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Clinical effectiveness and safety of brimonidine (0.2%) versus Dorzolamide (2.0%) in primary open angle

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ABSTRACT

A Comparison of efficacy & tolerability of brimonidine (0.2%) versus dorzolamide (2.0%) in primary open angle glaucoma or ocular hypertension. In this open, randomized, cross over comparative study, 30 subjects of primary open angle glaucoma with IOP > 22 mmHg were taken. The patients fulfilling the inclusion criteria and after verifying the exclusion criteria were included in the study after a written informed consent. These subjects were randomized to receive brimonidine (0.2%) TDS or dorzolamide (2.0%) TDS for 4 weeks. After a wash out period of 4 weeks the subjects were crossed over to other therapy. The IOP was measured at 8.00 am before dosing and at 10.00 am i.e. 2 hours after dosing at each baseline and at the end of each treatment period. Monotherapy with brimonidine (0.2%) TDS and dorzolamide (2.0%) TDS given for 4 weeks had caused overall reduction in IOP of 5.833+2.102mmHg (23.48%) and 5.433+ 2.582mmHg (22.42%) respectively at peak levels. The difference is statistically insignificant ($p>0.05$). Overall monotherapy with brimonidine and dorzolamide appear to produce equivalent IOP lowering efficacy and have well tolerated adverse effect profile, although a trend was observed at 10.00 a.m. of greater brimonidine efficacy compared with dorzolamide.

Keywords: Glaucoma, brimonidine, dorzolamide, clinical trial, POAG.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness throughout the world. New statistics gathered by WHO show that glaucoma is now the second leading cause of blindness globally after cataract (Kingman, 2004). Primary open angle glaucoma is defined by 3 criteria's which are firstly, an IOP consistently above 21 mmHg in at least one eye. Secondly, an open, normal appearing anterior chamber angle with no apparent ocular or systemic abnormality that might account for elevated IOP. Thirdly, typical glaucomatous visual field and/ or optic nerve head damage (Shields, 2005). Being asymptomatic, chronic and incurable diseases, the glaucomas by their very nature encourage non-compliance. The pathophysiology of open angle glaucoma includes a progressive decrease in the number of retinal ganglion cells when nerve fibers at the point where optic nerve exits, eye become pinched and die.

This condition leads to thinning and progressive enlargement of optic nerve cup. The loss of nerve fibers causes a permanently decreased visual field. (Grierson, 2000). IOP is the only treatable risk factor for open angle glaucoma (American Academy of Ophthalmology, 2000). In most patients with glaucoma, beta blockers are the treatment of initial choice. However, in almost 50% of the patients may not respond adequately therapy with beta-blockers does not reduce the intraocular pressure adequately. Therefore, there is a need for new class of topical IOP lowering agents that can be used alone or with beta blockers (Diestelhorst, 1996).

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The therapeutic arsenal against glaucoma has recently been extended with addition of newer drugs which have increased duration of action and decreased side effects leading to better compliance. (Hoyng, 2000). These include α_2 agonists like apraclonidine and brimonidine, topical carbonic anhydrase inhibitors dorzolamide, brinzolamide and prostaglandin analogs latanoprost, unoprostone, travoprost and prostamides like bimatoprost (Stewart et al., 2000).

Although the ultimate goal of a totally safe and perfectly tolerable drug has not been realized. An ideal antiglaucoma drug is which satisfies the criteria of reducing elevated IOP, provides long term IOP lowering efficacy, slows or prevents optic nerve damage, does not produce serious cardiovascular side effects, does not lead to serious ocular or systemic side effects (David, 1997).

Medline search revealed comparative clinical trials on brimonidine and dorzolamide in patients of POAG and evaluated its effectiveness clinically. But till date there has been no comparative study evaluating the efficacy of aforesaid disorder in Indian population. Hence, we conducted this randomized clinical trial. The primary objective of this trial was to demonstrate equivalence between brimonidine 0.2% ophthalmic solution and dorzolamide 2% ophthalmic solution in POAG and ocular hypertension. The secondary objective was to make a comparative assessment of their safety and tolerability profile.

MATERIALS AND METHODS

This was an open, randomized, cross over clinical trial. The present study was conducted in the Department of Pharmacology in association with Department of Ophthalmology at Government Medical College, Rajindra Hospital, Patiala. Subject recruitment was done from the ophthalmology outpatient department of the teaching hospital. All the study related documents were approved by the institutional Ethics committee and the trial was conducted in accordance with ICMR guidelines for biomedical research on human subjects and the declaration of Helsinki.

