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Comparative Study of Efficacies of Timolol Maleate and Brimonidine Tartrate in Primary Open Angle Glaucoma Patients as Monotherapy

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Abstract:
Background: *Glaucoma is one of the important causes of blindness in India along with cataract, refractive errors and corneal opacities. The common denominator of all the glaucomas is a characteristic optic neuropathy which derives from risk factor including increased intra ocular pressure.*
Aim: *The aim of the present study is to study the comparative efficacy of Timolol maleate (0.5%) and Brimonidine tartrate (0.2%) as monotherapy in human volunteers suffering from POAG for six months duration.*
Material And Methods: *This was a prospective randomized comparative study. 25 Patients of POAG cases for Brimonidine treatment and 25 Patients of POAG cases for Timolol treatment are evaluated by using Tonometer opthalmoscope and visual field analyzer*
Results: *Both Brimonidine and Timolo showed*
Intraocular pressure is significantly reduced in Brimonidine group (p=0.01;s) than in Timolol group at the end of 6 months period.
Conclusion: *The topical Brimonodine proved to be effective in lowering of intraocular pressure for long term treatment of POAG when compared to Timolol*
Keywords: *Brimonidine tartrate, Intra ocular pressure(IOP), primary open angle glaucoma(POAG), Timolol maleate.*

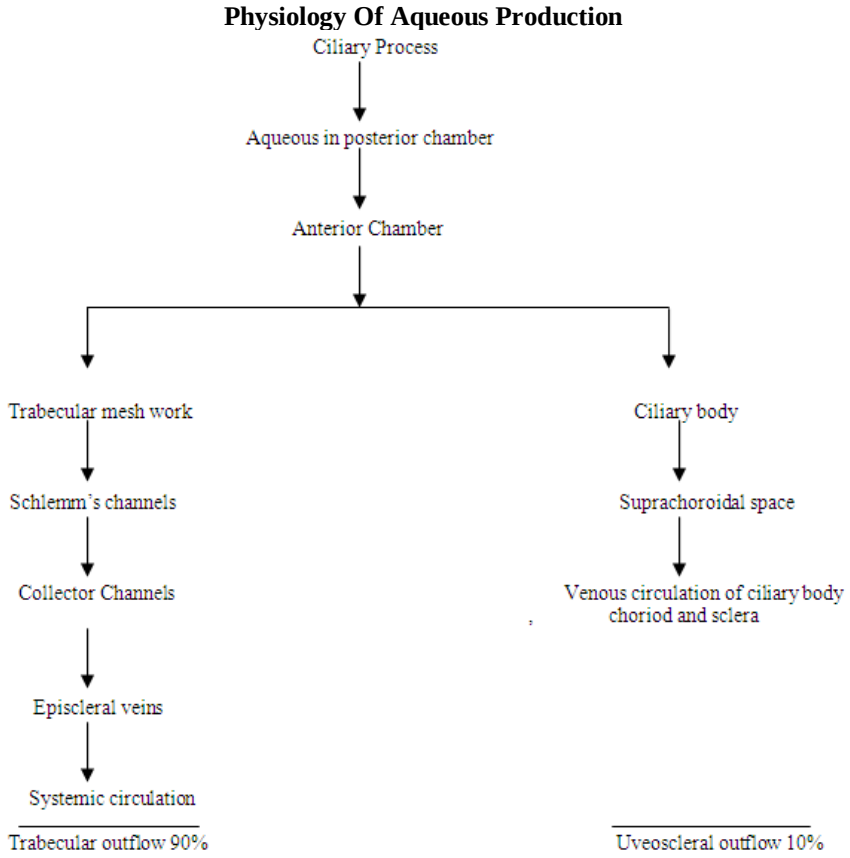
I. Introduction

Primary open angle glaucoma is a major worldwide health concern, because of its usually silent, progressive nature, and because it is the second leading preventable causes of blindness in the world[1]. With appropriate screening and treatment, glaucoma usually can be identified and its progress can be arrested before significant effect on vision occurs.

Intraocular Pressure is a function of the rate at which aqueous humor enters the eye and the rate of which it leaves the eye when inflow equals outflow, a steady state exists, and the pressure remains constant.

The principal ocular structures concerned with it are ciliary body, angle of anterior chamber and aqueous outflow system. Aqueous humor is secreted by the ciliary process and flows from the posterior chamber through the pupil into the anterior chamber. From the Anterior chamber the aqueous drained out by two routes[2]. 1.Trabecular outflow 2.Uveoscleral outflow.

