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Original Research Article

Efficacy and safety of topical 2% dorzolamide and 0.5% timolol in cases of open angle glaucoma in a tertiary care hospital of East Singhbhum: an observational, prospective and comparative study

Akash Chandra[1]*, Manish Kumar[1], Amrendra Narayan Mishra[2]

[1]Department of Pharmacology, IGIMS, Patna, Bihar, India
[2]Department of Pharmacology, MGM Medical College & Hospital, Jamshedpur, Jharkhand, India

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***Correspondence to:**
Dr. Akash Chandra,
Email: drakash1984@gmail.com

ABSTRACT

Background: Present study was undertaken to evaluate and compare the efficacy and side effects of 2% dorzolamide and 0.5% timolol in patients with open angle glaucoma.
Methods: There were 60 randomly selected patients were equally divided into Group I (n=30) and Group II (n=30). Further both groups were divided into IA (n=10), IB (n=20), IIA (n=10) and IIB (n=20). 2% Dorzolamide hydrochloride in Group IA and IIA and 0.5% Timolol maleate in Group IB and IIB was administered for 24 weeks. Patients were evaluated for general and ocular examinations on day of enrolment and then at the end of 1st, 4th, 8th and 24th week. Adverse effects of the drug during study period were also noted. Mean±SD, t value, p value and comparison between groups were analysed by graph pad software.
Results: At the end of 24 weeks difference in mean reduction of IOP was not significant with 6.2±1.85mm Hg (Right eye) and 5.55±1.68mm Hg (left eye) and 4.72±2.97mm Hg (Right eye) and 5.37±1.24mm Hg (left eye) in Group IA and Group IIA respectively. At the end of 24 weeks difference in mean reduction of IOP was not significant with 5.06±1.62mm Hg (Right eye) and 4.40±1.96mm Hg (left eye) and 4.30±1.41mm Hg (Right eye) and 4.12±2.08mm Hg (left eye) in Group IB and Group IIB respectively. Fall in both systolic and diastolic blood pressure in both the groups were significant. Both drug regimens were well-tolerated, and no serious drug-related adverse effects were reported.
Conclusions: Dorzolamide was more efficacious for reduction of intra ocular pressure, well-tolerated, had low allergic response and had a favourable ocular, cardiovascular and respiratory safety profile than Timolol.

Keywords: Intraocular pressure, Topical 2% dorzolamide, Topical 0.5% timolol, Primary open angle glaucoma

INTRODUCTION

Glaucoma is a chronic progressive optic neuropathy caused by a group of ocular conditions which lead to damage of optic nerve with loss of visual function.[1] Raised intraocular pressure is essentially due to an increased resistance to the circulation of the aqueous at the pupil or to its drainage through the angle of the anterior chamber.[2]

Normal intraocular pressure depends up on the formation and outflow of aqueous humour which is under the control of parasympathetic and sympathetic activities of the autonomic nervous system. Normal intraocular pressure is maintained at 10-21mm of Hg.[3]

The diagnosis of glaucoma is made after looking for a combination of clinical signs characteristic change in the optic nerve head, abnormalities in visual field and a rise in intraocular pressure.[4] The type of glaucoma is determined by the clinical features and the status of anterior chamber angle as determined by gonioscopy.[5]

Primary open angle glaucoma (POAG) characteristically has an adult onset and is a bilateral almost symmetrical

disease. Ocular examination shows an open anterior chamber angle, optic nerve head changes, visual field damage and an intraocular pressure of more than 21mm Hg. POAG is the commonest form of glaucoma in Caucasians and Africans. It occurs in the elderly rarely being seen earlier than 40years of age. The inheritance is thought to be multi factorial and polygenic.[6]

Timolol Maleate

It is a non selective β_1 and β_2 adrenergic antagonist. It reduces intra ocular pressure in normal and glaucomatous eyes without changing the visual acuity and accommodation on pupil size (Katz et al., 1976, Radius et al., 1978).[7,8] It is supplied in 0.25% and 0.5% concentration, which are administered every 12 to 24 hours. It penetrates the eye rapidly and following topical administration IOP begin to fall in ½ to 1 hour, reaches a maximum in 2 hours and returns to baseline in 24 to 48 hours. The aqueous production is reduced to 47% after one week of timolol treatment but only 25% after one year of treatment. This process has been called "Long Term Drift" and is due to a time dependent decrease in acellular sensitivity to adrenergic antagonist.[9]

