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Research Article

EFFECT OF BRINZOLAMIDE ON OCULAR HEMODYNAMICS IN GLAUCOMA PATIENTS

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ABSTRACT

Purpose: The single blind study was done to find out the effect of Fixed drug (FDC) combination Brinzolamide/Timolol Versus Free equivalent combination therapy of Brinzolamide plus Timolol on Ocular hemodynamics in patients of Primary Open Angle Glaucoma (POAG).

Methods: Two Groups were studied: Group 1- patient on 1% Brinzolamide/0.5% Timolol fixed dose combination and Group 2- patient on 1% Brinzolamide + 0.5% Timolol. A total of 40 study subjects were included who underwent measurement of IOP, Ocular Perfusion Pressure (OPP) and Ocular blood flow (OBF) by using Color Doppler.

Results: Both the Groups showed reduction in IOP from baseline. But there was no significant difference ($p<0.05$) in IOP reduction between the Groups at all visits. Increase in OPP was found to be statistically significant ($p=0.001$) within the Groups. OBF measurement, showed significant increase in velocity ($p=0.001$) of Central Retinal artery and Short Posterior Ciliary rtery within the Group. No significant change was observed in blood flow parameters of Ophthalmic artery.

Conclusion: The study showed that treatment with both Brinzolamide/Timolol-FDC and free equivalents of Brinzolamide+Timolol significantly reduced IOP and increased OBF parameters. So the combination therapy can be used in place of free equivalents with equal benefits.

Keywords: Brinzolamide, Timolol; Ocular Blood Flow; Colour Doppler; Central Retinal Artery; Short Posterior; Ciliary Artery; Ophthalmic Artery; Ocular Hemodynamics; Intraocular Pressure; Combination therapy

INTRODUCTION

According to WHO, Hypertension is defined as a systolic blood pressure (SBP) of 140 mmHg or more, or a diastolic blood pressure (DBP) of 90 mmHg or more. Hypertension is a common disease that is simply defined as persistently elevated arterial blood pressure (BP). Although elevated BP was perceived to be "essential" for adequate perfusion of essential organs during the early and middle 1900s, it is now identified as one of the most significant risk factors for cardiovascular (CV) disease. Increasing awareness and diagnosis of hypertension, and improving control of BP with appropriate treatment, are considered critical public health initiatives to reduce CV morbidity and mortality. Hypertension is an important public health challenge in both economically developing and developed countries. In India, cardiovascular diseases (CVDs) are estimated to be responsible for 1.5 million deaths annually. Hypertension is a major risk factor for CVDs, including stroke and myocardial infarction, and its burden is increasing disproportionately in developing countries as they undergo demographic transition. Glaucoma is a optic neuropathy characterized by progressive loss of optic nerve tissue with associated visual field loss & carries a potential risk of blinding [1]. Glaucomatous eye present with increased intraocular pressure (IOP) which is considered to be the strong risk factor for the development & progression of glaucoma [2]. The reduction of IOP is the only proven method to manage glaucoma [3].

Several studies have also shown the association of POAG with abnormal ocular blood flow (OBF) & Ocular Perfusion Pressure (OPP) [4]. The reduction of 20%-30% in IOP below

baseline is considered a rational management [5]. Most often single medication is insufficient to reduce IOP on long term & hence patient are shifted to a two drug regimen which can be given as individual drug or fixed combination therapy [6].

One such combination is timolol with brinzolamide in a concentration of 0.5% & 1% respectively which is approved by Drug Control General Of India in 2016 [7].

The main idea of focusing on fixed combination in glaucoma is

a) It avoids complex dosing schedule

b) It also avoids risk of first drug being "washed out" after instillation of 2nd drug if appropriate time gap is not followed

c) It minimizes toxic effects of cumulative exposure to preservatives and

d) It improves adherence to treatment thereby increasing efficacy [8].

This combinations has shown to reduce the IOP by 30-33% from the untreated baseline IOP of 25-27 mmHg [9]. Studies have shown better tolerability & less ocular discomfort with this combination with regards to safety profile [10]. Carbonic anhydrase inhibitors have shown to improve ocular blood flow due to vasodilatation caused by release of carbon dioxide [11].

So the study was done to evaluate the effect of fixed dose 1% Brinzolamide/ 0.5% timolol & its free equivalent combination on efficacy and ocular hemodynamics in glaucoma patients.

MATERIALS AND METHODS

The study was conducted at a tertiary care teaching hospital over a period of 18 months commencing from February 2019 to July 2020. It was a prospective, observational, single blind study. The patients were recruited from glaucoma clinic & outpatient department of ophthalmology of Lala Lajpat Rai Hospital (LLR), GSVM Medical College, Kanpur, U.P. diagnosed with primary open angle glaucoma (POAG) were included.