This trial was designed to demonstrate equivalence in the efficacy between the two treatment arms. The clinically acceptable effect for which equivalence could be declared was assumed as a difference in IOP lowering. The sample size was calculated using standard formula for sample size calculation for clinical trials.

Inclusion criteria

Adult subjects of either sex, in the age group of 25 to 70 years and clinically documented cases of Unilateral or bilateral primary open angle glaucoma (POAG) diagnosed by tonometry and gonioscopy with corrected visual acuity 20/40 or greater and no history of ocular trauma. The eye included in the study should have IOP >22mmHg.

Exclusion Criteria

Female patients who were pregnant or lactating or cases of any corneal pathology, with ocular infection, with history of

allergy to the drugs or patients who are taking drugs which can cause increase or decrease in IOP other than those used in the study or patients having history of any intraocular surgery or argon laser trabeculoplasty (ALT) within six months prior to study were excluded. Randomization of subjects who fulfilled the selection criteria was done using computerized random number list with recruitment rates in both arms in a 1:1 ratio.

Drugs used

Brimonidine is a selective α_2 agonist also known as UK-14,304 or AGN-190342 and is a lesser lipophilic analogue of clonidine. The molecular structure of brimonidine differs from apraclonidine and this gives brimonidine higher α_2 selectivity. After administration, brimonidine distributes into the posterior segment of the eye and may play a role in neuroprotection. (Chien DS et al., 1992). Chemical name of brimonidine is 5-Bromo 6-(2-imidazolyl-2-amino) quinoxaline-L-tartrate. This structure gives the molecule 1000 times more selectively for α_2 -receptors. Molecular weight of brimonidine is 442.24 and pH of the ophthalmic solution is 6.3-6.5. Brimonidine is available in a concentration of 0.2% solution. Each ml has 2 mg of brimonidine tartrate equivalent to 1.32 mg of brimonidine base. Preservatives like benzalkonium chloride (0.05mg/ml), polyvinyl alcohol, sodium chloride, sodium hydroxide and citric acid are added to adjust pH.

Brimonidine has a two pronged attack to reduce the IOP, firstly it decreases aqueous production and secondly it increases the outflow of aqueous by uveoscleral pathway. (Toris CB et al., 1995).

Dorzolamide hydrochloride is described chemically as (4S-trans)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-theino [2,3,6] thiopyrn-2-sulfonamide, 7-dioxidemono hydrochloride. Its empirical formula is C₁₀H₁₆N₂O₄S₃. HCl. Each ml contains Dorzolamide hydrochloride 2% w/v and Benzalkonium chloride 0.0075% w/v as preservatives. Dorzolamide is a first topically active carbonic anhydrase inhibitor (CAI). It is a potent and specific inhibitor of human carbonic anhydrase II, a predominant isoenzyme in the ciliary process which plays an important part in transfer of sodium carbonate and fluid in the aqueous humour. Thus inhibition of carbonic anhydrase II slows local bicarbonate production, decreasing sodium and fluid transport bringing about a subsequent decrease in aqueous humour production and lowering IOP.

Patient profile

30 newly detected cases attending the outdoors of Department of Ophthalmology, Govt. Medical College/ Rajindra Hospital, Patiala were enrolled in this study. All the particulars of the patients were noted, detailed history was taken and clinical examination was done and noted on proforma. There were 15 males and 15 females in 30 patients. Out of 30 patients, 16 patients had their right eye as the study eye while 14 patients had their left eye as the study eye. The age of patients was in the range of 40-70 years with a mean of 57.33±7.539 years.

Study visits and activities

The total duration of the study was 3 months. The patients were randomised to instill one of the study drugs for 4 weeks. After a wash out period of 4 weeks during which period no drug was given to the patients. The patients were crossed over to other study drug for another 4 weeks. During the study, patient visited the hospital on the Day 0 (visit 1), Week 2 visits clinically and the visual acuity, Intraocular pressure and Ophthalmoscopy were performed at the screening and on the subsequent visits. During the study period, subjects were not allowed to take any other systemic antibiotic or indigenous medicines for any medical or surgical cause. However, in cases of treatment failure or worsening of clinical condition, the subject was withdrawn from the trial prematurely. Bronchodilators like beta 2 agonists (salbutamol, levosalbutamol) by inhalational route, anticholinergics, theophylline derivatives and anti-inflammatory agents like inhalational corticosteroids were allowed. All the subjects participating in the trial were advised to stop smoking, and breathing exercises were advised for all subjects during the study period.

