A Comparative Study on Fixed Dose Combination of Brimonidine 0.2% and Timolol 0.5% vs. Monotherapy Brimonidine or Timolol in Patients with Primary Open Angle Glaucoma

Ashapurna Borgohain[1], Soumyadeep Majumdar[2], Soumya Swarup Chatterjee[3]

[1]Postgraduate Trainee, Department of Ophthalmology, Regional Institute of Ophthalmology, Medical College, Kolkata, West Bengal. [2]Assistant Professor, Department of Ophthalmology, Diamond Harbour Government Medical College and Hospital, Diamond Harbour, West Bengal. [3]Professor and Head, Department of Ophthalmology, Murshidabad Medical College, Murshidabad, West Bengal.

ABSTRACT

BACKGROUND

Glaucoma is the leading cause of irreversible blindness in India with around 12 million being affected. Primary Open Angle Glaucoma accounts for majority of these patients. With the choice of drugs to reduce intraocular pressure being plenty, confusion persists on which therapy is best for the patients. Our study aims to compare the efficacy of Fixed-Dose Combination of Brimonidine 0.2% and Timolol 0.5% vs. Monotherapy Brimonidine or Timolol with respect to lowering of intraocular pressure and also its effect on vertical cup disc ratio, mean deviation in automated perimetry, retinal nerve fibre layer thickness and their side effect profile.

METHODS

This is a prospective, parallel group, open label, randomized intervention trial conducted over 16 months among 180 patients with primary open angle glaucoma attending the glaucoma clinic of the Regional Institute of Ophthalmology, Kolkata. The patients were randomized into three groups 1) Brimonidine 0.2% and Timolol 0.5% fixed-dose combination, twice daily 2) Brimonidine monotherapy, thrice daily and 3) Timolol monotherapy, twice daily and followed up at 1, 3 and 6 months.

RESULTS

The mean reduction in intra ocular pressure was higher in the fixed-dose combination group (mean reduction - 9.3 ± 2.9) compared to the other two groups (mean change in Timolol group - 5.0 ± 2.0 and mean change in Brimonidine group - 4.5 ± 1.8) at 6 months follow up. The mean loss of retinal nerve fibre layer thickness was significant in the timolol group but not in the other two groups at 6 months. The changes in mean deviation from baseline to 6 months in Humphrey field analysis was not statistically significant in any of the groups. There was statistically significant progression of vertical cup disc ratio from baseline to 6 months in the timolol and brimonidine monotherapy groups.

CONCLUSIONS

Fixed-Dose Combination of Brimonidine and Timolol had superior efficacy in intraocular pressure reduction in patients with primary open angle glaucoma compared to the monotherapy with brimonidine or timolol. Fixed-Dose combination also decreased the progression of glaucoma compared to the other groups

KEYWORDS

Primary Open Angle Glaucoma, Brimonidine, Timolol

Corresponding Author:
Dr. Soumyadeep Majumdar,
Assistant Professor,
Department of Ophthalmology,
Diamond Harbour Government Medical College and Hospital,
Diamond Harbour, West Bengal.
E-mail: soumyanbmc@gmail.com

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BACKGROUND

Glaucoma is the leading cause of irreversible blindness with more than 60 million affected people worldwide and reaching 80 million by the year 2020.[1] In India, the estimated prevalence of glaucoma is 11.8 million and primary open angle glaucoma (POAG) compromises 6.48 million.[2] POAG results due to decrease in aqueous outflow facility due to increased resistance to aqueous outflow as a result of thickening and sclerosis of trabecular meshwork, narrowing of intertrabecular space and deposition of amorphous material in juxta canalicular space.[3] It is characterised by slowly progressive raised IOP, open appearing anterior chamber angle, characteristic optic disc cupping, and specific visual field defects.[4] Management of POAG is medical and surgical. The main goal is to preserve visual function by lowering intraocular pressure (IOP) to a level that is likely to prevent further optic nerve damage. With a wide variety of agents available with different mechanism of action, confusion persists as to which therapy is most efficacious in IOP reduction and stop progression of optic nerve damage and at the same time has less side effects and low cost which ensures patient compliance.

There are only very few studies comparing the efficacy of fixed dose combination therapy and monotherapy in management of POAG from Eastern India. The aim of our study was to compare the efficacy and safety of a Fixed-Dose Combination (FDC) of Brimonidine Tartrate (0.2%) and Timolol Maleate (0.5%) with either of the agents administered as monotherapy in patients of POAG.

