Safety and efficacy of two different formulations of brimonidine in the treatment of primary open-angle glaucoma

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ABSTRACT

Background
To compare the safety and efficacy to lower the intraocular pressure (IOP) of brimonidine (0.2%) and brimonidine purite (0.1%) in patients with primary open-angle glaucoma

Materials and methods
Sixty patients with primary open-angle glaucoma with IOP >21 mmHg were selected for the present study for a period of 42 days. The patients were randomly divided into group A and group B with 30 patients in each group. Brimonidine 0.2% twice daily was administered to all Group A patients and similarly brimonidine purite 0.1% was administered two times daily to Group B patients. Using Applanation Tonometry, IOP was recorded at baseline and the same procedure was carried out at 14 days, 28 days and 42 days respectively between morning 9.00 to 10 am, 30 minutes after the administration of eye drops.

Results
From the study it was found that the Mean IOP reduction in Group A was from 24.45 with standard deviation of 1.99 mmHg to 18.75 with standard deviation of 2.00 mmHg leading to a fall of 4.70 mmHg (22.22%) at the end of the study duration. Similarly the trend noticed in Group B was that the Mean IOP decreased from 24.80 with standard deviation 2.06 mmHg to 18.83 with standard deviation 2.10 mmHg leading to a fall of 5.87 mmHg (23.66%). Thus there was no statistically significant difference in IOP-lowering efficacy of the two formulations.

The important adverse effects reported the two study drugs were Conjunctival hyperemia, foreign body sensation, dry eye, and papillary reactions. Among the two formulations, Brimonidine 0.2% caused more effects than brimonidine 0.1%.

Conclusion
The two formulations of brimonidine resulted in statistically equal IOP lowering effect in patients of primary open-angle glaucoma with reduced systemic and ocular adverse reactions with brimonidine 0.1%.

Keywords: Brimonidine 0.2%, brimonidine purite 0.1%, primary open-angle glaucoma
INTRODUCTION

It is well known that elevated intraocular pressure (IOP) is one of the most significant risk factors for glaucomatous optic nerve damage and that lowering the IOP is the only proven treatment to prevent this nerve damage. Among the different ways of lowering of IOP, a method of reducing either the aqueous humor production or by increasing the outflow of aqueous humor through trabecular or uveoscleral pathway is found to be popular. Generally, the trabecular outflow in human eyes accounts for nearly 70%–95% of the aqueous humor outflow from the eye. The other 5%–30% of aqueous humor outflow is by the uveoscleral pathway, with a decline in the contribution of this pathway with age. The Equilibrium between production and drainage of aqueous humor will result in the maintenance of consistent IOP. Based on this aqueous humor dynamics there are five major groups of drugs used for the treatment of glaucoma; cholinergics, alpha-adrenergic agonists, beta-adrenergic antagonists, carbonic anhydrase inhibitors, and prostaglandin analogs.

α-agonists are the drugs which mediate their action through α-receptors, which are of two types; α1-receptors are present postsynaptically and cause the contraction of ciliary muscle and decrease the aqueous humor production. Whereas α2-receptors are present presynaptically and decrease aqueous humor production through cyclic adenosine monophosphate pathway. Three drugs are available in this group depending on α2-selectivity namely; clonidine, apraclonidine, and brimonidine. All these drugs increase uveoscleral outflow also.

Brimonidine tartrate is a highly selective α2-adrenergic agonist and is well tolerated both ocularly and systemically. In patients with bronchial asthma or cardiovascular disease, it is an effective and safer alternative to beta-blockers. It has also been demonstrated that Brimonidine also has neuroprotective properties. It has been shown that on starting the brimonidine therapy many patients of Glaucoma exhibit improved contrast sensitivity. Shi and Jiang observed in their studies that brimonidine is safe and effective in lowering IOP in glaucoma or ocular hypertension. Brimonidine 0.2% contains 0.05 mg benzalkonium chloride (BAK) at pH of 6.4. At higher concentration BAK is retained in ocular tissues for longer period of time and may cell death in dose-dependent manner. It is noted that a new formulation of brimonidine in the form of brimonidine purite 0.1% has been introduced to enhance safety and tolerability. In this formulation, the preservative has been changed from BAK to purite, and the concentration of active agent has been reduced by 25%. When administered into the eye, purite is converted into natural tear components; sodium and chloride ions, oxygen, and water. From the literature it is understood that 0.1% formulation of brimonidine purite allows decreased exposure to brimonidine, while IOP-lowering effect is same as that of the 0.2% formulation.

