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A COMPARATIVE STUDY OF EFFICACY AND TOLERABILITY OF DORZOLAMIDE AND TIMOLOL MALEATE IN PATIENTS WITH PRIMARY OPEN ANGLE GLAUCOMA

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ABSTRACT

Primary open angle glaucoma (POAG), the most common form of glaucoma, left untreated results in gradual loss of vision. Decreasing intra ocular pressure (IOP) by drugs can halt disease progression. The drugs currently available for treatment of POAG are -blockers, sympathomimetics, carbonic anhydrase inhibitors (CAIs) and prostaglandin analogues. To assess the safety and tolerability of 2% dorzolamide and 0.5% timolol maleate in POAG patients, a prospective, comparative study was undertaken, enrolling 60 patients with POAG (30 in each group) attending Ophthalmology out patient department in Kempe Gowda Institute of Medical Science hospital and research centre. Dorzolamide was instilled thrice daily and timolol maleate twice daily for 28days. IOP was measured on day zero, 14th and 28th day. Visual acuity and side effects were looked for at each visit.

The mean reduction of IOP was 19.95% with dorzolamide and 21.5% with timolol maleate. Both the drugs were tolerated very well without any systemic adverse effects and the local side effects were comparatively less with dorzolamide. Efficacy of dorzolamide in decreasing IOP in POAG patients was almost comparable to timolol, and dorzolamide appeared to be relatively better tolerated.

Keywords: *POAG; IOP; dorzolamide; timolol maleate.*

INTRODUCTION

Primary open angle glaucoma (POAG), the most common type of glaucoma is one of the leading causes of irreversible blindness world wide, majority of whom remain undiagnosed. It is a silent killer of the vision because the disease remains symptomless and majority of the patients being diagnosed only on routine examination and most of the time very late. POAG is characterized by raised intraocular pressure (IOP), increased cupping and visual field defect. 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.The disease progression can be halted by adequate lowering of the IOP, referred as target pressure, which may vary from individual to individual.

The modalities of treatment are medical, laser and surgical, each having their own advantages and disadvantages. Considering the patient compliance, cost effectiveness and inherent risk of surgical management, medical line of treatment to reduce IOP appears to be the first choice of treatment. The drugs currently available for treatment of POAG are - blockers, sympathomimetics, carbonic anhydrase inhibitors (CAIs) and prostaglandin analogues. Timolol, a non-selective -blocker, is one of the widely used topical agents, which reduces the IOP by decreasing the aqueous humor secretion[1]. However it carries the risk of worsening bronchospasm in asthmatics, worsening A-V block and masking hypoglycemia in IDDM.

Acetazolamide, an orally effective CAI is a very effective antiglaucoma drug but chronic medication is associated with unpleasant, troublesome and often serious adverse effects like metabolic acidosis, malaise, fatigue, depression and nephrolithiasis[2] and hence there is a need for topical carbonic anhydrase inhibitors. Dorzolamide is a topical CA inhibitor, which reduces IOP by decreasing aqueous humor production and secretion[1], and is used as an effective adjuvant or alternative when -blockers are contraindicated or ineffective to control IOP. As there are few studies done in Indian population, this study was taken up to assess the clinical efficacy and tolerability of 2 % dorzolamide eye drops instilled thrice daily in comparison with 0.5% timolol maleate eye drops instilled twice daily in producing clinically relevant reduction in IOP in patients with POAG.

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METHODOLOGY

This prospective study was done to assess the efficacy and tolerability of topical Dorzolamide in comparison with topical Timolol maleate to reduce IOP in patients suffering from POAG attending the Ophthalmology OPD of KIMS Hospital and Research Centre, Bangalore. After obtaining approval and clearance from the hospital ethical committee, 60 subjects were recruited for the study. Selective sample of 30 patients were administered with dorzolamide 2% eye drops and timolol maleate 0.5% eye drops respectively.

Inclusion criteria include male/ female patients between 20-60 years of age who were willing to give written informed consent and patients with unilateral or bilateral POAG with an IOP of at least 22mm Hg on previous treatment or 25mm Hg without treatment. Exclusion criteria include pregnant and lactating woman, patient with history of allergy or tolerance to CAIs, angle closure glaucoma, current use of contact lenses, intra ocular surgery within previous six months, argon laser trabeculoplasty within three months, any ocular inflammation or infection within past three months, bronchial asthma / chronic obstructive pulmonary disease, sinus bradycardia/second or third degree heart block, overt cardiac failure and cardiogenic shock. Informed consent was obtained after fully explaining the procedure and the consequences, in patients' own language. A thorough evaluation of all the patients was done by detailed history taking followed by general, systemic and ocular examination. In patients who were previously receiving antiglaucoma drugs a sufficient wash out period was allowed - five days for cholinergic drugs, one week for adrenergic agonists and three weeks for -blockers.