Objectives

1. To compare the efficacy of fixed-dose combination of Brimonidine Tartrate (0.2%) and Timolol Maleate (0.5%) v/s monotherapy with Brimonidine or Timolol in lowering IOP in patients with primary open angle glaucoma.
2. To evaluate the effect of fixed-dose combination of Brimonidine Tartrate (0.2%) and Timolol Maleate (0.5%) v/s monotherapy Brimonidine or Timolol on vertical cup-disc ratio, mean deviation (MD) in (24-2) Automated Perimetry, retinal nerve fibre layer thickness (superotemporal and inferotemporal).
3. To assess the side effect profile of fixed-dose combination of Brimonidine Tartrate (0.2%) and Timolol Maleate (0.5%) v/s monotherapy with Brimonidine or Timolol in patients of primary open angle glaucoma.

METHODS

This was a Prospective, Parallel Group, Open Label, Randomized Intervention Trial held in the Regional Institute of Ophthalmology, Medical College, Kolkata for a duration of 16 months from January 2018 to April 2019. Sample size of the study was 180 which included 60 eyes in 60 patients in each of the three groups studied.

Inclusion Criteria

1. Newly diagnosed patients or those who had discontinued antiglaucoma drugs for more than 4 weeks voluntarily
2. of either sex
3. age more than 40 years
4. diagnosed as unilateral primary open angle glaucoma with IOP of ≥22 mmHg with open anterior chamber angle, characteristic optic disc cupping and /or visual field loss,
5. Snellen's visual acuity of 6/60 or better

Exclusion Criteria

1. Patients of angle closure glaucoma and secondary glaucoma.
2. Active ocular infection (including ocular herpes simples) and inflammation
3. Any abnormality preventing reliable applanation tonometry or examination of the ocular fundus.
4. Hypersensitivity to study medications.
5. Cardiopulmonary conditions that precluded safe administration of a topical beta-blocker.
6. Use of systemic medication that affect IOP.
7. Use of corticosteroids <30 days before screening.
8. Risk of visual field or visual acuity worsening as a consequence of participation in the study, if IOP is not controlled or there is progression with the particular group of drugs during the study.

Patients included in the study were randomized into three groups after taking an informed consent.

1. Fixed-Dose Combination (FDC) of Brimonidine Tartrate (0.2%) and Timolol Maleate (0.5%), one drop twice daily.
2. Monotherapy Brimonidine Tartrate (0.2%), one drop thrice daily.
3. Monotherapy Timolol Maleate (0.5%), one drop twice daily.

Study Tools

- Snellen's visual acuity chart
- Slit lamp biomicroscope and Volk + 78D double aspheric fundus viewing lens
- Goldman two mirror gonioscope
- Heine's Direct ophthalmoscope
- Appasamy Associates Indirect ophthalmoscope and Volk +20D indirect bio lens
- Goldman applanation tonometer
- Humphrey Field Analyzer (HFA)
- Spectral Domain OCT (HRA + OCT, SPECTRALIS)

Parameters Studied

- Best corrected Visual acuity (BCVA) with Snellen's chart converted to LogMAR
- Anterior segment evaluation:
  - Eyelid, conjunctiva, cornea, anterior chamber, iris, pupil and lens.
- Vertical cup disc ratio (VCDR)

- Intraocular pressure (IOP) (measured between 10-12 pm)
- Retinal nerve fibre layer thickness (RNFL) (superotemporal)
- Retinal nerve fibre layer thickness (RNFL) (inferotemporal)
- Visual field: Mean Deviation (MD)
- Gonioscopy as baseline parameter