Best corrected visual acuity was done with a Snellen's chart and recorded as decimal notation, $6/6 = 1$, $6/9 = 0.7$, $6/12 = 0.5$, $6/24 = 0.25$. Visual acuity was done on all the visits. Examination of lids, adnexa and lacrimal apparatus was done using diffuse light. Biomicroscopy of anterior segment was done using Carl Zeiss slit lamp to note any abnormality especially regarding conjunctival hyperemia. Direct Ophthalmoscopy and slit lamp biomicroscopy with 78D lens was done to assess cup disc ratio (CD ratio) on all visits. Goldman applanation tonometer was used to measure intraocular pressure. The Goldmann applanation tonometer is a variable force applanation tonometer and works on the principle of constant area applanation. It determines the amount of force required to flatten an area of cornea 3.06 mm in diameter. (Coad CT, 1984). Throughout the study patients were monitored for ocular and systemic safety parameters. Patients were queried about side effects of drugs like burning, stinging, foreign body sensation or ocular pruritus. The adverse events were reported whenever the patient or examiner noted symptoms or findings. All observations were tabulated and subjected to statistical analysis.

RESULTS

30 eyes of 30 patients fulfilling the patient selection criteria and having POAG or ocular hypertension with IOP >22 mmHg were enrolled in the study. They were randomized to instill one of the study drugs for 4 weeks after initial evaluation. After a wash out period of 4 weeks during which period no drug was given to the patients. The patients were crossed over to other study drug for 4 weeks. In Group A patients instilled brimonidine (0.2%) three times daily. In Group B the patients instilled dorzolamide (2%) three times daily. Patients were examined at baseline (day 0) and subsequent visits were on 2 weeks and 4 weeks as per proforma attached. The study was conducted over a 3 months period and patients were analyzed for IOP changes, visual

acuity, cup disc ratio and ocular adverse effects of drugs.

In present study, the mean IOP at Baseline was 24.83 ± 2.0 mmHg and 24.43 ± 2.3 mmHg for group A and B at trough (8.00 a.m.) respectively. There was no statistical difference between the two groups ($p > 0.05$). In group A (brimonidine), The reduction in IOP at 8 a.m. at 2 weeks was 5.5 ± 2.330 mmHg and at 4 weeks was 5.833 ± 2.102 mmHg equivalent to a percentage reduction of 22.15% and 23.48% at 2 weeks and 4 weeks respectively. In group B (dorzolamide), the reduction in IOP at 8 a.m. at 2 weeks was 5.667 ± 2.529 and at 4 weeks 5.733 ± 2.518 , which is equivalent to percentage reduction in IOP of 22.79% and 23.46% at 2 weeks and 4 weeks respectively.

In group A (brimonidine), the reduction in IOP at 2 weeks was 5.899 ± 2.280 mmHg and at 4 weeks is 6.066 ± 2.377 mmHg equivalent to a percentage reduction of 24.02% and 24.69% IOP at 10 a.m. at 2 weeks and 4 weeks respectively. In group B (Dorzolamide), the reduction in IOP at 2 weeks is 5.233 ± 2.623 and at 4 weeks was 5.433 ± 2.582 , which is equivalent to a reduction in IOP at 10 a.m. of 21.51% and 22.42% at 2 weeks and 4 weeks respectively (Table 1).

Between the groups, IOP was analyzed by paired 't' test. As shown in table, there was no statistically significant difference in reduction in IOP between two groups at all follow up visits. at 8 am. ($p > 0.05$) (Table 2). Although a trend was observed at 10.00 of greater brimonidine efficacy compared with dorzolamide, the difference is statistically insignificant ($p > 0.05$) (Table 3). Visual acuity was converted from Snellen's chart into decimal system for statistical analysis. visual acuity in both group A and group B ranged from 0.1-1.0. Mean visual acuity recorded in group A was 0.506 ± 0.28 and same in group B. No change in visual acuity was observed in both groups on subsequent visits. The difference is statistically insignificant ($p > 0.05$).

All patients were having cup disc ratio in the range of 0.4-0.7. In group A, the mean cup disc ratio at baseline was 0.523 ± 0.086 and in group B, the mean cup disc ratio was 0.523 ± 0.086 . After start of treatment it increased marginally in both groups on subsequent visits but remained in the range of 0.4-0.7. At the end of 4 weeks the CD ratio was 0.544 ± 0.081 in group A and 0.544 ± 0.081 in group B.

Cup disc ratio increased in both groups as compared to baseline on subsequent visits, but this increase was statistically insignificant ($p > 0.05$). Safety/tolerability evaluation was based upon self reported adverse events on case record forms. Conjunctival hyperemia was present in 8 patients in group A and 7 patients in group B after starting the medication.