Dorzolamide

It is a topically used carbonic anhydrase inhibitor developed to circumvent systemic side effects of acetazolamide. It is available in 2% eye drops. It lowers intra ocular tension by 20%; Ocular stinging, burning sensation, itching, bitter taste are side effects. It causes shallowing of the anterior chamber and leads to transient Myopia. It does not give change in pupil size, no diminution of vision in dim light and in patient with cataract.[10]

The present study was undertaken to evaluate and compare the efficacy and side effects of these two drugs in patients with Glaucoma and increased intra ocular pressure.

METHODS

Study was carried out at Department of Pharmacology and Ophthalmology of MGM Medical College and Hospital, Jamshedpur, East Singhbhum, Jharkhand, India. Duration of the study was 12 months (from March 2013 to February 2014). There were 60 diagnosed cases of primary open angle glaucoma were randomly selected from the Department of Ophthalmology (outpatient and indoor) of MGM Medical College and Hospital, Jamshedpur, Jharkhand. This study was approved from Institutional Ethics Committee of MGM Medical College and Hospital.

Inclusion criteria

- Patients of all age above 35 years and all sex were included in this study.
- Patients of primary open angle glaucoma with IOP between 20 to 40mm of Hg.

Exclusion criteria

- Patients had glaucoma other than primary open angle, other ocular diseases or history of intraocular surgery.
- Patients on systemic beta-blockers.
- Patients suffering from obstructive pulmonary disease or hypertension/hypotension

Plan of study

The randomly selected patients (n=60) were equally divided into two groups Group I (IOP between 20 to 30 mm of Hg, n=30) and Group II (IOP between 31 to 40 mm of Hg, n=30) according to their intra-ocular pressure (IOP) measured by Schiotz tonometer. Further both group divided into IA (n=10), IB (n=20), IIA (n=10) and IIB (n=20).

a) Group IA and IIA- 2% Dorzolamide hydrochloride one drop thrice daily in both eyes was administered.
b) Group IB and IIB- 0.5% Timolol maleate one drop twice daily in both eyes was administered.

During each visit following examinations were done on day of enrolment and then at the end of 1st, 4th, 8th and 24th week.

a) *History and Chief complaints:* The history of any ocular or systemic and complaints suggestive of narrow angle and open-angle glaucoma. Duration of illness and family history of glaucoma, if any, were noted. Antiglaucoma medication, if taken previously was also noted.
b) *General examination*: includes pulse rate, heart rate and blood pressure.
c) *Ocular examination:* includes external examination by torch light, slit-lamp examination, Distant visual acuity tested by illuminated Snellen's chart, Schiotz tonometry, Gonioscopy, fundus examination and field analysis by Octopus auto-field analyser, Ophthalmoscopy and slit lamp biomicroscopy.
d) Any complaint regarding adverse effects of the drug during study period was noted.

All the patients were instructed not to administer their eye-drops on the morning of the check-up visits (1st, 4th, 8th and 24th week) in order to measure drug efficacy 12 hours after the previous evening dose.

Statistical analysis

Statistical analysis of data obtained were presented in tabular form. Mean±SD, t value, p value and comparison between groups were done by Graph Pad software. p value <0.05 was considered significant.

RESULTS

In Table 1, Group I and II, male patients were 14 (46.75%) and female patients were 16 (53.25%) respectively in both

the groups. Mean age was 63.6±8.14 years, 61.2±9.6 years, 63.3±10.56 years and 57.5±10.4 years in Group IA, IB, IIA and IIB patients.

Table 1: Age and sex distribution.