A) Inclusion Criteria

- Patient of age > 40 yrs
- Newly diagnosed patient with IOP >21 mmHg with open angle on gonioscopy & disc findings suggestive of glaucoma with corresponding visual field defect

B) Exclusion Criteria

- Advanced glaucoma (IOP>36 mmHg)
- Glaucoma other than POAG
- Pregnant & lactating woman
- Ocular trauma
- Ocular infection or inflammation
- Any retinal disease
- Any intraocular surgery <6 months before the study
- Any chronic illness (COPD, Asthma, Diabetes, Hypertension, etc.)
- History of allergy to medication prescribed during the study

There were 143 patients screened out of which 82 were diagnosed with POAG. Seventy one patients were randomized by computer generated automated numbers out of which 40 patients (20 in each Group) completed the study. The patients with Group-1 were treated with fixed drug combination of 1% Brinzolamide/0.5% Timolol & Group 2 subjects were treated with free equivalent combination of 1% Brinzolamide + 0.5% Timolol.

Written and informed consent as per the tenants of Helsinki's was taken from each patient and the study was approved by institutional ethics committee (EC/BHMR/2020/16 dated 18/08/2020).

The patients were subjected to detailed examination including best corrected visual acuity, IOP (Goldmann Applanation Tonometer), four mirror gonioscopy, disc photography, Humphrey's visual fields, blood pressure and ocular blood flow (OBF) parameters measurement. The OBF parameters were measured by an independent examiner blinded to the patients. It was done by color doppler (Sonosite Inc, USA) of 13.5 MHz probe in three retro orbital arteries : Central retinal artery (CRA), Short posterior ciliary arteries (SPCA) and Ophthalmic Artery (OA). The parameters measured were peak systolic velocity (PSV), end diastolic velocity (EDV) and resistivity index (RI) before starting treatment and 3 months after instillation of the drugs.

The ocular perfusion pressure (OPP) was calculated by following formula:

OPP = 2/3 MAP – IOP where MAP = Mean Arterial Pressure

Statistical Analysis was done by SPSS software version 20. All the data were entered in excel spread sheet. Mean & standard deviation were calculated and comparison between the Groups was done using unpaired t test. P – value of < 0.05 was taken as significant.

OBSERVATION AND RESULTS

The patients' demographic data is given in **Table 1**. Mean age of the patients were comparable and both the Groups had more number of females.

The mean baseline IOP in Group 1 was 25.75 ± 3.14 & in Group 2 was 25.47 ± 3.05 mm Hg (p value 0.77) that decreased at 12 weeks by 31.6% in Group 1 (17.6 ± 1.58) and by 29.7% in Group 2 (17.9 ± 1.08). The reduction in IOP was comparable in both the Groups (p-value = 0.64) as shown in **Figure 1.**

