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Efficacy and Safety of Timolol 0.5% Versus Brimonidine 0.2% in Lowering IOP in Cases of Primary Open Angle Glaucoma

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Abstract

Aims: To compare the efficacy and safety of Timolol maleate 0.5% and Brimonidine 0.2% in lowering IOP in cases of Primary Open Angle Glaucoma. *Settings and Design:* A single center randomized clinical trial was conducted in which the clinical outcome (efficacy) and safety profile of twice daily brimonidine tartarate 0.2% were compared with those of Timolol maleate 0.5% in patients with POAG for one year between November 2013 to October 2014. *Materials and Method:* Fifty patients were enrolled, twenty five in the Brimonidine group and twenty five in the Timolol group. Patients used drugs twice daily for five weeks, and were followed up at baseline visit and at weeks three and five. Clinical success meant reduction of intraocular pressure (IOP), Data about safety and adverse events were analyzed. *Statistical Analysis Used:* Student test. *Results:* Both drugs showed sustained ocular hypotensive efficacy in the study period of one year. At baseline the mean IOP was 24.34 ± 2.82 mm Hg in the timolol group and 24.16 ± 2.76 mm Hg in the brimonidine group. The IOP readings after treatment at 3rd and 5th week were significantly lower in both groups ($P < 0.001$) with no significant statistical difference between the two groups. 20% of the patients in Timolol group and 8% of patients in Brimonidine group, reported mild adverse events. *Conclusions:* Both the drugs have same efficacy and safety profile.

Keywords: Brimonidine; Glaucoma; Timolol.

Introduction

Glaucoma is second only to cataract as a cause of blindness worldwide[1] . It affects about 50 million and blinds 8 million people worldwide. These dismal figures are despite the fact that in the case of open angle glaucoma, early treatment can prevent progression of the disease. Primary open angle glaucoma is a symptom complex characterized by raised Intraocular pressure (IOP), increased cupping and visual field defects. It is called "creeping thief of the sight" because the disease remains symptomless and majority of the patients are being diagnosed only on routine examination and most of the time very late. Elevated IOP is a major risk factor that contributes to the optic nerve damage directly due to pressure effect and indirectly by reducing the blood supply to the optic nerve head (ischemia of the optic nerve head) and subsequent visual field loss in patients with primary open angle glaucoma. The disease progression can be halted by adequately lowering the IOP. The three modalities of treatment are medical, laser and surgical. Medical line of treatment to reduce intraocular pressure appears to be the first choice of treatment. Timolol, a topical non selective β-blocker which reduces the IOP by decreasing the aqueous humor secretion, Brimonidine a topical alpha 2 agonist is also used. In this study the efficacy and safety of these drugs are evaluated.

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Subjects and Methods

The present randomized double blind controlled study was carried out to compare the efficacy between Brimonidine 0.2% twice daily and Timolol 0.5% twice daily in the reduction of Intraocular pressure, in patients suffering from open angle glaucoma.

Study Period: 1 year

Sample Size: 50 patients of POAG.

Ethical Clearance: Obtained from the institutional ethical committee board.

Inclusion Criteria

Patients with open angle glaucoma were subjected to this study protocol.

Exclusion Criteria

1. Patients with angle closure glaucoma.
2. Patients with congenital glaucoma.
3. Patients with secondary glaucoma

Evaluation of all the patients included detailed history collection followed by systemic and ocular examination.

- Determination of visual acuity was done by Snellen's chart and near vision chart.
- External ocular examination was done.
- Detailed torch light examination was done including pupillary reflex and anterior chamber depth.

Detailed Slit Lamp Examination for Assessing

1. Depth of peripheral anterior chamber by comparing it with peripheral corneal thickness.
2. Pupillary reaction in both the eyes.
3. Presence of posterior synechiae.

- Gonioscopy was performed by using Goldman three mirror lens.

Grading of angle width was done according to Shaffer's grading.

- Intraocular pressure measurement was done with Schiotz tonometer and Perkins applanation tonometer at morning 9 a.m, afternoon 1 p.m and evening 5 p.m.
- The mean diurnal IOP was defined as the mean of the measurements at 9 a.m., 1 p.m. and 5 p.m.
- Visual field evaluation was done by using Humphrey field analyser.
- The pupils were then dilated with a combination of 10% phenylephrine and tropicamide 0.8% drops were instilled every 5 min over a 15 min interval.

This was followed by detailed examination by fundoscopy and 90 D lens examination on slit lamp.

- Measurement of blood pressure was done.
- Other investigations included, Urine examination for detection of sugar and albumin.

Follow-up

Patients were followed up at 3rd week, 5th week and following assessment was done.

- Visual acuity.
- IOP at 9 am, 1 pm and 5 pm.
- Any side effects of drugs.
- The levels of significance (p value) was calculated by student's 't' test.

