e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2024; 14(6); 60-65

Original Research Article

Comparison of Monotherapy Timolol with Fixed Dose Combination Brimonidine-Timolol in Primary Open Angle Glaucoma

Urvashi C. Davawala[1*], Anil P. Singh[2], Dharmesh P. Pandavadara[3], Kamalsinh R. Dodiya[4]

[1]Senior Resident, Department of Pharmacology, PDU Medical College and Hospital, Rajkot
[2]Head of the Department, Department of Pharmacology, PDU Medical College and Hospital, Rajkot
[3]Senior Resident, Department of Ophthalmology, PDU Medical College and Hospital, Rajkot
[4]Head of the Department, Department of Ophthalmology, PDU Medical College and Hospital, Rajkot

Received: 18-03-2024 / Revised: 21-04-2024 / Accepted: 26-05-2024
Corresponding author: Dr. Urvashi C. Davawala
Conflict of interest: Nil

Abstract:

Background: Glaucoma is the leading cause of irreversible blindness worldwide. It is estimated that around 80 million people have glaucoma worldwide. Primary open-angle glaucoma (POAG) is a bilateral, symmetrical disease, has adult onset. Ocular examination shows an open anterior chamber angle, glaucomatous optic disc changes, visual field defect and an intraocular pressure of >21 mmHg. Reduction of raised IOP is important to protect against visual field loss in patients with open-angle glaucoma. Topical antiglaucoma drugs which reduced elevated IOP are miotics, adrenergic agonists, b-blockers, carbonic anhydrase inhibitors and prostaglandins.

Aims and Objectives: This study was conducted to compare and evaluate effectiveness, safety and compliance of monotherapy 0.5% Timolol with fixed dose combination of 0.15% Brimonidine and 0.5% Timolol in newly diagnosed patients of POAG.

Methods: This was a prospective, observational study conducted in Ophthalmology department of PDU medical college and hospital, Rajkot. 60 patients enrolled into study. 30 patients (54 eyes) were in Timolol group and other 30 patients (50 eyes) were in Brimonidine-Timolol fixed dose combination (BT FDC) group. Data was collected at baseline, 2 weeks, 6 weeks and 10 weeks.

Result: There was significant lowering ($p<0.0001$) in mean IOP at 2, 6 and 10 weeks compare to baseline in both treatment groups. But there was more significant reduction ($p<0.0001$) in IOP in BT FDC group compared to Timolol group. Like, at 10th weeks, mean IOP reduction in Timolol group was 13.5 mmHg (48.15%) and in BT FDC group was 17.82 mmHg (54%) which was significantly more ($p<0.0001$).

Conclusion: There is faster and greater reduction of IOP with FDC Brimonidine-Timolol than monotherapy Timolol in POAG.

Keywords: Primary open angle glaucoma, Timolol, Brimonidine, FDC, Monotherapy.

Introduction

Glaucoma is defined as a disturbance of the structural or functional integrity of the optic nerve that can usually be arrested or diminished by adequate lowering of IOP.[1] Glaucoma is the leading cause of irreversible blindness worldwide.[2] It is estimated that around 80 million people have glaucoma worldwide.[3] Among Indians adults aged 40 years and above, prevalence of glaucoma is between 2.7 and 4.3%.[4]

Glaucomas are mainly divide into Primary adult glaucoma which consists of two separate conditions—open-angle and angle-closure glaucoma, Secondary glaucomas due to a specific anomaly or disease of the eye, and Congenital or developmental glaucomas.[5] Primary open-angle glaucoma (POAG) is a bilateral, symmetrical disease, has adult onset. Ocular examination shows an open anterior chamber angle, glaucomatous optic disc changes, visual field defect and an intraocular pressure of >21 mmHg.[5] Raised intraocular pressure in POAG lead to an increased resistance to the outflow of aqueous at the trabecular meshwork.[5]

Treatment options available are medicines, laser or surgery. They mainly use to lower raised IOP.[5] Topical antiglaucoma drugs available are miotics, adrenergic agonists, b-blockers, carbonic anhydrase

inhibitors and prostaglandins.[6] Pharmacotherapy usually begins with a single topical agent.

Patients on monotherapy frequently require additional agents to achieve adequate IOP control.[7] Timolol is a nonselective β-blocker, reduce IOP by decreasing aqueous humour synthesis. Brimonidine is an α-agonist and, reduce IOP by decreasing aqueous humour synthesis and increases uveoscleral outflow.[6]

Topical Timolol have been the first line of drugs till recently. Several fixed dose combinations of commonly used IOP lowering medications have been developed and available in the market worldwide.[8] This study was conducted to compare and evaluate effectiveness, safety and compliance of monotherapy 0.5% Timolol with fixed dose combination of 0.15% Brimonidine and 0.5% Timolol in newly diagnosed patients of POAG.