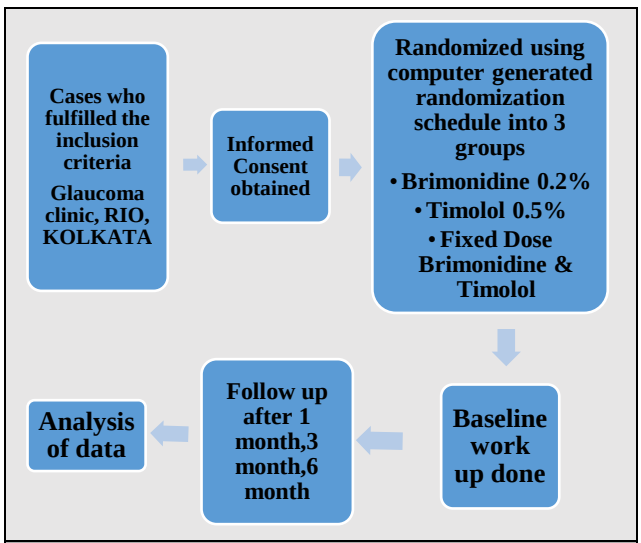

Figure 1. Study Protocol

Statistical Analysis was done using IBM IPSS version 25. A p value <0.05 was taken for statistical significance. Ethical clearance was taken from Institutional Ethics Committee, Medical College & Hospital, Kolkata prior to the study.

RESULTS

Baseline characteristics are summarized in Table 1. The mean age in the Brimonidine and Timolol FDC group, Timolol monotherapy and Brimonidine group were 52.65 ±7.75, 48.6±6.13 and 47.9 ±5.23 years respectively. Majority of the patients were females. Brimonidine Timolol FDC group the mean change of IOP from baseline to 1 month was 8.333 ±2.903 (p = <0.0001). However, the change from 1– 3 months and from 3 – 6 months was 0.900 ±3.068 (p = 0.027) and 0.200± 2.596 (p = 0.553) respectively. In the timolol group the mean change of IOP baseline to 1 month was significant that is 5.000 ± 1.584 (p =<0.0001) while change from 1-3 months and 3-6 months was -0.200 ±1.675 and 0.300 ± 1.907 (p = 0.359) which was statistically not significant. While in the brimonidine group the mean IOP change from baseline to 1 month was significant, 3.767 (p=<0.0001) which increased to 4.467 ±1.89 at 6 months (p =<0.0001). But the mean change from 1-3 months was 0.867± 1.926(p =0.001) and -0.167±1.531 (p =0.403) respectively (figure 2). The mean changes in VCDR in Brimonidine Timolol FDC group from baseline to 1 month, 3 month, 6 months which was not significant with mean changes with p value as -0.0083±0.042 (p =0.133), -0.0100±0.044 (p= 0.083), -0.0117±0.049 (p =0.070) respectively. In the brimonidine group, the mean change of VCDR from baseline to 6 months was statistically significant -0.010±0.054 (p = 0.01). In the timolol group too there was a significant progression of VCDR from baseline to 6 months with mean change of -0.0200±0.0605 (p=0.013) (figure 3).

The mean visual acuity changes in Brimonidine Timolol FDC group at 1, 3, 6 months with p values are -0.00833±0.059 (p =0.279), -0.01667 ± 0.069 (p =0.067), -0.01833±0.091 (p =0.124) which are not statistically significant. Whereas in Timolol group the mean change from baseline to 1, 3 months is not significant -0.00167±0.092 (p =0.890), -0.02833 ±0.096 (p = 0.052) respectively but from baseline to 6 months is statistically significant -0.03667 ±0.113 (p=0.027). In the brimonidine group mean visual acuity change from baseline to 6 months is significant -0.02000±0.091 (p=0.027).

There was no statistically significant change in mean changes in Mean Deviation in HFA in the FDC group or the brimonidine group. However, in Timolol group, mean change from baseline to 6 months is significant 0.31783±1.608 (p value<0.0001). There was no statistically significant change in the superior-temporal or infero-temporal RNFL thickness in the FDC group and brimonidine group from baseline to 6 months. However, in the timolol group there was significant change of RNFL thickness from baseline to 6 months (superior-temporal RNFL = 1.783±1.342 µm, p <0.0001 & inferior temporal RNFL 1.350±3.995 µm, p =0.011).

Dry eye was seen in equal frequency (8.3%) in the timolol group and brimonidine timolol FDC group, whereas allergic keratoconjunctivitis was more common in the brimonidine group (8.3%). In the FDC group watering was more commonly encountered (6.6%) (Figure 4).