Outcome was Defined as Follows

Complete success

I.O.P. ≤ 15 mm Hg with any group.

Partial success

I.O.P. ≤ 21 mm Hg with any group.

Complete success

I.O.P. ≥ 21 mm Hg with any group.

Hypotony was defined as I.O.P. < 6 mm Hg.

Because all patients were treated bilaterally, the mean IOP from both the eyes were used as an experimental unit in the analysis. The change from the baseline was calculated separately for each eye and then the changes from both the eyes were averaged. A p value less than or equal to 0.05 was considered statistically significant for the treatment effects.

Results

Out of 50 patients 27 patients (54%) belonged to the 41-60 year age group. 14 patients (56%) of these belonged to group I and 13 patients (52%) to group II. 19 patients were above 60 years (38%). 10 patients

(40%) belonged to group I and 9 patients (36%) to group II.4 patients were between 20-40 years (8%), out of which 1 patient (4%) belonged to group I and 3 patients (12%) to group II.

30 patients (60%) were male and 20 (40%) were female. In group I, 16 (64%) were male and 9 (26%) were female. In group II, 14 (56%) were male and 11 (44%) were female.

52% patients had sluggishly reacting pupils, 6% patients had non reacting pupils.

The maximum number of 19 patients (38%) had best spectacle corrected visual acuity of ≤ 6/60, 12 patients (48%) of these belonged to group I and 7 (28%) to group II. 16 patients (44%) had best spectacle corrected visual acuity between 6/6 – 6/12, 5 (20%) of these belonged to group I and 11 (44%) to group II. BCVA between 6/18 – 6/36 with 15 patients (30%), out of which 8 (32%) belonged to group I and 7 (28%) to group II. [T able 1]

Mean diurnal baseline IOP of 34 patients (68%) was between 21 – 25 mm Hg, of 15 patients (30%) was between 26 – 30 mm Hg and 1 patient (2%) had mean diurnal baseline IOP between 31 – 35 mm Hg. In group I, mean diurnal baseline IOP of 16 patients (64%) was between 21 – 25 mm Hg, of 8 patients (32%) was between 26-30 mm Hg, and of 1 patient (4%) was between 31 – 35 mm Hg. In group II, mean diurnal baseline IOP of 18 patients (72%) was between 21 – 25 mm Hg and 7 patients (28%) was between 26 – 30 mm Hg. (Table 2)

Table 1: Best corrected visual acuity

Visual Acuity	Group I		Group II		Total	
	No.	%	No.	%	No.	%
≤ 6/60	12	48%	7	28%	19	38%
6/36 – 6/18	08	32%	7	28%	15	30%
6/12 – 6/6	05	20%	11	44%	16	32%
Total	25	100%	25	100%	50	100%

Table 2: Baseline IOP

Baseline IOP (mm Hg)	Group I		Group II		Total	
	No.	%	No.	%	No.	%
21 – 25	16	64%	18	72%	34	68%
26 – 30	08	32%	07	28%	15	30%
31 – 35	01	04%	00	00%	01	02%
Total	25	100%	25	100%	50	100%

Table 3: Cup disc Ratio

C : D ratio	Group I		Group II		Total	
	No.	%	No.	%	No.	%
0.3 – 0.5	05	20%	08	32%	13	26%
0.6 – 0.8	18	72%	14	56%	32	64%
0.9	02	08%	03	12%	05	10%
Total	25	100%	25	100%	50	100%

Table 4: Field defects

Field constriction	Group I		Group II		Total	
	No.	%	No.	%	No.	%
Normal	01	04%	05	20%	06	12%
Early field defects	02	08%	04	16%	06	12%
Arcuate scotoma	12	48%	08	32%	20	40%
Biarcuate scotoma and residual fields	10	40%	08	32%	18	36%
Total	25	100%	25	100%	50	100%

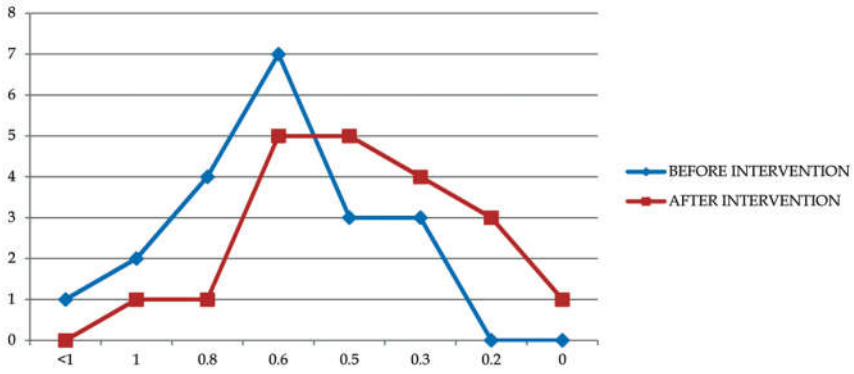
32 patients (64%) had Cup-Disc ratio between 0.6 to 0.8. 18 patients (72%) of these belonged to group I and 14 (56%) to group II. 13 patients (26%) had Cup-Disc ratio between 0.3 – 0.5. 5 patients (20%) of these belonged to group I and 8 (32%) to group II. Five patients (10%) had Cup-Disc ratio of 0.9. Two patients (8%) of these belonged to group I and 3 patients (12%) to group II. (Table 3)