Materials and Methods

This is a single centre, prospective, observational, comparative study conducted in Ophthalmology department of PDU Medical College and Hospital, Rajkot. The study was started after approval from institutional ethics committee (Approval number - PDUMCR/IEC/26/2021). Total study duration was 15 months.

Sample size was calculated according to formula, = $\frac{(Z\alpha+\beta)^2*2*SD^2}{(mean\ difference)^2}$

Here Zα at 95% confidence interval= 1.96, β= 0.84, SD = 2.16 and mean difference= 1.7. So, with 20% dropout 30 patients in Timolol monotherapy group and 30 patients in Brimonidine-Timolol fixed dose combination group (BT FDC) included in the study.

Inclusion Criteria: Newly diagnosed POAG patients; diagnosed as unilateral/bilateral POAG (If bilateral POAG with same aetiology in both eyes, both eyes included in the study); POAG with IOP of >22mmHg with open anterior chamber angle, characteristic optic disc cupping and /or visual field loss and Snellen's visual acuity of 6/60 or better.

Exclusion Criteria: Patients of angle closure glaucoma and secondary glaucoma; active ocular infection and inflammation; hypersensitivity to study medications; cardiopulmonary conditions like bradycardia, asthma, COPD, cardiac failure etc in which B blockers are not use safely; use of systemic medication like oral steroids, tetracycline, quinine etc that affect IOP.

Methodology

The patients were provided the patient information sheet and written informed consent was taken before enrolling all patients for the study. Newly diagnosed POAG patients included according to inclusion criteria. Patients was reviewed for their follow up visit 2 weeks, 6 weeks, 10 weeks after initiation of therapy for POAG.

Data was recorded like demographic details, intraocular pressure (IOP), and visual acuity, Cup/Disc ratio (CDR) at baseline and follow-up visits. Effectiveness of drugs checked by reduction in intraocular pressure from baseline, change in CDR from baseline in subsequent follow up. For safety, participants were asked for any side effects such as burning, itching, dry eye etc after instillation of Timolol and BT FDC eye drops.

Compliance to the treatment was checked by using standardized questionnaire (e.g., number of doses missed, dose is taken at correct time not, etc.) and direct observation. Statistical analysis was done through the statistical software Graph Pad Prism 9.4.1 (681). Within group analysis done by paired t test. For comparison of two treatment group unpaired t test was used. All the statistical tests were interpreted at 5% significance level.

Result

60 patients enrolled into study. 37 patients were male and 23 patients were female. Mean (range) age of the patients was 58.51 (34-75). Out of 60, 30 patients were in Timolol group and other 30 patients were in Brimonidine-Timolol fixed dose combination group (BT FDC). In patients whom both eyes were involved, both were taken as two independent sample. So, in Timolol group 6 patients had unilateral glaucoma and 24 patients had bilateral glaucoma so total sample size was 54 eyes.