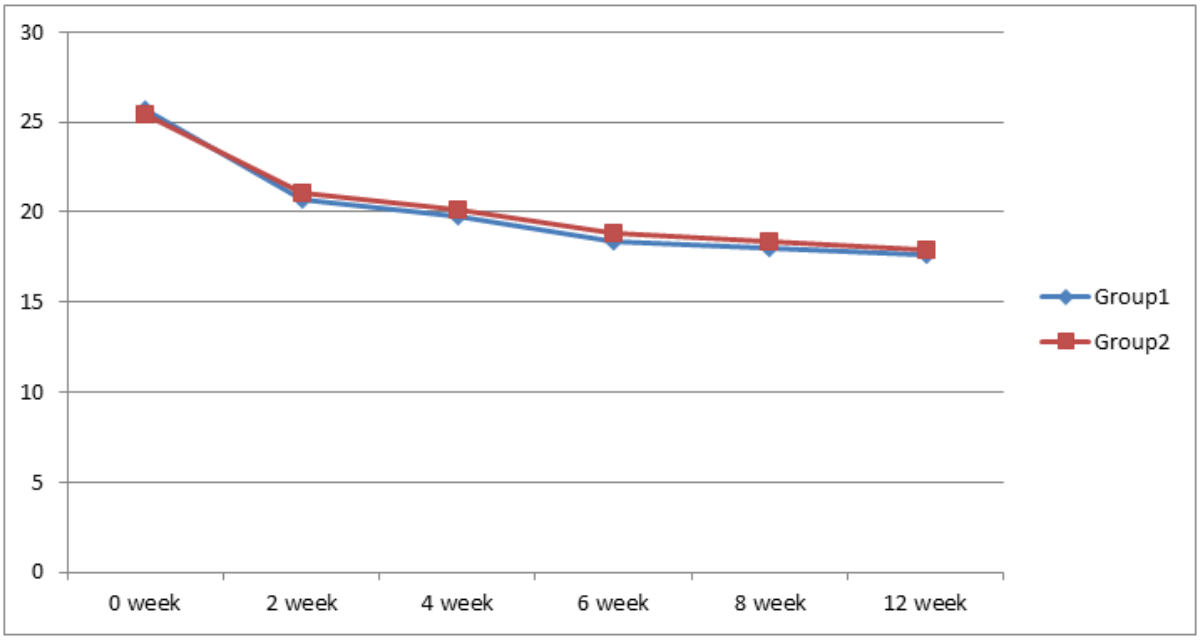

Figure 1: Comparison of mean IOP reduction from baseline in between the Groups at each visit.

Table 1: Patients' demographic details in both Group 1 & Group 2.

Parameters	**Group-1**	**Group-2**	**Total**
No. of Patients	20	20	40
Age (mean ± SD) yrs	53.63 ± 23.46	55.25 ± 24.75	55.43 ± 18.01
Gender			
Male	40% (n=8)	45% (n=9)	42.50%
Female	60% (n=12)	55% (n=11)	57.50%
Group-1 (1% Brinz/0.5% Tim –FDC) Group-2 (1% Brinz+0.5% Tim)			

The comparison of systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate & ocular perfusion pressure between the Group1 & Group 2 is shown in **Table 2.** The heart rate decreased significantly in both the Groups at 3 months follow up and OPP increased in both the Groups with no significant difference in between two Groups **(Table 2).**

Table 2: Comparison of Systolic, diastolic blood pressure, mean arterial pressure, heart rate & ocular perfusion pressure between the Group 1 & Group 2.

Parameters	**Group-1 (n=20)**		**Group-2 (n=20)**		**P value**
	Baseline	**At 12 weeks**	**Baseline**	**At 12 weeks**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	
Systolic BP (mmHg)	117.3 ± 6.14	116.1 ± 6.13	117.2 ± 5.63	116.3 ± 6.06	
Diastolic BP (mmHg)	78.4 ± 3.70	77.5 ± 4.49	80.2 ± 2.97	79.2 ± 1.51	
Mean arterial pressure	92.25 ± 2.47	92.25 ± 3.25	92.45 ± 2.56	91.4 ± 2.46	>0.05

(mmHg)					
Heart rate (beats/min)	76.3 ± 2.18	70 ± 1.1	76.1 ± 2.13	70.2 ± 1.10	<0.001
Ocular perfusion pressure (mmHg)	34.75 ± 5.42	43.58 ± 2.98	36.56 ± 3.43	43.12 ± 1.76	<0.001

The detailed ocular blood flow parameters in CRA, OA and SPCA measurements are shown in **Tables 3 and 4**. The PSV/EDV increased and RI index decreased in CRA and SPCA after 12 weeks of drug instillation in both the Groups ($p<0.05$). The comparison in between the two Groups did not show statistically significant results. The change in the parameters of ophthalmic artery was not significant at the end of 12 weeks in both the Groups **(Table 5).**

Table 3: Ocular blood flow parameters in central retinal artery after 12 weeks from baseline in Group-1 & Group-2.

Parameters of Central retinal artery (CRA)	**Baseline (mean ± SD)**	**At 12 week**	**p-value**
Group-1 (n=20)			
Peak systolic velocity (cm/sec)	10.96 ± 2.05	11.15 ± 1.90	<0.001
End diastolic velocity (cm/sec)	2.16 ± 0.33	2.29 ± 0.50	<0.01
Resistivity index	0.79 ± 0.04	0.78 ± 0.04	<0.01
Group-2 (n=20)			
Peak systolic velocity (cm/sec)	9.85 ± 1.15	10.10 ± 1.14	<0.01
End diastolic velocity (cm/sec)	2.15 ± 0.38	2.23 ± 0.39	<0.01
Resistivity index	0.78 ± 0.05	0.77 ± 0.06	<0.01

Table 4: Ocular Blood flow parameters in ophthalmic artery after 12 weeks from baseline in Group-1 & Group-2.