Laboratory Investigations- Haemoglobin, WBC count-total and differential count, Blood urea, serum electrolytes- sodium, potassium, fasting blood sugar and urine analysis were done at baseline and at the end of 4 weeks. Duration of therapy was 4 weeks. Patient compliance was monitored by daily drug reminder chart. The follow up examination was done at the end of 14th and 28th day to assess visual acuity, IOP and any side effect of the drug

RESULTS & DISCUSSION

In this study, the clinical efficacy and tolerability of topical dorzolamide was assessed in comparison with topical timolol maleate in patients with POAG and the study intends long-term reduction in IOP. The patients recruited for the study fulfilled the inclusion and exclusion criteria and the compliance was monitored by daily drug reminder chart during follow up visits.

Among the patients with POAG enrolled for the study, the mean age was 52.03yrs in DRZ group and 54.5yrs in TML group and the difference was not statistically significant **(**p > 0.05). 42 patients (70%) from both the groups were in the age group of 51-60 years, 13 patients (21.67%) were in the age group of 41-50 yrs, 4 patients (6.67%) were in the age group of 31-40 yrs and only one patient was under 30 years (Fig 1). Though the occurrence of POAG is unusual less than 40 years [3], in our study 5 patients (8.33%) were under 40 years. 19 patients were male and 11 were female in DRZ group, 17 male and 13 female in TML group (Fig 2), and the gender difference was not statistically significant **(**p > 0.05) between the two groups. 36 patients (60%) from both the groups were males reflecting the higher prevalence of POAG in males[4].

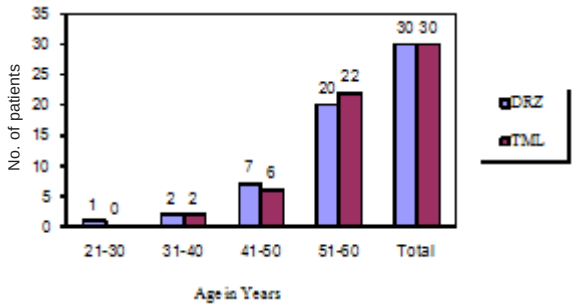

Fig. 1. *Age Distribution*

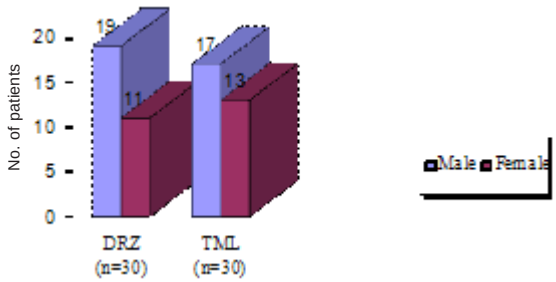

Fig. 2. *Sex Distribution*

The past history for systemic diseases was recorded and analyzed in all the patients from both the groups (Table 1). 13 patients (21.67%) were known diabetics, 6 patients (10%) were known hypertensives and 5 patients (8.33%) had both diabetes and hypertension. Thus, 18 patients (30%) were known diabetics reflecting higher prevalence of POAG in diabetic population [5] and diabetes mellitus being a known risk factor for POAG [6]. All these diabetic patients were well controlled with medication. Totally 11 patients (18.33%) were known hypertensives but well controlled with drug therapy. While there is a clear association between diabetes mellitus and POAG, the association of POAG and hypertension is not very clear[7,8]. 18 patients (30%) from both the groups had myopia corrected with glasses. This is consistent with the higher prevalence of POAG in myopes and also increased frequency of myopia in patients with POAG [9]. Only two patients from DRZ group received antiglaucoma therapy (topical timolol maleate 0.5%), which was withdrawn 21 days before starting dorzolamide.

Table 1. *Past History*

Past history	DRZ (n=30)	TML (n=30)	Total (n=60)
	n (%)	n (%)	n (%)
Diabetes mellitus	08(26.67)	5(16.67)	13(21.67)
Hypertension	04(13.33)	02(6.67)	06(10.00)
Hypertension with diabetes mellitus	03(10.00)	02(6.67)	05(8.33)
Myopia	11(36.67)	07(23.33)	18(30.00)
Antiglaucoma therapy	02(06.67)	00(0.00)	02(3.33)

45 patients (75%) from both the groups presented with diminution of vision often associated with other symptoms like headache, watering, itching etc (Table 2). Patients with POAG may remain asymptomatic in the early stages and as the disease advances may present with various symptoms due to damage to the optic nerve head. There was no much difference in the symptom pattern between the two groups.