Characteristics of pts	Group IA	Group IB	Group IIA	Group IIB
Total no. of patients entering the study	10	20	10	20
Male	3	11	4	10
Female	7	9	6	10
Mean age	63.6± 8.14	61.2 ±9.60	63.3 ±10.56	57.5 ±10.40

In Table 2, the mean IOP of Group IA, IB, IIA, IIB in the right and left respectively was 27.02±3.86 and 25.95±2.16, 25.93±3.67 and 24.17±2.07, 30.0±6.31 and 33.02±1.09, 33.33±2.53 and 32.79±4.31 mm Hg (at pre-treatment), 22.32±2.80 and 21.89±2.01, 21.06±3.12 and 20.63±1.68, 24.92±5.18 and 26.89±2.51, 29.51±2.08 and 29.87±4.62 (at week 1), 20.02±1.98 and 20.08±1.71, 20.49±1.61 and 19.42±2.11, 26.12±3.78 and 27.43±2.86, 29.41±2.81 and 28.16±3.19 mmHg (at week 4), 19.05±2.01 and 20.24±1.26, 20.67±1.91 and 19.46±1.74, 25.91±3.51 and 27.18±1.81, 28.80±3.81 and 28.42±3.19mm Hg (at week 8), 20.82±2.46 and 20.40±1.60, 20.87±2.54 and 19.77±1.93, 25.28±3.59 and 27.65±2.18, 29.03±2.65 and 28.67±3.56 (at 24th Week). Mean reduction of IOP was significant in all the groups and in both the eyes at the end of 24th week of treatment in comparison to the pre-treatment IOP.

In Table 3, mean reduction of IOP after 24 weeks in group IA and Group IB was significant in both the eyes. Mean reduction of IOP after 24 weeks in Group IIA and IIB was not significant in right eye but significant in left eye.

Table 2: Intraocular pressure in Group - IA, IB, IIA and IIB.

	Group	Right Eye			Left Eye		
		IOP (mm Hg) (Mean±SD)	t value	p Value	IOP (mm Hg) (Mean±SD)	t value	p value
Pre-treatment	IA	27.02±3.86			25.95±2.16		
	IB	25.93±3.67			24.17±2.07		
	IIA	30.0±6.31			33.02±1.09		
	IIB	33.33±2.53			32.79±4.31		
End of week 1	IA	22.32±2.80			21.89±2.01		
	IB	21.06±3.12			20.63±1.68		
	IIA	24.92±5.18			26.89±2.51		
	IIB	29.51±2.08			29.87±4.62		
End of week 4	IA	20.02±1.98			20.08±1.71		
	IB	20.49±1.61			19.42±2.11		
	IIA	26.12±3.78			27.43±2.86		
	IIB	29.41±2.81			28.16±3.19		
End of week 8	IA	19.05±2.01			20.24±1.26		
	IB	20.67±1.91			19.46±1.74		
	IIA	25.91±3.51			27.18±1.81		
	IIB	28.80±3.81			28.42±3.19		
End of week 24	IA	20.82±2.46	17.32	<0.001	20.40±1.60	12.87	<0.001
	IB	20.87±2.54	23.7	<0.001	19.77±1.93	17.85	<0.001
	IIA	25.28±3.59	4.5	<0.001	27.65±2.18	12.18	<0.001
	IIB	29.03±2.65	21.7	<0.001	28.67±3.56	13.85	<0.001

Table 3: Statistical comparison of IOP reduction by different drug in same group.

Group	Drug	IOP Reduction (mm Hg) (Mean±SD)		Right eye		Left eye	
		Right Eye	Left Eye	t value	p value	t value	p value
I A	Dorzolamide hydrochloride (2%)	6.2±1.85	5.55±1.68	2.22	<0.05	2.18	<0.05
IB	Timolol maleate 0.5%	5.06±1.62	4.40±1.96				
IIA	Dorzolamide hydrochloride (2%)	4.72±2.97	5.37±1.24	0.62	>0.05	3.28	<0.001
IIB	Timolol maleate 0.5%	4.30±1.41	4.12±2.08				

Table 4: Statistical comparison of IOP reduction by same drug in different group.