12% patients had early visual field defects, 40% patients had arcuate scotoma and 36% patients had severe damage with extensive visual field loss to small residual field.(Table 4)

The mean diurnal baseline IOP was 24.34 ± 2.82

mmHg. The mean diurnal IOPs at 3rd and 5th week were 18.64 ± 3.87 and 17.67 ± 3.73 respectively. The mean reduction in IOP from baseline to 3rd week was 5.70 ± 1.88 and mean % reduction was 23.93% ± 9.06%. Similarly, the mean reduction in IOP from baseline to 5th week was 6.67 ± 2.15 and mean % reduction was 27.77% ± 9.50%. In group II, the mean diurnal baseline IOP was 24.16 ± 2.76, the mean diurnal baseline IOPs at 3rd and 5th week were 18.39 ± 3.52 and 16.92 ± 3.47 respectively.

The mean reduction in IOP from baseline to 3rd week was 5.76 ± 1.65 and mean % reduction was 24.28% ± 7.99. Similarly, the mean reduction in IOP from baseline to 5th week was 7.23 ± 2.33 and mean % reduction was 30.21% ± 9.71%.(Graph 1)



Graph 1: Mean iop and mean reduction in IOP

5 patients had adverse events, of which 3 had burning / stinging in the eyes and 2 had conjunctival hyperemia. In group II, 2 patients had foreign body sensation in the eyes. A total of 7 patients (14%) had adverse events of which 5 patients (20%) were in group I and 2 (8%) were in group II.

23 patients (46%) had complete success, 9 (36%) of these belonged to group I and 14 (56%) to group II. 18 patients (36%) had partial success. 11 (44%) of these belonged to group I and 7 (28%) to group II. 9 patients (18%) had complete failure, of which 5 patients (20%) belonged to group I and 4 patients (16%) belonged to group II.

Discussion

In a study to measure the 4 years risk of open angle glaucoma found that, incidence rate of primary open angle glaucoma increased from 1.2% at age 40 – 49 years to 4.2% at age of 70 or more [2]. Another study noted that one of the factors that predict the onset of primary open angle glaucoma is older age [3]. In the present study, 8% patients were below 40 years of age, POAG is by no means limited to those over 40 years.

Our study suggests higher prevalence among Men.

Our study shows majority of patients had poor visual acuity, which determines glaucoma as one of the leading causes of blindness. A study done at Arvind Eye Hospital, Madurai included 5150 patients to determine the prevalence of blindness and vision impairment in a rural population of Southern India. Visual impairment was defined as best corrected visual acuity < 6/18, and blindness was defined using both Indian (<6/60) and World Health Organization (<3/60) definition[4]. Authors concluded that 4.3% patients had visual acuity < 3/36 and 11.4% patients had visual acuity < 6/60 [5].

Pupillary reaction is an important factor in diagnosing primary open angle glaucoma. Pupillary dynamics in 13 patients with primary open angle glaucoma was evaluated. Out of 13 patients, abnormal light reflex was detected in all eyes of 6 patients, afferent papillary defect pattern was detected in 13 eyes and only one patient was found to be normal [6].

Khadikova E. V. (1997), in their study of papillary reactions in normal subjects aged over 40 and in patients with POAG, found that in POAG the changes in the papillary reaction are more when compared to normal subjects which is due to dystrophy of the iris and ciliary body.

Majority of the patients (68%) had mean diurnal baseline intraocular pressure between 21 to 25 mm Hg and 30% had between 26 to 30 mm Hg. Several studies have shown an incidence of new onset glaucomatous damage in previously unaffected patients, was about 2.6%- 3% for IOP 21 to 25 mm Hg, 12 to 26% incidence for IOP 26 to 30 mm Hg and approximately 42% for those higher than 30mm Hg.

Thus, chances of glaucoma damage increases with increase in IOP in accordance to the study conducted at which was studied relationship between Intraocular pressure and primary open angle glaucoma in 5308 patients and found that the risk of glaucomatous damage increases with the height of the IOP, particularly at levels of 21 to 29 and 30 mm Hg and above [7].

74% patients had Cup-Disc ratio above 0.6. Increased Cup-Disc ratio is one of the risk factors for the development of glaucomatous visual field loss. This is in accordance with a study showing eyes with the combination of IOP consistently above 20mm Hg and Cup-Disc ratio of 0.5 or more, were at higher risk of developing glaucomatous damage [8].