In the present study these two formulations of brimonidine are used and their IOP lowering efficacy and safety are compared in patients of primary open-angle glaucoma.

MATERIALS AND METHODS

The present study was conducted in the Department of Glaucoma, sarojini Devi eye hospital, Hyderabad with the permission of institutional ethics committee. Sixty patients of primary open-angle glaucoma were enrolled into this study and informed written consent was obtained from them. The patients were randomly divided into two groups of 30 in each group. In case of patients with bilateral primary open-angle glaucoma, both the eyes were treated, but only one eye was considered for analysis. The baseline IOP was >21 mmHg in all patients. Patients who were already on treatment for glaucoma were included in the study, but after a washout period of 28 days. However, patients with a history of acute angle-closure glaucoma, history of any intraocular surgery, history of argon laser trabeculoplasty, and pregnant/lactating females, known sensitivity to the study drugs and any ocular inflammation, were not taken in the present study. Group A consisted of 30 patients of primary open-angle glaucoma. The patients in this group were administered 1 drop of brimonidine 0.2% (with BAK as preservative) ophthalmic solution twice daily at 9:00 am and 9:00 pm. Group B consisted of 30 patients of primary open-angle glaucoma. Patients in this group were administered 1 drop of brimonidine 0.1% with purite ophthalmic solution twice daily at 9:00 am and 9:00 pm. The patients were followed at 14, 28, and 42 days. IOP was measured with Goldmann applanation tonometer at 9:00–10:00 am.
at each visit around half an hour after administration of eye drops.

**STATISTICAL ANALYSIS USED**

Statistical analysis was carried out using paired *t*-test for comparing IOP at baseline and at 42 days, and ANOVA test was used for comparing IOP at each visit among the two groups.

**RESULTS**

Sixty eyes of 60 patients were diagnosed as primary open-angle glaucoma were randomly assigned into 2 groups of 30 patients each. Demographic profile of these patients is presented in [Table 1].

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Mean Age and SD</th>
<th>No. of Male patients</th>
<th>No. of Female Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>30</td>
<td>53.66 (6.98)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Group B</td>
<td>30</td>
<td>50.15 (7.1)</td>
<td>22</td>
<td>8</td>
</tr>
</tbody>
</table>

SD : Standard Deviation in parenthesis

There was no statistically significant difference between the two groups (*P* > 0.05) regarding all the demographic parameters of selected patients. The mean IOP lowering at the end of 42 days in Group A was 4.70 mmHg with standard deviation 1.28 (22.22%) mmHg and 5.87 with standard deviation 1.03 mmHg (23.66%) in Group B. Both the formulations of brimonidine caused significant reduction in IOP (*P* < 0.001) compared to base line IOP in patients of primary open-angle glaucoma; however, statistically significant difference (*P* > 0.05) was not observed in IOP-lowering efficacy among the two formulations of brimonidine and is presented in [Table 2].

<table>
<thead>
<tr>
<th>Time period</th>
<th>Group A Mean and SD</th>
<th>Group B Mean and SD</th>
<th>F</th>
<th>ANOVA (Level of Significance)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Line</td>
<td>24.45(1.99)</td>
<td>24.80(2.06)</td>
<td>0.062</td>
<td>0.92</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>14 days</td>
<td>22.15 (1.80)</td>
<td>19.65(2.00)</td>
<td>0.232</td>
<td>0.78</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>28 days</td>
<td>20.00 (2.00)</td>
<td>19.10(1.98)</td>
<td>0.220</td>
<td>0.77</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>42 days</td>
<td>19.75(2.00)</td>
<td>19.03(2.09)</td>
<td>0.169</td>
<td>0.82</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Treatment-related adverse effects were either systemic or ocular/periocular. Only two patients in Group A complained of drowsiness and fatigue. Conjunctival hyperemia was the most commonly observed side effect in three patients in Group A and one patient in Group B. Dry eye occurred in three patients in Group A and none in Group B. Foreign body sensation was complained by one patient in Group A and none in Group B. Papillary reaction was seen in two patients in Group A and one patient in Group B.