Drug	Group	IOP Reduction (mm Hg) (Mean±SD)		Right eye		Left eye	
		Right Eye	Left Eye	t value	p value	t value	p value
Dorzolamide hydrochloride (2%)	Gr. IA	6.2±1.85	5.55±1.68	2.49	<0.05	0.31	<0.05
	Gr. IIA	4.72±2.97	5.37±1.24				
Timolol maleate 0.5%	Gr. IB	5.06±1.62	4.40±1.96	2.22	<0.05	0.27	<0.05
	Gr. IIB	4.30±1.41	4.12±2.08				

Table 5: Effect of dorzolamide and timolol on blood pressure (MEAN±SD).

	Dorzolamide hydrochloride (2%) (Mean±SD)		Timolol maleate (0.5%) (Mean±SD)	
	Systolic B.P. (mm Hg)	Diastolic B.P. (mm Hg)	Systolic B.P. (mm Hg)	Diastolic B.P. (mm Hg)
Pre-treatment	129.75±5.34	82.25±4.20	131.0±10.69	85.86±5.69
End of week 24	127.0±4.78	79.75±3.10	126.0±10.05	82.57±5.05
Difference	2.75±3.37	2.5±2.07	5.0±3.48	3.29±2.78
t- value	2.31	3.42	5.37	4.42
p- value	<0.05	<0.05	<0.001	<0.001

In Table 4, mean reduction of IOP after 24 weeks in Group IA and IIA and Group IB and IIB was significant in both the eyes.

In Table 5, dorzolamide mean systolic and diastolic blood pressure was 129.75±5.34 and 82.25±4.20 mm Hg and 127.0±4.78 and 79.75±3.10 mm Hg at pre-treatment and at the end of 24th week respectively. In Timolol group mean systolic and diastolic blood pressure was 131.0±10.69 and 85.86±5.69 mm Hg and 126.0±10.05 and 82.57±5.05 mm Hg at pre-treatment and at the end of 24th week respectively.

Table 6: Effect of dorzolamide and timolol on heart rate (MEAN±SD).

	Dorzolamide hydrochloride (2%) (Beats / min.) (Mean±SD)	Timolol maleate 0.5% (Beats / min.) (Mean±SD)
Pre-treatment	76.75±6.23	78.17±3.12
End of week 24	75.0±7.09	74.17±3.66
Difference	1.87±1.55	4.0±2.26
t- value	3.41	6.14
p- value	<0.01	<0.001

There was a significant fall in both systolic and diastolic blood pressure in Dorzolamide group at the end of week 24. But Timolol group showed more significant fall in systolic and diastolic blood pressure at the end of week 24.

In Table 6, mean pre-treatment heart rate of 76.75±6.23 beats/min and 78.17±3.12 beats/min in Dorzolamide and Timolol group respectively. At the end of 24 weeks of treatment there was a mean reduction of 1.87±1.55 in Dorzolamide group and 4.0±2.26 beats/ min in Timolol group.

DISCUSSION

Timely and adequate control of glaucoma is very important to prevent further silent loss of vision. The treatment of glaucoma is primarily directed towards lowering intra ocular pressure. This can be brought about by conservative medical treatment, laser therapy or by surgery.

In Table 2, Group IA- Mean IOP before starting the treatment and at the end of 24 weeks of treatment was 27.02±3.86 mm Hg and 20.82±2.46 mm Hg in right eye and 25.95±2.16 mm Hg and 20.40±1.60 mm Hg in left eye respectively. In Group IIA, Mean IOP before starting the treatment and at the end of 24 weeks of treatment were 30.0±6.31 and 25.28±3.59 mm Hg in the right eye and 33.02±1.09 and 27.65±2.18 mm Hg in the left eye respectively.

Julia A Balfour and Michelle J Wilde reported in clinical trials in patients with open angle glaucoma or ocular hypertension, Dorzolamide hydrochloride (2%) 3 times daily generally lower intraocular pressure by approximately 4-6mm Hg at peak (2-hour post dose) and 3- 4.5mm Hg at trough (8 hours post dose). Overall the percent reduction at the IOP from the baseline at the end of treatment period was 9.81% at trough and 20.80% at peak drug levels by monotherapy.[11] A. Scardillo reported 20% reduction of IOP after instillation of 2% Dorzolamide hydrochloride three times daily into the conjunctival sac of affected eyes.[12]