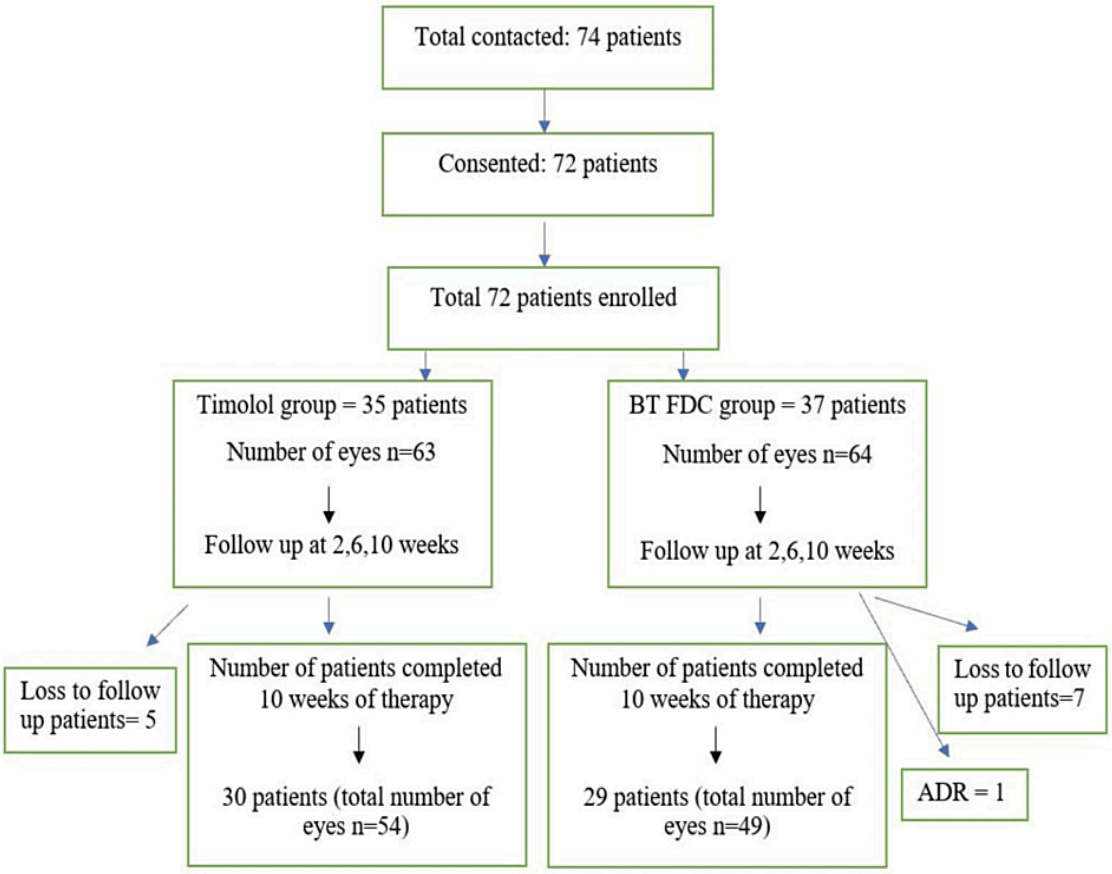
In BT FDC group 10 patients had unilateral glaucoma and 20 patients had bilateral glaucoma so total sample size was 50 eyes as can be seen in Flowchart 1. Follow up done at 2, 6, 10 weeks for each patient. Mean IOP at baseline and follow up visits were shown in Table 2. Within group comparison by paired t test shows both Timolol and BT FDC were effective in lowering mean IOP from baseline at 2,6 and 10 weeks. Mean IOP reduction at 2,6 and 10 weeks was significantly more (unpaired t test, $p<0.0001$) in BT FDC group as compared with Timolol group as shown in Table 3. Like, at 10^{th} weeks, mean IOP reduction in Timolol group was 13.5 mmHg (48.15%) and in BT FDC group was 17.82 mmHg (54%) which was significantly more ($p<0.0001$).

In both groups mean changes from baseline CDR values showed no significant differences $p > 0.05$ as shown in Table 4.There were no any serious side-effects observed in this study. Only two adverse drug reactions were observed during study period up to 10 weeks of drug administration. One patient in Timolol group complained of dryness of eye at 2 weeks of follow up and it was probably

associated with Timolol, as per the WHO causality assessment scale.

One patient in BT FDC group had severe itching and burning in eye at 6 weeks of follow up and it was possibly associated with Brimonidine-Timolol FDC, as per the WHO causality assessment scale. So, Ophthalmologist advised to stop BT FDC. This patient's data until stoppage of BT FDC were included in analysis. Both reactions were non-serious. Both reactions were mild according to Hartwing Scale. Both reactions were definitely preventable according to Modified Schumock and Thornton scale.

Overall compliance of the patients was good. Compliance in Timolol group was 73.33% and in BT FDC was 76.66%. This difference was not statistically significant ($p>0.05$) Reason for non-compliance were forgetfulness in most of the patients. Other reasons were difficulty in instillation of eye drops and run out of drops. Though there is no significant difference in both the group among compliant and non-compliant patients in mean IOP reduction from baseline ($p>0.05$).