Parameters in Ophthalmic Artery (OA)	**Baseline (mean ± SD)**	**At 12 week**	**p-value**
Group-1 (n=20)			
Peak systolic velocity (cm/sec)	31.4 ± 4.97	33.1 ± 9.59	0.13
End diastolic velocity (cm/sec)	9.1 ± 2.97	9.73 ± 4.52	0.09
Resistivity index	0.7 ± 0.09	0.7 ± 0.07	Nc
Group-2 (n=20)			
Peak systolic velocity (cm/sec)	31.05 ± 5.76	32.65 ± 9.6	0.07
End diastolic velocity (cm/sec)	8.84 ± 4.85	9.77 ± 5.66	0.18
Resistivity index	0.7 ± 0.10	0.7 ± 0.08	Nc

Table 5: Ocular Blood flow parameters in Short posterior ciliary artery after 12 weeks from baseline in Group-1 & Group-2.

Parameters of Short Posterior Ciliary Artery (SPCA)	**Baseline (mean ± SD)**	**At 12 week**	**p-value**
C1 (n=20)			
Peak systolic velocity (cm/sec)	12.3 ± 2.46	13.8 ± 2.15	<0.001
End diastolic velocity (cm/sec)	4.3 ± 0.70	5.1 ± 0.55	<0.001
Resistance index	0.63 ± 0.07	0.62 ± 0.08	<0.001
Group-2 (n=20)			
Peak systolic velocity (cm/sec)	11.57 ± 1.18	11.67 ± 1.39	<0.001
End diastolic velocity (cm/sec)	3.71 ± 0.69	3.99 ± 1.02	<0.001
Resistance index	0.68 ± 0.05	0.66 ± 0.08	<0.001

DISCUSSION

The management of glaucoma requires long term management and also necessitates the use of more than one medication due to insufficient reduction of IOP but multitherapy means more bottles & great complexity for the patient. Fixed Dose Combinations (FDCs) found increase acceptance due to their simplified drug regimen. A FDC should be either superior or equivalent to its free form on concomitant administration. In view of this, the objective of current study was to see the effect of 1% Brinzolamide /0.5% timolol fixed dose combination versus its free equivalent on concomitant administration in context of efficacy on IOP and ocular blood flow.

The reduction in IOP with both FDCs and free equivalent forms were significant at the end of 12

weeks and were comparable ($p>0.05$) signifying that combination therapy is efficacious in reducing IOP and thus decreasing the amount of preservative to ocular surface because of one bottle used by the patient. Thus reducing the adverse effect on ocular surface and also convenience of dosing schedule for the patient [12].

We found no significant change in mean arterial pressure ($p>0.05$) however ocular perfusion pressure in both the Groups was significantly increased ($p<0.001$) which has been seen in other studies too [13,14]. This fact can be attributed to reduction in IOP also as OPP is dependent on IOP. The compressing force exerted by IOP causes the vortex veins to behave as Starling resistors, i.e., maintaining an intraluminal pressure slightly higher than IOP to prevent them from collapsing. So sometimes this may lead to non-linear results in OPP especially at low IOP [15].

Ocular hemodynamics were assessed by a blinded examiner and it was found that within the Groups systolic, diastolic blood flow velocity significantly increased in CRA & SPCA. We can say that increase in velocity is mainly due to Brinzolamide as timolol has not being found to increase blood flow velocity [16,17]. The mechanism behind the increasing retrobulbar blood flow is mainly by vasodilation. Carbonic anhydrase catalyses carbon dioxide (CO2) hydration & inter conversion to carbonic acid (H_2CO_3) which freely dissociates into HCO3- & Protons. Blockade of carbonic anhydrase in local tissues may therefore increase tissue CO2 concentrations and lowers tissue pH resulting in vascular dilatation & increase blood flow [17]. It is also seen that as Brinzolamide is lipophilic in nature at physiological pH that favors the ability to move across the lipid membrane barriers. The additional increase in OBF parameters besides reducing IOP can improve the functional loss in glaucoma patients. Although this needs to be further evaluated and analysed to see whether the increase in OBF really translates into beneficial effects on patients' functional disability.

The conclusion was drawn that treatment with both Brinzolamide/Timolol-FDC & free equivalent forms of Brinzolamide + Timolol significantly reduced IOP throughout 12 weeks duration. When compared, IOP lowering efficacy was similar with both Groups. With regards to OBF parameters & OPP, both Groups showed similar effect. Increased blood flow parameters were seen in central retinal artery & short posterior ciliary artery from baseline at 12 weeks follow up. OPP was significantly increased in both Group1 & Group 2. Although the effect of increased blood flow parameters on functional improvements still needs to be assessed.

In terms of optimizing IOP control, providing better tolerability thus improving patients' compliance subsequently minimizing associated healthcare costs, FDCs like 1% Brinzolamide/0.5% timolol becomes an important component of glaucoma management & can be used as a better alternative to their free equivalents.

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