According to Table 3 mean reduction of IOP was 6.2±1.85mm Hg and 5.55±1.68mm Hg in the right and left eye respectively in Group IA at the end of 24 weeks of treatment. In Group IIA, mean reduction of IOP was 4.72±2.97mm Hg and 5.37±1.24mm Hg in the right and left eye respectively at the end of 24 weeks of treatment. In Group IB, mean IOP before and at the end of 24 weeks of treatment were 25.93±3.67 and 20.87±2.54mm Hg in right eye and 24.17±2.07 and 19.77±1.93mm Hg in left eye respectively. In Group IIB, the mean IOP before and at the end of 24 weeks of treatment were 33.33±2.53 and 29.03±2.65mm Hg in right eye and 32.79±4.31 and 28.67±3.56mm Hg in the left eye respectively. There was significant difference in the mean reduction of IOP in the present study.

Ayman A, Hamed M, Hany A, Salem and Mostafa AH reported a mean IOP reduction ranging from 3.8 to 5.1 mm Hg by Timolol maleate 0.5% in 14 patients for 4 weeks.[13]

In another study by Melamed S and David R in 2000 on 46 patients receiving Timolol maleate 0.5% reported a mean IOP reduction of 5.57mm Hg. Also reported a mean reduction of IOP ranged from 5.8 to 6.6mm Hg at 2-hour peak. At 12-hour trough the Timolol group had mean IOP lowering ranging from 3.8 to 4.8 mm Hg.[14]

According to Table 4, mean reduction of IOP was 6.2±1.85mm Hg and 5.55±1.68mm Hg in the right and left eye respectively in Group IA at the end of 24 weeks of treatment. In Group IIA, mean reduction of IOP was 4.72±2.97mm Hg and 5.37±1.24mm Hg in the right and left eye respectively at the end of 24 weeks of treatment. Mean reduction of IOP was 5.06±1.62mm Hg and 4.40±1.96mm Hg in the right and left eye respectively in Group IB at the end of 24 weeks of treatment. In Group IIB, mean reduction of IOP was 4.30±1.41mm Hg and 4.12±2.08mm Hg in the right and left eye respectively at the end of 24 weeks of treatment. There was significant difference of mean IOP reduction between the present study and the study conducted earlier by the above-mentioned authors.

Insufficient responses i.e. the IOP reduction of less than 10% at the end of week 2, was seen in 1 patient in Group IA, 2 patients in Group IB, 1 patient in Group IIA and 2 patients in Group IIB. 2 patients, one from Group IA and other from Group IIA did not turn-up after week 4. All of those patients were excluded from further study.

According to Table 5, there was significant fall in both systolic and diastolic blood pressure in both the groups. However, fall of mean blood pressure was more in Timolol group than Dorzolamide group. A similar and significant decrease of mean pressure without clinical symptoms were noted by Derick RJ et al.[15]

In Table 6, mean pre-treatment heart rate of 76.75±6.23 beats/min and 78.17±3.12 beats/min in Dorzolamide and Timolol group respectively. At the end of 24 weeks of treatment there was a significant mean reduction of 1.87±1.55 beats/min in Dorzolamide group and 4.0±2.26 beats/ min in Timolol group.

Both drug regimens were well-tolerated, and no serious drug-related adverse effects were reported. In present study 3 patients who were hypertensive and 2 patients who were asthmatic were on Dorzolamide and showed no exaggeration of these systemic problems.

In the present study, ocular burning sensation, ocular stinging sensation and bitter taste were reported significantly and more frequently in patients receiving Dorzolamide hydrochloride 2% while ocular irritation and dryness of mouth reported more often in timolol treated patients. Ellen Strahman et al, reported in 1995, the most frequently reported symptom among patients receiving Dorzolamide was bitter taste (27%) compared with smaller proportion of patients receiving timolol (7%).[16]

CONCLUSION

Dorzolamide had an edge over Timolol as far as reduction of intra ocular pressure in concerned. Dorzolamide was well-tolerated, low allergic response and had a favourable ocular and systemic safety profile. Dorzolamide had lesser effect on cardiovascular parameters than Timolol and can be used safely in patients with asthmatic and chronic obstructive pulmonary disease.

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