Variables	Brimonidine Timolol FDC	Timolol	Brimonidine
Age (years)	52.65 ±7.75	48.6±6.13	47.9 ±5.23
Gender- Males	45%	50%	46%
Visual Acuity (logMAR)	0.358 ±0.273	0.271±0.22	0.313±0.363
Intraocular Pressure (mm of Hg)	23.93±1.84	22.73±1.219	23.33±1.36
VCDR	0.675±0.09	0.663±0.08	0.69±0.07
MD-HFA (dB)	-6.77±3.36	-6.007±2.12	-5.35±1.78
ST-RNFL (µm)	81.10±17.1	84.92±13.755	85.08±8.02
IT-RNFL (µm)	82.18±18.8	82.17±10.542	83.03± 6.93

Table 1. Baseline Characteristics

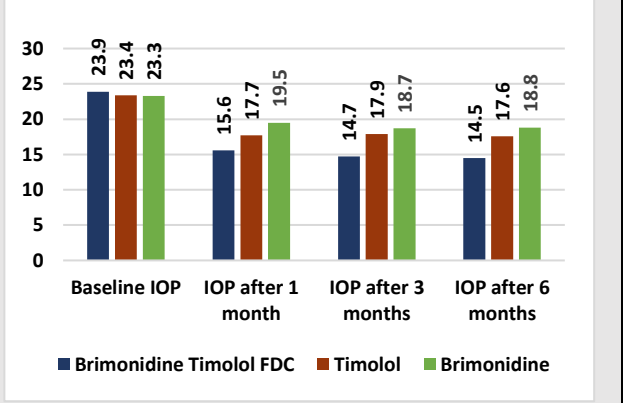

Figure 2. Mean Change in Intraocular Pressure in the Three Groups

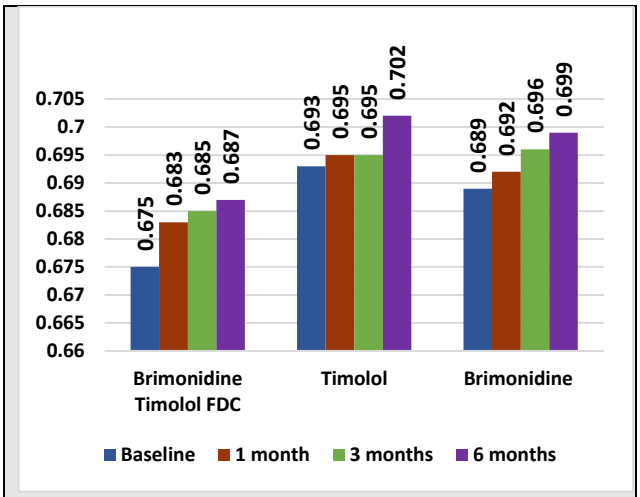

Figure 3. Mean Change in Vertical Cup Disc Ratio (VCDR) in the 3 Groups

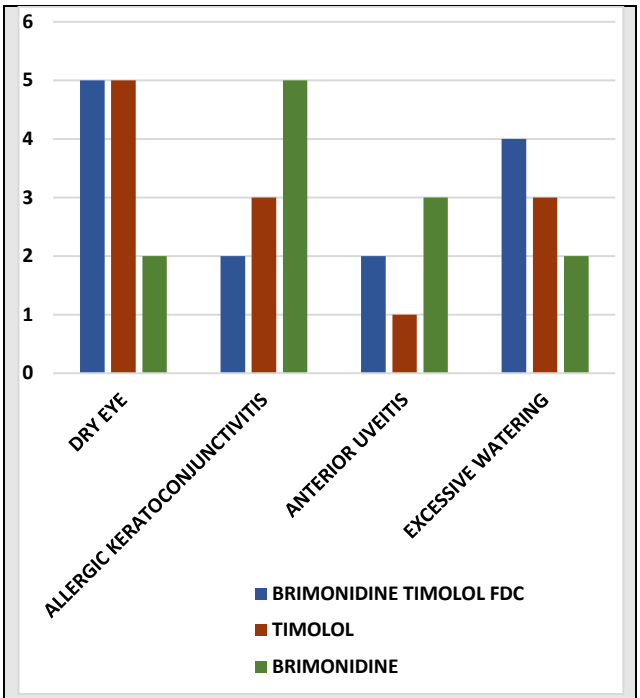

Figure 4. Side Effect Profile

DISCUSSION

In our study we found that the efficacy of Brimonidine 0.2%+ Timolol 0.5% FDC in lowering IOP is more compared to monotherapy with Brimonidine 0.2% or Timolol 0.5%. Tidake P et al studies of 100 eyes in 50 patients with POAG patients in Maharashtra and found that the mean age was 54.22±13.28. 54% were females. The mean IOP was 27.49±5.50 mmHg and mean cup disc ratio was 0.65±0.1.[5] Our baseline characteristics were similar to this study with respect to mean age, IOP and vertical cup disc ratio. Cho et al (2010) suggest that brimonidine/timolol FDC has beneficial IOP-lowering effects and significant effects on pupil size. After 6 months of treatment with the brimonidine/timolol fixed combination, the mean diurnal IOP in primary open-angle glaucoma (POAG) decreased from 21.4 ± 2.0 to 14.5 ± 3.1 mmHg (32.2%, P <0.001).[6]

