye fulfilling the inclusion criteria and excluding the exclusion criteria was the study eye.

III. Results

Table1: Comparison of age of Group 1 and Group 2

Age (in yrs)	Group 1	Group 2
	No.(%age)	No. (%age)
41-50	4 (20%)	4 (20%)
51-60	7 (35%)	5 (25%)
61-70	7 (35%)	8 (40%)
71-80	2 (10%)	3 (15%)
Total	20 (100%)	20 (100%)
Range(yrs)	46-73	48-72
Mean + SD(yrs)	63.25+7.51	59.70+7.96
t value	1.449	
p value	0.155	
Significant	NS	

Mean age of Group 1 was 63.25 (+7.51) years and Group 2 was 59.70(+7.96) years. Age of most of the patients was in the range of 50-70 years.

Table 2: Comparison of mean IOP at different visits in Group 1 at 9am , 11am and 4pm on 15th day

		Range	Mean+SD(mmHg)	Reduction		Statistics	
				mm Hg	%age	t value	p value
Baseline		25-32	28.13±2.17				
Day15	9am	16-23	19.60±2.29	8.53±1.12	30.32%	29.635	<0.001**
	11am	15-22	18.67±2.16	9.47±1.13	33.67%	32.577	<0.001**
	4pm	15-22	18.31±2.26	10.00±1.31	35.55%	29.580	<0.001**

p<0.001; Highly Significant

Table 3: Comparison of mean IOP at different visits in Group 1 at 9am , 11am and 4pm on 31st day

		Range	Mean+SD(mmHg)	Reduction		Statistics	
				mm Hg	%age	t value	p value
Baseline		25-32	28.13±2.17				
Day 31	9am	15-22	18.80±2.11	9.33±1.17	33.17%	30.760	<0.001**
	11am	13-20	18.07±1.91	10.07±1.22	35.80%	31.884	<0.001**
	4pm	14-20	17.53±2.13	10.60±1.06	37.68%	38.891	<0.001**

p<0.001; Highly Significant

Table 4: Comparison of mean IOP at different visits in Group 2 at 9am , 11am and 4pm on 15th day

		Range	Mean+SD(mmHg)	Reduction		Statistics	
				mm Hg	%age	t value	p value
Baseline		23-31	27.47±2.50				
Day 15	9am	15-22	18.47±2.36	9.00±1.13	32.76%	30.741	<0.001**
	11am	15-22	17.00±2.20	10.47±1.19	38.11%	34.144	<0.001**
	4pm	15-22	17.13±2.17	10.33±1.50	37.60%	26.751	<0.001**

p<0.001; Highly Significant

Table 5: Comparison of mean IOP at different visits in Group 2 at 9am , 11am and 4pm on 31st day

		Range	Mean+SD(mmHg)	Reduction		Statistics	
				mm Hg	%age	t value	p value
Baseline		23-31	27.47±2.50				
Day 31	9am	15-23	19.20±2.31	8.27±1.10	30.11%	29.112	<0.001**
	11am	15-22	17.73±2.43	9.73±1.58	35.42%	23.864	<0.001**

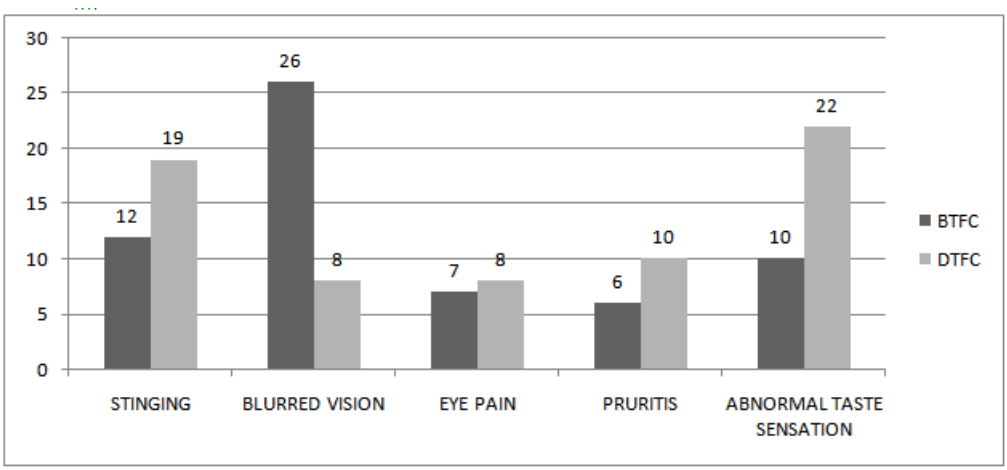
	4pm	15-23	18.07±2.02	9.40±1.35	34.22%	26.923	<0.001**