Table 2. *Chief Complaints*

Chief complaints	DRZ - n (%)	TML - n (%)	Total - n (%)
Diminution of vision	13(43.33)	16(53.33)	29(48.33)
Headache	06(20.00)	02(06.67)	08(13.33)
Headache with diminution of vision	07(23.33)	04(13.33)	11(18.33)
Frequent changing of glasses	02(6.67)	02(6.67)	04(6.67)
Watering with diminution of vision	01(3.33)	02(6.67)	03(5.00)
Diminution of vision with frequent changing of glasses	00(0.00)	01(3.33)	01(1.67)
Diminution of vision with Itching	01(3.33)	00(0.00)	01(1.67)
Headache with frequent changing of glasses	00(0.00)	01(3.33)	01(1.67)
Frequent blinking	00(0.00)	01(3.33)	01(1.67)
Redness	00(0.00)	01(3.33)	01(1.67)

Gonioscopic examination for grading the angle width was done in all the patients (Table 3), 17 patients had grade 3 and 43 patients had grade 4 open angle respectively. Table 4 summarizes CD ratio in all patients on fundoscopic examination. 13 patients had CD ratio of 0.8, 12 patients had 0.6 and 11 patients had 0.7 respectively. CD ratio reflects the extent of optic nerve damage due to glaucoma (glaucomatous cupping). In the present study, there was no change in CD ratio in any of the patients throughout the study period. The corrected vision recorded on day 0 in both the groups remained the same throughout the study period indicating that there was no further detioration in visual acuity.

Table 3. *Grading of angle width on Gonioscopy*

Angle width	DRZ (n=30)	TML (n=30)	Total (n=60)
Grade 3	11	06	17
Grade 4	19	24	43

Table 4. *CD Ratio on Fundus Examination*

CD ratio	DRZ (n=30)	TML (n=30)	Total (n=60)
0.3	1	1	02
0.4	3	3	06
0.5	4	4	08
0.6	7	5	12
0.7	6	5	11
0.8	6	7	13
0.9	2	4	06
Total	1	1	02

The effect of drugs on IOP is depicted in Table 5. The IOP (in mm of Hg) was recorded immediately before instillation (trough), 2 hours after instillation (peak), on 14th day and 28th day, and the percent reduction of IOP from the trough was calculated at the end of 28 days in both the groups. Two patients from DRZ group dropped out from second visit and they were lost for follow up. The decrease in IOP in both the groups was significant after 2 hours but there was no further significant decrease on 14th day and 28th day, indicating that the maximum reduction in IOP has occurred within 2 hours (Fig 3). However, the effect was well maintained up to 28 days. The extent of decrease in IOP in the two groups was almost comparable at different phases of measurement. The mean fall of IOP towards the end of the study period was 5.25 (± 2.22) mm Hg in DRZ group and 5.87 (± 1.86) mm Hg in TML group, the percentage decrease in IOP was 19.95% and 21.58% in DRZ group and TML group respectively, and the difference was not statistically significant (p>0.05). There was no significant difference in the extent of IOP reduction in the different age groups, sex, and also in the pre existing disease states.

Table 5. *Effect of Drugs on IOP (Mm 0f Hg)*

	DRZ				TML			
	N	Mean	SD	p-value	n	Mean	SD	p-value
Trough (0 hour)	30	26.31	2.12	NA	30	27.19	2.65	NA
Peak (2 hours)	30	21.43	2.45	p<0.01	30	21.56	1.86	p< 0.01
14 days	28	21.23	2.14	p<0.01	30	21.44	1.95	p< 0.01
28 days	28	21.06	2.22	p<0.01	30	21.32	1.86	p< 0.01
% Reduction	19.95				21.58			
Between the groups, p - value	p > 0.05							

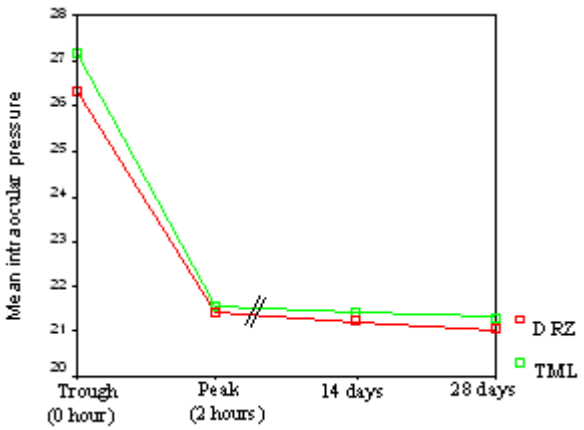

Fig. 3. *Effect of drugs on IOP*

No side effects were observed and reported at peak, but certain side effects were evident at 14th and 28th day. The side effects recorded were headache, burning sensation, bitter taste and itching. On the whole, only 10% of the patients (n=6) from DRZ group and 15% of the patients (n=9) from TML group experienced the side effects (Fig 4). Burning sensation and itching was relatively more common in the TML group. In general both the drugs were well tolerated, though dorzolamide appeared to be comparatively better tolerated. Since

the side effects did not occur at peak but appeared only later it seems that they may be related to the duration of administration. However, there were no significant changes in the laboratory parameters from the baseline values to those measured at the end of the study period in both the groups.