Flowchart 1: Recruitment of patients

Table 1: Patient demographics and baseline characteristics

Male: Female	37:23	
Age, mean, (range), years	58.51 (34-75)	
Age groups 31-40 41-50 51-60 61-70 71-80	No. of patients 3 13 17 21 6	
Baseline values:	Timolol	FDC BT
IOP mean ± SD, mmHg	28.04 ± 2.27	33 ± 5.15
CDR mean ± SD	0.54 ± 0.13	0.49 ± 0.12

Table 2: Within group comparison of baseline mean IOP with 2,6 and 10 weeks values

Study visit	IOP mean ± SD, mmHg	
	Timolol	BT FDC
Baseline	28.04 ± 2.27	33 ± 5.15
2weeks	17.17±2.07*	18.74±3.87*
6weeks	15.80±1.86*	15.70±2.11*
10weeks	14.54 ± 2.09*	15.18 ± 2.02*

***P<0.0001 compared with baseline value within group paired t-test,**

Table 3: Comparison of both treatment groups on mean IOP reduction at 2, 6, and 10 weeks

Treatment groups	IOP reduction mean ± SD, mmHg		
	Baseline - 2week	Baseline - 6week	Baseline - 10week
Timolol	10.87 ± 2.51	12.24 ± 2.71	13.5 ± 3.29
BT FDC	14.26 ± 5.24	17.3 ± 5.08	17.82 ± 5.45
Unpaired T test P value	<0.0001	<0.0001	<0.0001

Table 4: Changes in CDR among study groups

Treatment groups	CDR mean ± SD		Paired t-test P Value
	CDR at baseline	CDR at10 weeks	
Timolol	0.54 ± 0.13	0.54 ± 0.13	1
BT FDC	0.49 ± 0.12	0.50 ± 0.13	0.32

Discussion

Reduction of raised IOP is important to protect visual field loss in patients with open-angle glaucoma.[9] In our study we compare the IOP lowering effect of monotherapy Timolol and FDC Brimonidine-Timolol.

Male: female ratio in our study was 1.6 and in other studies like Georgalas I. et al[10] 1.08, Mehani R. et al[11] 2.09, Chakraborty D. et al[12] 3.54. These studies showing more prevalence of POAG in male than in female but in Kumari A. et al[13] study M:F (0.88) more patients were in female group. In our study maximum number of POAG patients were in 51-60, 61-70 age group which were 17, 21 respectively. Maximum number of patients in Mehani R. et al[11] study were in 51-60 age group (n=25), 61-70 age group (n=17) and in Parameswaran R. et al[14] study 50-64 age group (n=21) which were near to our study. Mean(range) age of patients 58.51 (34-75) years in our study, 62.2 (46–72) years in Arici M. et al[15] study, 63.5 years (39 - 83) years in Georgalas I. et al[10] study. So, prevalence of POAG is more common in this age group.

In our study in Timolol group total number of eyes was 54 and in FDC-BT group total number of eyes were 50. Similarly other studies Ozer M. et al[16], Mishra D. et al[17], Jain K. et al[18], Kumari A. et al[13] and Parameswaran R. et al[14] also included both eyes in their study.

Effectiveness of drugs was evaluated by reduction in intraocular pressure from baseline, change in CDR from baseline in subsequent follow up. Clinician needs to reduced IOP up to 20%–30 % from the baseline IOP. With ≥ 0.8 CDR, old age and other risk factors, the target pressure should be lowered [19]. Till now no validated formula available for target IOP.[20] Long-term studies have shown that stabilization of POAG required to maintain IOP < 16–18 mmHg[5]

Both Timolol and BT FDC were effective in lowering IOP at 2,6 and 10 weeks from baseline as shown in Table 2. Both able to lower IOP within desired limits in 2weeks. But mean IOP reduction at 2,6 and 10 weeks in BT FDC group was significantly more ($p<0.0001$) as compared to Timolol group as shown in Table 3. There was fastest and greater reduction of IOP in BT FDC group compared to Timolol group. At 10 weeks, mean IOP reduction in BT FDC group was 17.82 mmHg (54%) and in Timolol group was 13.5 mmHg (48.15%). So, we found that Brimonidine-Timolol FDC was more effective in lowering IOP (Table 3). Previous studies shown that BT FDC [10,11,15,16] and Timolol monotherapy [17,21] significantly lowered IOP from baseline.

Previous similar studies [12,14,22,23] also showed higher efficacy of BT FDC in lowering IOP compared with timolol monotherapy. In Chakraborty D. et al[12] study, at 16 weeks mean IOP reduction in Timolol and BT FDC were 13.97 and 15.04 respectively. In our study mean IOP reduction in Timolol and BT FDC group was 13.5 and 17.82 respectively at 10 week which is near to Chakraborty D. et al study. A 12 months randomized study showed decrease in IOP from baseline was 7.6 mm Hg and 6.2 mm Hg with BT FDC and Timolol respectively.[24] Arici M. et al study showed that the mean IOP was significantly reduced by an average of 5.44 ± 1.98 mmHg

compared with baseline value with the use of Timolol and Brimonidine combination.[15] In our study, there were no significant changes in cup disk ratio in both the treatment group at 2, 6, 10 weeks follow up visit from baseline value ($P > 0.05$). Chakraborty D. et al[12], Goni F.[25] Studies also shown similar result.