p<0.001; Highly Significant

Table 6: Comparison of mean IOP at different visits of Group 1 and Group 2

Table 7: Treatment related adverse events

		Group 1	Group 2	Difference	p value
		Mean+SD (mmHg)	Mean+SD (mmHg)		
Baseline		28.13±2.17	27.47±2.50	0.667	0.442
Day 15	9am	19.60±2.29	18.47±2.36	1.133	0.193
	11am	18.67±2.16	17.00±2.20	1.667	0.056
	4pm	18.31±2.26	17.13±2.17	1.000	0.227
Day 31	9am	18.80±2.11	19.20±2.31	0.400	0.624
	11am	18.07±1.91	17.73±2.43	0.333	0.680
	4pm	17.53±2.13	18.07±2.02	0.533	0.488



IV. Discussion

The crossover design used in this study allowed us for within-patient comparisons rather than between-patient comparisons.Both Brinzolamide and Dorzolamide are highly specific, reversible inhibitor of carbonic anhydrase present in the lens, cornea, ciliary body and retina. C/I in renal failure and sulfonamide allergy.Timolol ,being a beta blocker ,is subjected to circadian rhythm and less effective at night. C/I in asthma and heart block. Because the BTFC is formulated as a suspension, this is the likely reason for it to cause transient blurring of vision than DTFC which is formulated as a solution. Dorzolamide require an acidic pH (around 5.6) to optimize solubility whereas Brinzolamide is adequately soluble at pH 7.2. The difference in pH of the two fixed combinations explain the difference in comfort reported by the patients .In our study, in Group 1 on 15th day and in Group 2 on 31st day of the study (BTFC), significant IOP reduction was seen i.e 8.53-10.00 mmHg and 8.27-9.73 mmHg from the baseline IOP, respectively. In Group 2 on 15th day and in Group 1 on 31st day of the study (DTFC),significant IOP reduction was seen i.e 9.3-10.60 mmHg and 9.00-10.47 mmHg from the baseline IOP, respectively. Hence BTFC produced mean IOP reductions ranging from 8.27 to 10.00 mmHg (30.32-35.55%) whereas DTFC produced mean IOP reductions ranging from 9.00 to 10.60 mmHg (32.76-37.68%) (p<0.001). Difference in mean IOP reduction of the two groups recorded on different times was statistically insignificant (p>0.05). Manni G et al conducted a study in 2009 on 437 patients of POAG and found that BTFC produced mean IOP reductions ranging from 7.2 to 9.2 mmHg whereas DTFC produced mean IOP reductions ranging from 7.4 to 8.9 mmHg .Sezgin Akcay BI et al conducted a study in 2013 on 114 patients of POAG and found that BTFC produced mean IOP reductions ranging from 6.42 to 9.74 mmHg whereas DTFC produced mean IOP reductions ranging from 8.16 to 12.41 mmHg

V. Conclusion

1. The mean age of presentation was 63.25+7.51 years in Group 1 and 59.70+7.96 years in Group 2.

2. Age of most of the patients was in the range of 61-70 years.

3. BTFC produced mean IOP reductions ranging from 8.27 to 10.01 mmHg (30.32-35.55%) whereas DTFC produced mean IOP reductions ranging from 9.01 to 10.60 mmHg (32.76-37.68%) (p<0.001)

4. The difference in the IOP reduction of BTFC and DTFC was similar in both the groups and statistically non significant (p>0.05)

5. BTFC being a suspension was associated with blurring of vision whereas DTFC being prepared in acidic pH was associated with stinging and abnormal taste sensation.

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