Sherwood MB (2006) showed that the twice-daily fixed brimonidine-timolol therapy provides sustained IOP lowering superior to monotherapy with either thrice-daily brimonidine or twice-daily timolol and is better tolerated than brimonidine but less well tolerated than timolol.[7] The mean decrease from baseline IOP during 12-month follow-up was 4.4 to 7.6 mmHg with fixed brimonidine-timolol, 2.7 to 5.5 mmHg with brimonidine, and 3.9 to 6.2 mmHg with timolol. Mean IOP reductions were significantly greater with fixed brimonidine-timolol compared with timolol at all measurements (P ≤.002). The incidence of treatment-related adverse events in the fixed-combination group was lower than that in the brimonidine group (P = .006) but higher than that in the timolol group (P<.001).[7]

Joshi et al (2013) conducted a study to compare the efficacy and safety of fixed combination of brimonidine and timolol with individual components used as monotherapy in patients of primary open angle glaucoma.[8] The mean reduction in intraocular pressure in brimonidine, timolol, and brimonidine-timolol group were 4.29 ± 1.97 mmHg, 4.34 ± 1.21 mmHg, and 5.54 ± 1.87 mmHg respectively at 2 weeks and 4.86 ± 1.16 mmHg, 5.42 ± 1.50 mmHg, and 7.36 ± 2.58 mmHg respectively at 6 weeks. When values of mean reduction in intraocular pressure were compared between brimonidine-timolol fixed combination with brimonidine and timolol, it was found to be statistically significant (P <0.05) at 2 weeks and highly significant (0.001) at 6 weeks. In our study, the mean reduction of IOP was similar to the previously mentioned studies with greater reduction in the Brimonidine Timolol FDC group compared to the monotherapy with brimonidine or timolol from baseline to 6 months.

In the present study, we found that mean changes in VCDR and visual acuity in brimonidine timolol FDC group and brimonidine group from baseline to 1 month, 3 month, 6 months was not significant; however, significant changes were seen in the timolol group. Yavas et al found no significant change was seen in the visual field and optic disk morphology in any group.[9]

Smedowski et al (2017) evaluated the retinal nerve fibre layer (RNFL) thickness loss in primary open-angle glaucoma (POAG) patients treated topically with anti-glaucoma drops containing brimonidine and timolol combination or solely timolol.[10] Mean annual loss of RNFL thickness in the overall study group treated with timolol monotherapy was 1.8 ± 1.5 µm, while in group treated with brimonidine + timolol combination therapy it was 1.7 ± 1.5 µm (p >0.05). No significant differences were observed for the visual field mean deviation.[10] In our study, the mean loss of superior temporal RNFL was significant in the timolol group from baseline to 3 and 6 months which was 1.467±1.282 µm (p <0.0001), 1.783±1.342 µm (p <0.0001) respectively while in the brimonidine group and brimonidine timolol FDC group the loss was not statistically significant. The mean loss of inferior temporal RNFL in timolol group from baseline to 6 month was 1.350±3.995 (p =0.011) which is statistically

significant while it was not in the Brimonidine and Brimonidine timolol group. The changes in mean deviation from baseline to 6 months in Humphrey field analysis was not statistically significant in any of the groups.

With respect to side effects our study found that dry eye was seen in equal frequency in the timolol 0.5% and brimonidine timolol FDC group, whereas allergic keratoconjunctivitis was more common in the brimonidine 0.2% group. In the Brimonidine timolol FDC group watering was more commonly encountered. Joshi et al who found that the overall frequency of adverse effects was similar in all three groups.[8]

Limitations

- The small sample size.
- Short follow up period.
- Observer variations in measuring IOP.
- Diurnal variation of IOP.
- Un-monitored administration of drugs by patients at home.

CONCLUSIONS

Fixed Dose combination of Brimonidine + Timolol has a superior efficacy in reduction in intraocular pressure and preventing progression of glaucoma compared to monotherapy with Brimonidine or Timolol.

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