In group A, during the 4 weeks study, 1 patient developed moderate conjunctival hyperaemia whereas in group B it was not observed in a single patient. Importantly conjunctival hyperaemia was not associated with intraocular inflammation or other sequelae. Burning and stinging sensation in the eye was observed in 2 patients in group B treated with dorzolamide while in 1 patient in group A treated with brimonidine. Ocular allergy and foreign body sensation was reported in one patient each in group A and B.

Dryness of eyes was reported in 2 patients of group A treated with brimonidine while in 1 patient in group B treated with dorzolamide. In group B, during the 4 week study photophobia was seen in one patient, while it was not reported in a single patient in group A treated with brimonidine.

DISCUSSION

The results of this study proved that brimonidine (0.2%) is therapeutically comparable to dorzolamide (2.0%) in clinically suspected cases of POAG, both in terms of efficacy and safety. After a 4 week treatment with brimonidine (0.2%) and dorzolamide (2.0%) the IOP lowering was 24.69 % and 22.42 % respectively. The mean IOP at 10 a.m. (Peak was 18.5 ± 1.13 mmHg (24.69%) and 18.8 ± 1.064 mmHg (22.42%) for group A and group B respectively (Table 1). The difference was statistically insignificant ($p > 0.05$). (Table 3). The result of present study were very much consistent with study (Sharpe et al., 2004) as well as with another study done on glaucoma (Whitson et al., 2004).

Table 1 : Comparative IOP changes between two groups at 2 weeks and 4weeks at 10 a.m.

Duration	Group A (brimonidine) (n=15)		Group B (dorzolamide) (n=15)	
	Diff.±SD (mmHg)	%age reduction	Diff.±SD (mmHg)	%age reduction
Week 2 10 a.m.	5.899±2.280	24.02	5.233±2.623	21.51
Week 4 10 a.m.	6.066±2.377	24.69	5.433±2.582	22.42

SD= Standard deviation of mean.

Table 2 : Statistical comparison of IOP changes between group A and B on each visit at 8 a.m.

Duration	Diff. In IOP between two groups (mm of Hg)	SE	't' value	'p' value	Sig.
Day 0 8 a.m.	0.4	0.367	1.089	>0.05	NS
Week 2 8 a.m.	0.5	0.274	1.825	>0.05	NS
Week 4 8 a.m.	0.3	0.280	1.071	>0.05	NS

SE=standard error of mean; NS= p value shows that the difference is not significant.

Table 3 Statistical comparison of IOP changes between group A and B on each visit at 10 a.m.

Duration	Diff. In IOP between two groups	SE	't' value	'p' value	Sig.
Visit 1	0.333	0.281	1.185	> 0.05	NS
2 week 10 a.m.	-0.1	0.285	0.351	>0.05	NS
4 week 10 a.m.	0.367	0.265	1.385	>0.05	NS

SE= standard error of mean; NS= p value shows that the difference is not significant.

Although a trend was observed at 10.00 of greater brimonidine efficacy compared with dorzolamide, the difference is statistically insignificant ($p > 0.05$) (Table 3). Stewart et al (2000) showed at 10.00 mean IOP of 17.8 ± 2.7 mmHg (22.92%) and

18.6 ± 3.4 mmHg (26.25%) for brimonidine and dorzolamide respectively. A trend of higher efficacy with brimonidine compared with dorzolamide at 10.00 a.m. was seen. (Stewart et al., 2000).

The tolerability and safety evaluation was based upon self reported adverse events on case record forms. Most of the adverse effects were ocular or periocular and mild in severity and did not warrant discontinuation of therapy. Dorzolamide was associated with more frequent stinging and burning. While Brimonidine was associated with more frequent dry eye. Conjunctival hyperaemia is seen in group A only. While photophobia is seen in group B only.

No significant difference was found between the brimonidine three times daily and dorzolamide three times daily in the number of reports of the above mentioned events. Most of the adverse events were mild in severity and led to no discontinuation of therapy. There were two subjects in each group who were categorized as treatment failure and had to be put on other treatment after 4 weeks.

Both the drugs were well tolerated and safe throughout the study. Overall, monotherapy with dorzolamide and brimonidine appear to produce equivalent IOP lowering effect and have well tolerated adverse event profile.

CONCLUSION

The results of this study demonstrated that overall monotherapy with brimonidine 0.2% and dorzolamide 2.0% appear to produce equivalent IOP-lowering efficacy and have well tolerated adverse effect profile. During this study, visual acuity and cup disc-ratio remained stable in both groups.

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