The anterior chamber of the eye is the site of several tissues controlled by the Autonomic Nervous System. These tissues include papillary dilator and constrictor muscles in the iris and the ciliary muscle and the secretary epithelium of the ciliary body[3]. Aqueous humor is secreted by the epithelium of the ciliary body, flows through the anterior chamber, and exits via the canal of Schlemm. In the eye β receptors are largely of β2 subtype[4]. Blockade of the β adrenoceptors associated with the ciliary epithelium causes decreased secretion of aqueous.



The risk factors[5] of POAG includes the elevated IOP, age, race, sex, steroid usage, family history, diabetes mellitus, endocrine disorders, myopics, migraine, disc haemorrhages, environmental conditions, food & drugs. The pathology of POAG includes optic nerve damage, IOP changes, optic disc changes, visual field defects.

The chemical name of brimonidine tartrate is 5–bromo–6–(2-imidazolidinylideneamino) quinoxaline L-tartrate. It is an off-white to pale yellow powder. It binds to pre and post synaptic $\propto_2$ receptors. By binding presynaptic receptors, the drugs reduce the amount of neurotramsmitter release from sympathetic nerve stimulation and there by lower Intraocular pressure. By binding to post synaptic $\propto_2$ receptors, these drugs stimulat the G_i pathway, reducing cellular cyclic AMP production, thereby reducing aqueous humor production[6,7]. Its peak Intraocular pressure reduction efficacy is comparable to that of Timolol and does not cause cardiopulmonary side effects as reported with Timolol[8]. It produces sustained longterm ocular hypotensive effect[9]. It has no contraindication in patients with pulmonary disease[10]. It may have neuroprotective effect[11,12]. Brimonidine seems to have the capacity to increase fibroblast growth factor (FGF), which stimulates a cell to live in the apoptosis[13] Brimonidine had less progression of Retinal Nerve Fiber Layer damage following brimonidine 0.2% therapy compared to timolol 0.5% in ocular hypertensives[14]. Brimonidine, $\propto_2$ agonist inhibit vitreal glutamate and aspartate accumulation and preserve retinal function after transient ischemia[15]. Timolol is the 1st topical β adrenergic antagonist used for the treatment of glaucoma and elevated intraocular pressure. It inhibits bothβ_1 and β_2 receptors. β adrenoceptors are located on epithelium which enhance the aqueous secretion via increased cyclic AMP-PkA pathway. β blockade, blunts adrenergic activation of this pathway by preventing catecholamine stimulation of the β receptor, there by decrease the intracellular CAMP and decrease the aqueous production.

II. Materials & Methods

In the present comparative study a total of 50 POAG patients attending the Department of Ophthalmology, S.V.R.R.G. Hospital Tirupati, were recruited as trial subjects after obtaining permission from institutional ethics committee. All subjects were clinically examined and evaluated for fulfillment of inclusion and exclusion criteria and disability for study enrollment was confirmed. In our study 25 patients of POAG on Brimonidine treatment were compared with 25 patients on Timolol treatment and the doses were Brimonidine

tartrate-0.2% eye drops twice daily and Timolol maleate-0.5% eye drops twice daily. Patients were admitted for 24-48 hours & discharged. All the patients were asked to come after 1 month, 3 months, 6 months for the follow up. Fundus changes, intraocular pressure, visual fields of these patients during this visits were taken. Intra ocular pressure was done by Applantation tonometer, fundus examination was done by direct opthalmoscopy and visual fields by perimetry.

III. Results

Among the 50 patients satisfying the inclusion criteria 25 patients received Brimonidine therapy. The mean age of patients taking Brimonidine was 45.6 ± 6.55 years while that of the patients taking Timolol was 46.44 ± 6.31. in both study groups the sex distributionis exactly similar. Thus both the study groups were comparable with regard to the age and sex distribution

Table 1: **IOP Readings in Bromonidine Group**

S.No.	Time period	Right Eye	Left Eye
1.	Initial visit	25.91± 7.30	26.26 ±5.43
2.	After 24 hours	21.24 ±4.03	21.56 ±2.34
3.	After 1 month	19.57 ± 2.31	20.47 ± 1.35
4.	After 3 months	19.22 ± 1.45	20.00 ±1.40
5.	After 6 months	18.52 ± 1.26	19.73 ± 1.34
Statistical significance			
	1 vs 2	t = 2.80; P= 0.007;S	t = 3.97; P = 0.0002;S
	1 vs 3	t = 4.14; P= 0.00013;S	t = 5.17; P= 0.0001;S
	1 vs 4	t = 4.49; P = 0.001;S	t = 5.58; P = 0.00 1; S
	1 vs 5	t = 4. 98; P = 0.001; S	t = 5.83; P = 0.00 1; S