**DISCUSSION**

Glaucoma is an important cause of bilateral blindness second only to cataract. It is a disease which requires life long treatment[13] Brimonidine tartrate is a highly selective alpha2-adrenergic receptor agonist. It acts by both decreasing the aqueous humor production and increasing the uveoscleral outflow. The IOP-lowering efficacy and safety of brimonidine 0.2%, and brimonidine purite 0.1% were compared in this study. Mean reduction in IOP was 4.70 mmHg with standard deviation 1.28 (22.22%) in Group A and 5.87 with standard deviation 1.03 mmHg (23.66%) in Group B at 42 days of follow-up. The lowering of IOP was found to be statistically significant (*P* < 0.001) in both the groups. However, there was no statistically significant difference (*P* > 0.05) in IOP lowering effect between the two groups. Both the formulations had nearly equal reduction in IOP. Noeker in his study in patients of POAG, compared IOP-lowering efficacy of brimonidine purite 0.1% and brimonidine tartrate 0.2%.[10] In his study the baseline IOP was 25.1 ± 3.7 mmHg for brimonidine purite 0.1% and
24.1 ± 3.0 mmHg for brimonidine 0.2%. Mean change from baseline IOP at each time point ranged from −5.7 to −6.5 mmHg with brimonidine purite 0.1% and from −5.3 to −6.2 mmHg with brimonidine tartrate 0.2%. The results are in concurrence to the present study. Katz and Mundorf et al. in their study. also compared the efficacy and safety of brimonidine purite 0.1% twice daily with brimonidine 0.2% twice daily in patients with primary open-angle glaucoma.[12],[13] The difference in mean IOP between the brimonidine purite 0.1% and brimonidine 0.2% treatment group was <1 mmHg at all time points. They concluded that brimonidine purite 0.1% provided IOP-lowering effect comparable to brimonidine 0.2% in patients of primary open-angle glaucoma. These studies indicate that brimonidine purite 0.1% is equally efficacious when compared to brimonidine 0.2% and has added the advantage of reduced side effects. In the present study, these two formulations have been compared simultaneously in patients of primary open-angle glaucoma and found to be equally efficacious in IOP-lowering capacity.

Major ocular side effect noticed in the present study was conjunctival hyperemia seen in 10% in Group A and 2% in Group B. Papillary reaction was seen in 6% in Group A and 2% in Group B. Foreign body sensation was seen in 2% in Group A and 0% in Group B. Dry eye and burning sensation were complained by 10% of patients of Group A only. Systemic adverse effects in the form of drowsiness and fatigue were complained by two patients in Group A. On the other hand none of the patients in Group B presented with any systemic side effects. Kim et al. compared efficacy and safety of brimonidine 0.2% versus brimonidine purite 0.1% in Asian patients with glaucoma and found that brimonidine 0.2% causes more allergic conjunctivitis than brimonidine purite 0.1%.[14]

Both the formulations of brimonidine are well tolerated and do not cause any serious side effect requiring discontinuation of the drug; however, brimonidine 0.2% causes more side effects compared to brimonidine purite 0.1%. These could be related to the presence of BAK, which is more toxic than other preservatives and is retained in ocular tissue for a longer duration and may cause cell death in a dose-dependent manner.[9] In the formulations where the preservative has been changed from BAK to purite and the concentration of active agent has been reduced to 0.1%, the dose-related adverse effects were also reduced, and hence, brimonidine purite 0.1% is a better drug than brimonidine 0.2% for patients of primary open-angle glaucoma.

CONCLUSION

Both the formulations of brimonidine produced statistically equal effect in lowering the IOP in patients with primary open-angle glaucoma, but brimonidine purite 0.1% is a better drug than brimonidine 0.2% because of better systemic and ocular safety profile, and the use of antiglaucoma medications with preservative such as purite may have long-term benefits for the ocular surface health of patients requiring long term use of topical medications.

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REFERENCES