Only two adverse drug reactions were observed during our study period of 10 weeks. One patient in Timolol group complained of dryness of eye at 2 weeks and one patient in BT FDC group had severe itching and burning in eye at 6 weeks. Most common side effects reported in other studies of Timolol [12-14,17,23] were hyperaemia, dryness, discomfort, stinging, burning and of BT FDC [12-14,16,23] were foreign body sensation, itching, burning, ocular pain, hyperaemia, stinging, dryness.

Compliance with therapy is a major issue affecting treatment success in chronic diseases, such as glaucoma.[25] Compliance with anti-glaucoma drugs is an important factor in the prevention of visual impairment.[26] There are no any specific and sensitive determinants to measure compliance accurately.[27] In our study, out of 60 patients total 15(25%) patients have poor compliance. 75% patients were 100% adherence to therapy. Though there was no significant difference in both the group among compliant and non-compliant patients in mean IOP reduction from baseline. In our study we observed that with 92% compliance IOP was maintained within desired range. In Kass M et al[27] study, compliance with timolol monotherapy was 78.6% and 86.1% with timolol and one or more other antiglaucoma medications. Forgetfulness is the most common reason for non - compliance in our study and Olthoff C et al study.[28]

Conclusion

In this study, both monotherapy Timolol and fixed dose combination Brimonidine-Timolol showed significant reduction of IOP at 2,6 and 10 weeks compared to baseline value. There was more significant reduction of IOP with fixed dose combination Brimonidine-Timolol compared to monotherapy Timolol at 2, 6, 10 weeks. So, based on our study, it is concluded that there is faster and greater reduction of IOP with fixed dose combination Brimonidine-Timolol than monotherapy Timolol in primary open angle glaucoma.

Limitations of study

Follow up period is short (10weeks), so assessment of long-term effects on maintenance of IOP and side effects of drugs prescribed will require further evaluation. Drugs were prescribed according to baseline IOP, optic nerve damaged and visual field defect. Patients with greater IOP and greater optic nerve damage were prescribed fixed drug dose combination of Brimonidine-Timolol. Compliance was checked by questionnaire so patient might forget history of missed doses.

References

1. Robert S, Becker B. Introduction and classification of the glaucomas. In: Stamper R, Lieberman M, Drake M, editors. Becker-Shaffer's diagnosis and therapy of the glaucomas. 8th ed. China: Elsevier; 2009; 1–7.
2. Allison K, Patel D, Alabi O. Epidemiology of Glaucoma: The Past, Present, and Predictions for the Future. Cureus. 2020; 12:1-9.
3. World glaucoma week. 2024. Accessed: 12 Feb. 2024: https://www.worldglaucoma week.org/what-is-glaucoma/
4. Rewri P. Towards better management of glaucoma in India. Indian J Ophthalmol. 2023 Mar; 71(3):686-688.
5. Parson J. Parsons Diseases of the Eye. 22nd ed. Sihota R, Tandon R, editors. Elsevier. Haryana: Elsevier; 2020;287–308.
6. Tripathi K. Antiadrenergic Drugs (Adrenergic Receptor Antagonists) and Drugs for Glaucoma. In: Tripathi M, editor. Essentials of Medical Pharmacology. 8th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2019; 153–73.
7. Frampton J. Topical Brimonidine 0.2% Timolol 0.5% Ophthalmic Solution In Glaucoma and Ocular Hypertension. Drugs Aging. 2006; 23:753-761.
8. Padala S, Sripada R, Gundabattula SBP, Tadi KJ, Nallamothula PR, Raveshi F, et al. A comparative study on the efficacy of brinzolamide/timolol versus brinzolamide/ brimonidine fixed drug combinations in primary open-angle glaucoma. Futur J Pharm Sci. 2020 Dec;6(38):1–7.
9. Webers CA, Beckers HJ, Nuijts RM, Schouten JS. Pharmacological management of primary open-angle glaucoma second-line options and beyond. Drugs Aging. 2008; 25:729-759.
10. Papaconstantinou D, Georgalas I, Kourtis N, Pitsas C, Karmiris E, Koutsandrea C, et al. Preliminary results following the use of a fixed combination of timolol-brimonidine in patients with ocular hypertension and primary open-angle glaucoma. Clin Ophthalmol [Internet]. 2009; 3:227–230.
11. Mehani R, Gupta S, Yadav MVK, Shukla SD. A comparative study on safety and efficacy of travoprost and brimonidine / timolol fixed combination in patients of primary open - angle glaucoma. Int J Basic Clin Pharmacol. 2015;4(5):976–80.
12. Chakraborty D, Bagchi C, Tripathi S. A comparative study of timolol plus either brimonidine (0.2%) or dorzolamide (2%) or