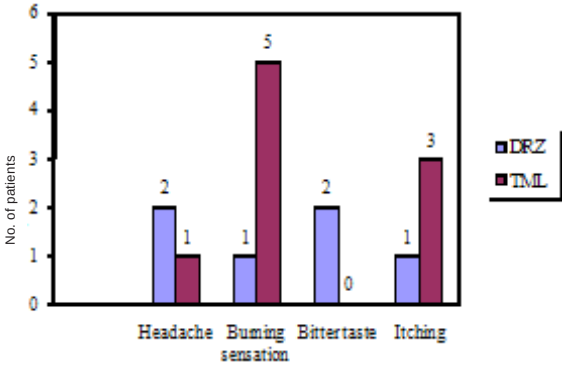

Fig. 4. *Side effects*

In the present study, with both the drugs, the fall in IOP was maximum within 2 hours indicating rapid onset of action. Though there was little further decrease in IOP the effect was well maintained and hence ensuring sustained decrease in IOP without much fluctuation. For POAG topical medication has almost replaced the systemic administration[10] and only in exceptional situations characterized by very high elevation of IOP oral or parenteral acetazolamide may be employed to supplement topical medication. Among the topical medications, most widely used drugs are timolol maleate, betaxolol, latanoprost, pilocarpine, brimonidine, etc., and dorzolamide being a new development. Dorzolamide being a topical CA inhibitor is free from systemic adverse effects metabolic acidosis, crystalluria, and hyperkalemia unlike oral acetazolamide and represents a novel approach in the long-term management of POAG. Studies have shown that the efficacy in lowering IOP was comparable to oral acetazolamide and topical timolol[11], betaxolol[11] and brimonidine[12] though some studies have shown timolol to be marginally better[11]. In the present study dorzolamide achieved nearly 20% decrease in IOP, which is almost consistent with several other studies, which have reported 10-26% reduction in IOP with monotherapy[12]. The extent of reduction in IOP was sufficient enough to be clinically significant to prevent long-term complications of glaucoma[13]. In all these studies dorzolamide was found to be very well tolerated with virtually no systemic adverse effects unlike oral CAIs.

In the present study, only 10% of patients receiving dorzolamide experienced mild side effects like bitter taste, headache and burning sensation in the eye. In timolol group 15% patients experienced side effects, which mainly included burning sensation. With both the drugs, the side effects were not evident at peak but developed with repeated administration and therefore seem to be related to the duration of administration and hence the occurrence of side effects being of much concern with long-term administration. The laboratory investigations done at baseline and also on 28th day did not show significant changes in both the groups.

Thus, the present study suggests that the efficacy of topical dorzolamide in reducing IOP in POAG is almost comparable to topical timolol maleate, and dorzolamide was relatively better tolerated than timolol maleate and also totally free from systemic and biochemical adverse effects characteristic of oral CAIs. In view of its distinct advantages over oral CAIs because of its total lack of systemic and biochemical adverse effects and also over topical beta-blockers because of its absolute safety in patients with obstructive airway disease, cardio vascular diseases like sinus bradycardia, heart block, cardiac failure, and ventricular dysfunction, etc., dorzolamide can be considered as the mainstay or primary therapy in POAG and preoperative reduction of IOP. Thus, dorzolamide can be better option or preferable drug in the naturalistic setting of the general population. Though dorzolamide can be effective as monotherapy, in patients with inadequate response it can be combined with timolol and this combination appears to be synergistic for achieving maximal reduction in IOP[14]. Since there is no additional advantage by using dorzolamide in concentration more than 2% [15], such a combination would be of considerable clinical advantage for achieving maximum IOP reduction. Further detailed and extensive studies in Indian population with dorzolamide alone or other topical CAIs, and also fixed dose combination of dorzolamide (or other topical CAIs) and timolol seems to be worth undertaking.

CONCLUSION

The present study suggests that efficacy of topical dorzolamide in decreasing IOP in patients with POAG was almost comparable to topical timolol maleate. Both the drugs were very well tolerated throughout the study period and the side effects were mild and local in nature and dorzolamide appeared to be relatively better tolerated. In view of its safety in patients with obstructive airway disease and cardiovascular diseases and also freedom from systemic and biochemical adverse effects, dorzolamide can be considered as the front line IOP lowering agent in POAG patients.

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