Table 2: IOP Readings in Timolol Group

S.No	Time period	Right Eye	Left Eye
1.	Initial visit	25.11±7.48	24.69 ± 6.86
2.	After 24 hours	21.45±5.08	20.60 ±5.09
3.	After 1 month	20.56±4.18	20.53 ± 3.22
4.	After 3 months	21.14±2.63	20.86 ±2.76
5	After 6 months	21.04±2.56	20.40 ± 2.66
Statistical significance			
	1 vs 2	t = 2.02; P= 0.048;S	t = 2.39; P= 0.02;S
	1 vs 3	t = 2.65; P = 0.01;S	t = 2.74; P = 0.008;S
	1 vs 4	t = 2. 50; P = 0.01; S	t = 2.58; P = 0.01; S
	1 vs 5	t = 2. 57; P=0.01; S	t = 2.91; P= 0.005;S

Table 3: IOP Reading (Right eye) in both study groups compared

S.No	Time period	Brimonidine group (N = 25)	Timolol group (N= 25)	Statistical significance
1.	Initial visit	25.91±7.30	25.11 ± 7.48	t =0.38; P=0.72; NS
2.	After 24 hours	21.24±4.03	21.45 ±5.08	t =0.16; P=0.87; NS
3.	After 1 month	19.57± 2.31	20.56 ± 4.18	t =1.03; P=0.30; NS
4.	After 3 months	19.22 ± 1.45	21.14 ±2.63	t =3.19; P=0.002; S
5	After 6 months	18. 52 ±1.26	21.04 ± 2.56	t =4.41; P=0.001; S

Table 4: IOP Readings (Left eye)in both Study groups compared

S.No	Time period	Brimonidine group (N = 25)	Timolol group (N= 25)	Statistical significance
1.	Initial visit	26.26±5.43	24.69 ± 6.86	t =0.89; P=0.37; NS
2.	After 24 hours	21.56±2.34	20.60 ±5.09	t =0.85; P=0.39; NS
3.	After 1 month	20.47± 1.35	20.53 ± 3.22	t =0.08; P=0.93; NS
4.	After 3 months	19.60 ± 1.40	20.86 ±2.76	t =2..03; P=0.047; S
5	After 6 months	19. 14 ±1.34	20.40 ± 2.66	t =2.11; P=0.04; S

Chart-1: Intraocular pressure in the study groups compared after 24 hours & 1 month