latanoprost (0.005%) dual therapy in suboptimal responde1. Chakraborty D, Bagchi C, Tripathi S. A comparative study of timolol plus either brimonidine (0.2%) or dorzolami. Natl J Physiol Pharm Pharmacol. 2022; 12(3): 336–42.
13. Kumari A, Jha AK. Timolol Maleate V / s Timolol Maleate with Brimonidine in the management of open-angle glaucoma patients with moderate intraocular pressure. J Cardiovasc Dis Res. 2021;12(04):1620–6.
14. Parameswaran R, Satyanarayana V, Nithisha T. Comparative study between timolol maleate and timolol - brimonidine combination in treatment of open-angle glaucoma of moderate intraocular pressure in a tertiary care hospital. Indian J Pharm Pharmacol. 2021; 8:151-155.
15. Arici MK, Sayici M, Toker MI, Erdoğan H, Topalkara A. A short-term study of the additive effect of timolol and brimonidine on intraocular pressure. Eye. 2002; 16:39–43.
16. Ozer MA, Acar M, Yildirim C. Intraocular pressure-lowering effects of commonly used fixed combination drugs with timolol in the management of primary open angle glaucoma. Int J Ophthalmol. 2014; 7:832–6.
17. Mishra D, Sinha B, Kumar M. Comparing the efficacy of latanoprost (0.005%), bimatoprost (0.03%), travoprost (0.004%), and timolol (0.5%) in the treatment of primary open angle glaucoma. Korean J Ophthalmol. 2014 Oct 1;28(5):399–407.
18. Jain K, Rastogi P S, Chander A, Ansari M. A comparative study of topical fixed dose combination of brimonidine (0.2%) plus brinzolamide (1%) versus brimonidine (0.2%) plus timolol (0.5%) in patients of primary open angle glaucoma. Indian J Clin Exp Ophthalmol. 2021; 7:112-117.
19. Robert S, Becker B. Primary open angle glaucoma. In: Stamper R, Lieberman M, Drake M, editors. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas. 8th ed. China: Elsevier; 2009; 239–65.
20. Weinreb R. World glaucoma association (WGA) consensus statements: 2004–2007. In: Stamper R, editor. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas. 8th ed. China: Elsevier; 2009; 553–60.
21. Kumar M, Sree Devi KV SDV. A Comparative study between Timolol and Timolol in combination with newer anti glaucoma drugs in the treatment of POAG. Int J Sci [Internet]. 2015;4(4):944–6. Available from: https://www.ijsr.net
22. Joshi SR, Akat PB, Ramanand JB, Ramanand SJ, Karande VB, Jain SS. Evaluation of brimonidine-timolol fixed combination in patients of primary open - angle glaucoma. Indian J Ophthalmol. 2013; 61:765-767.
23. 23. Craven ER, Walters TR, Williams R, Chou C, Cheetham JK, Schiffman R; Combigan Study Group. Brimonidine and timolol fixed-combination therapy versus monotherapy: A 3-month randomized trial in patients with glaucoma or ocular hypertension. J Ocul Pharmacol Ther. 2005; 21:337-348.
24. Sherwood MB, Craven ER, Chou C, Dubiner HB, Batoosingh AL, Schiffman RM, Whitcup SM. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: A 12-month randomized trial. Arch Ophthalmol. 2006; 124:1230-1238.
25. Goni F. 12-week study comparing the fixed combination of brimonidine and timolol with concomitant use of the individual components in patients with glaucoma and ocular hypertension. Eur J Ophthalmol. 2005;15(5):581–90.
26. Zimmerman TJ, Zalta AH. Facilitating patient compliance in glaucoma therapy. Surv Ophthalmol. 1983; 28:252–7.
27. Kass M, Gordon M, Morley R, Goldberg J. Compliance with Topical Timolol Treatment. Am J Ophthalmol. 1987;103(2):188–93.
28. Olthoff C, Schouten J, Van De Borne B, Webers C. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension: An evidence-based review. Am Acad Ophthalmol. 2005;112:953–61.