In this study, there is no much difference of mean diurnal baseline IOP between the two groups. (P>0.8). In group I, at the end of 3rd week follow-up the mean diurnal IOP was 18.64 ± 3.87 mm Hg, thus effecting a fall of 5.7 ± 1.88 mm Hg (which is 23.93% of the initial levels). In group II, at the end of 3rd week follow-up, the mean diurnal IOP was 18.39 ± 3.52 mm Hg, thus effecting a fall of 5.76 ± 1.65 mm Hg which is 24.28% of the initial levels.

The intraocular pressure lowering was similar in both Timolol and Brimonidine groups. At baseline, the mean IOP was 24.34 in Timolol group and 24.16 in Brimonidine group showing no statistically significant difference. (P > 0.8).

The IOP readings after treatment were significantly lower than baseline in both groups. The application of paired 't' test showed that the mean reduction in diurnal IOP at 3rd and 5th week of group II was significant (P<0.001).

The majority of patients in both treatment groups achieved clinical success with their 5 week treatment regimen. The clinical success rate was 80% in Timolol group and 84% in Brimonidine group. There was no statistically significant difference in both groups.

In a study to evaluate the efficacy of Brimonidine and Timolol for glaucoma it was found that with mean baseline IOP was 24.48 ± 2.29 mm Hg with Brimonidine and 23.32 ± 0.82 mm Hg with Timolol group, significantly lower IOP readings were noted when baseline values were compared to values at all visits (weeks 2 and 4).

In a study of 483 patients, Brimonidine produced significantly greater mean decreases of IOP (P≤0.007), when compared to Timolol at all follow up visits (12 month study)[9].

A reduction of IOP of 7.7 mm Hg with Timolol and 6.9 mm Hg with Brimonidine, was seen which intended hence showing almost similar clinical effectiveness in reducing the intraocular pressure.

A study of 30 patients revealed that, within group differences, reduction of IOP was significant, but the mean reduction of IOP when brimonidine (19.8±3.1) and Timolol (17.7±2.9) were compared was statistically not significant [10].

Another animal study on rats showed a very significant reduction of retinal ganglion cell loss with Brimonidine when compared to Timolol, thus indicating the neuroprotectiveness of brimonidine [11].

7 patients had reported mild adverse events. An extensive study reported that 17% patients of Brimonidine group and 9% patients of Timolol group had have mild adverse events 10% patients of Brimonidine group had ocular allergy [12].

An overall similar incidence of adverse events in both treatment groups, with no serious adverse event in either of the groups has been reported. Significantly more ocular burning and stinging was reported in Timolol group (43.6%) (P < 0.001)[13].

Patients receiving Timolol had significantly (P<0.04) lower heart rates than did patients receiving Brimonidine.

A compilation of review of more than 3,000 reports of adverse events was attributed to topical Timolol maleate, which included 267(55%) patients experiencing cardiac arrhythmia or a bronchospasm related event[14].

We had complete success in 9 patients (36%) in group I and in 14 patients (56%) in group II. 11 patients (44%) in group I and 7 patients (28%) in group II had partial success.

Five patients (20%) with complete failure were in group I and four patients (16%) were in group II.

30% reduction or more in mean diurnal IOP was achieved by 71% of patients in Brimonidine group and by 64% of patients in Timolol group.

Another study found after 6 weeks of treatment that the diurnal IOP measured for Timolol maleate (17.7±2.7mm Hg) and Brimonidine tartarate (19.0 ± 2.4 mm Hg) had a statistical difference between the two groups [15].

In a study of 40 patients for a period of one year showed clinical success rate of 81.8% was seen in the Timolol group and 86.2% in the Brimonidine group making no statistically significant difference between them (P = 0.817) [16].

Conclusion

Old age, male gender, high intraocular pressure, increased cup-disc ratio are high risk factors for the development of primary open angle glaucoma.

Abnormal pupillary reaction is a good predictor for this disease. Systemic diseases like hypertension and diabetes are predisposing factors for primary open angle glaucoma. As the disease remains symptomless for long and majority of the patients are being diagnosed only on routine examination, it is recommended to perform applanation tonometry in all individuals above 40 years of age, as a preliminary screening method.

This study indicates that in a small population, both Timolol maleate 0.5% and Brimonidine tartarate 0.2% eye drops are equally effective in lowering intraocular pressure and also showed sustained ocular hypotensive efficacy in the study period. However, the clinical success rate showed no significant statistical difference.

The treatment related adverse events were all ocular and none were severe in intensity. Both these drugs had a safe prescribing profile but Brimomidine has an added advantage of providing neuroprotection to ganglion cells; and Timolol has a guarded usage in patients with co-morbid respiratory and cardiovascular conditions.

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