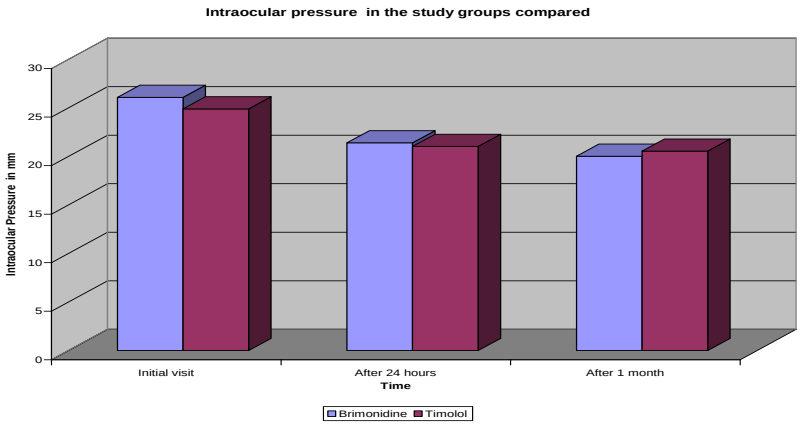


Chart-2: Intraocular pressure in the study groups compared after 3 & 6 months

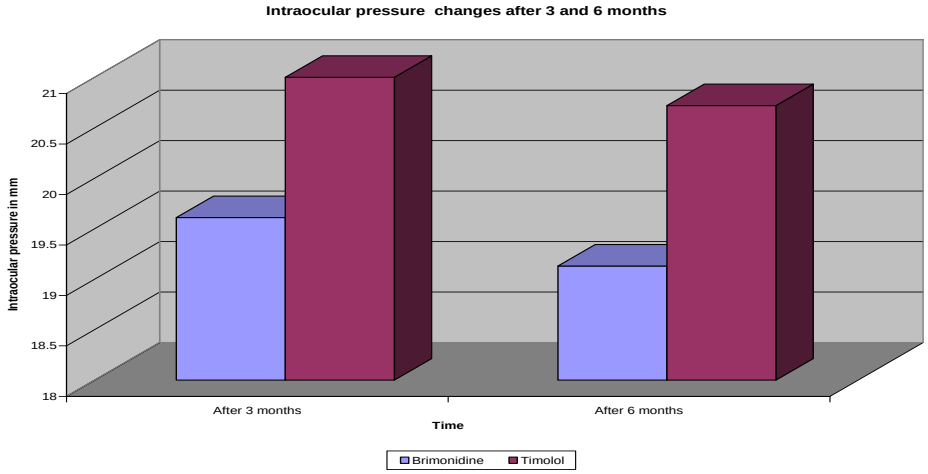


Table 5: IOP Reading in both Study groups compared

Time period	Brimonidine group (N= 25)	Timolol group (N=25)	Statistical significance
Initial Visit	26.09 ± 6.38	24.90±7.11	t=0.62; P= 0.53; NS
After 24 hours	21.40±3.27	21.03±5.06	t= 0.30; P=0.76; NS
After 1 month	20.02±1.92	20.55±3.69	t= 0.63; P= 0.52; NS
After 3 months	19.61±1.47	21.00±2.68	t= 1.85; P= 0.07; NS
After 6 months	19.13±1.43	20.72±2.61	t= 2.67 P= 0.01; S

IV. Discussion

The study consists of a total of 50 cases selected from the ophthalmology Out Patient department. Patients with intraocular pressure > 21 mm Hg were taken into study with angles wide open on gonioscopy examination. After examining the patients the investigations were done. Slit lamp examination, visual acuity, direct and indirect ophthalmic examination, intraocular pressure recording with Applanation tonometer, visual field analysis with perimetry was done before treatment.

After the investigations, the patients were divided randomly into two groups. Group 1 received topical Brimonidine twice daily for 6 months period. Group II received topical Timolol twice daily for 6 months period. Patients in group I and II were told to come to the ophthalmic O.P after 1 month, 3 months, 6 months to asses the clinical efficacy in lowering of intraocular pressure.

Brimonidine used twice daily as monotherapy had intraocular pressure lowering better than Timolol in 6 months clinical study. Brimonidine had peak intraocular pressure lowering effect ranged from 4.67 mm of Hg

to 7.39 mm Hg as compared to Timolol group, which had mean intraocular pressure lowering of 3.66 mm of Hg to 4.07 mm of Hg in right eye. The difference between two groups was only 1.01 mm to 3.32 mm.

In left eye the Brimonidine had lowering of intraocular pressure ranged from 4.70 mm to 7.12 mm Hg as compared to Timolol group which had mean intraocular pressure lowering of 4.09 mm to 4.29 mm Hg. The difference between two groups was only 2.42 mm of Hg to 0.2 mm

The average intraocular pressure reduction irrespective of eye is Brimonidine had mean intraocular pressure lowering 6.96 mm Hg as compared to Timolol group which had mean intraocular pressure lowering of 4.18 mm Hg. intraocular pressure lowering was sustained for 6 months in Brimonidine group when compared to Timolol group. Timolol shows fluctuations in intraocular pressure reduction during 6 months period. The main disadvantage is due to action on β_1 receptors in heart and β_2 receptors in bronchus. Due to this it has to be used with caution in cardiovascular and asthmatic patients[16]. It was observed that greater mean decrease in IOP was observed in patients treated with Brimonidine to Timolol[17].

Brimonidine is safe and effective in lowering intraocular pressure in glaucomatous eyes[18]. Brimonidine provides a sustained long term ocular hypotensive effect[19] is well tolerated, and has a low rate of allergic response[20]

Both the drugs were well tolerated. The incidence of adverse events were similar in both treatment groups, except for ocular allergy, and conjunctival follicles which occurred in the brimonidine group. These patients were kept for a short period in lubricating eye drops (Hydroxy methyl cellulose). Burning and stinging in eyes occurred more frequently in the Timolol group. The fluctuations of intraocular pressure levels occurred during this 6 months period in group II.

In this present study intraocular pressure is reduced significantly in Brimonidine group **(P = 0.01; s)** than in timolol group at the end of 6 months period**.**

V. Conclusion

In the present study it was observed that both the drugs had good efficacy in lowering of intraocular pressure, but the reduction of intraocular pressure was better with Brimonidine than with Timolol. The difference in lowing of intraocular pressure reading in Brimonidine is 6.96 mm Hg compared to Timolol which had 4.18 mm Hg. Brimonidine significantly reduces intraocular pressure after 6 months **(P = 0.01; s)** and lowering of intraocular pressure is sustained through out the period. Fluctuations of intraocular pressure were not observed with Brimonidine when compared to Timolol during the period of 6 months.

So the topical Brimonodine proved to be effective is lowering of intraocular pressure for long term treatment of Primary Open Angle Glaucoma when compared to Timolol.

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