ISSN 3006-2543 (Online)
ISSN 1990-3863 (Print)

A
S
J
O

Al-Shifa
Journal of Ophthalmology

Vol. 19, No. 1, January – March 2023

QUARTERLY PUBLISHED

Logo

- **Editorial: Artificial Intelligence and Glaucoma**
- **Asynchronous Learning and Cognitive Performance**
- **Posterior Subcapsular Opacification After Cataract Surgery**
- **Pediatric Ocular Trauma**
- **Combination Drugs Efficacy in Primary Open Angle Glaucoma**
- **Retinopathy of Prematurity**

Abstracts available at https://www.asjoalshifaeye.org and http://www.pakmedinet.com/ASJO
Manuscript submission through online platform ejmanager.com

Indexed in Index Medicus -EMR

Recognized by Pakistan Medical & Dental Council – IP/033

Al-Shifa Journal of Ophthalmology

Editorial inquiries should be addressed to Prof. Dr. Tayyab Afghani, Department of Orbit and Oculoplastics, Al-Shifa Trust Eye Hospital, Jhelum Road Rawalpindi, Pakistan.
Tel: 0092 51 5487821-25, Fax: 0092 51 5487827: Email:aqrcpio@yahoo.com ;
Website: www.asjoalshifaeye.org

To Study the Efficacy of Brinzolamide 1%/Brimonidine 0.2% (Fixed Combination) in Patients of Primary Open-Angle Glaucoma Who were Already on Treatment on Topical Drugs

Sidrah Riaz[1], Norin Iftikhar Bano[2], Muhammad Tariq Khan[1], Tariq Mehmood Qureshi[2], Umair Tariq Mirza[3], Amna Iftikhar Arshad[2]

Abstract:

Objective: To evaluate the IOP lowering efficacy of combination of Brinzolamide 1% and Brimonidine 0.2% in the treatment of primary open-angle glaucoma (POAG) who were already using one or more topical anti-glaucoma drops (AGT).

Methods: The Prospective therapeutic trial study was conducted at Al Ehsan Welfare Eye Hospital from 2019 to 2020. All patients with POAG with age above 40 years and insufficient IOP control, using either with one or two topical anti-glaucoma drugs (not combination) were enrolled in the study and were followed for 6 months regarding IOP control, after shifting patients on the combination of AGT drops. A detailed history was taken from all enrolled patients and clinical examination was performed. Applanation tonometry by Goldman applanation tonometer, gonioscopy and cup disc ratio were documented. Patients used topical combination eye drop (Brinzolamide 1% and Brimonidine 0.2%) used at 8am ± 30 minutes and 8pm ± 30 minutes (12 hourly) in both eyes. Follow-up was done at 1 week, 2 weeks, 4 weeks, 3 months and 6 months. Follow-up visits included IOP measurement and documentation of any side effects noted by patients. Mean IOP lowering and safety profile of BBFC at 6 months follow-up was noted. One sample t-test was performed to see the significance of results.

Results: IOP lowering effect of BBFC (brinzolamide and brimonidine fixed combination) was observed in all 31 patients from baseline IOP. The most common ocular adverse effect was conjunctival hyperemia followed by blurred vision.

Conclusion: Brinzolamide and brimonidine fixed combination, used twice daily, is safe with minimal side effects. It is effective treatment option for patients with POAG in whom IOP is not controlled with mono-therapy and in whom beta-blockers or prostaglandin analogues are contraindicated. *Al-Shifa Journal of Ophthalmology 2023; 19(1): 26-32.*

1. *Akhtar Saeed Medical and Dental College, Bahria Town, Lahore*
2. *Al Ehsan Eye Hospital, Lahore*
3. *Mohi Uddin Islamic Medical College, Mirpur, AJK*

Originally Received: 8 Feb 2023
Revised: 17 Feb 2023
Accepted: 28 Feb 2023

Correspondence to:
Sidrah Riaz
Akhtar Saeed Medical and Dental College, Lahore

Introduction:

Glaucoma as it is the leading cause of irreversible blindness globally. It is estimated that 57.5 million people are suffering from primary open angle glaucoma[1,2]. Glaucoma is a group of progressive optic neuropathies characterized by degeneration of retinal ganglion cells and retinal nerve fiber layer resulting in damage to the optic nerve head. The primary open-angle glaucoma (POAG) is the most common form of glaucoma [3]. Intraocular pressure (IOP) is only modifiable factor in glaucoma so reduction of the intraocular pressure is the only

proven treatment to treat the disease so all medical therapies are aimed at reducing IOP. Decrease in IOP in cases of POAG is offered to these patients to decrease progressive optic neuropathy. Treatment of glaucoma is started with topical mono-therapy but many patients require more than one anti-glaucoma topical drugs to achieve target IOP. The use of multiple drops is very cumbersome for the patients leading to non-compliance. Fixed-combination (FC) therapies combine two hypotensive agents in a single bottle thus helpful in increasing the compliance and decreasing the eye exposure to harmful preservatives. Carbonic anhydrase inhibitors / beta blockers fixed combination (FC) is available for topical use since a long time. They are useful but there is limitation for its use in patients with respiratory and cardiac problems.

In April 2013, the US Food and Drug Administration (FDA) approved a new fixed-combination topical anti- glaucoma medication containing brinzolamide 1% and brimonidine 0.2% (BBFC). Brinzolamide is a carbonic anhydrase inhibitor which decreases aqueous production and Brimonidine is an alpha 2-agonist which increases aqueous outflow so it has dual action.

Materials and Methods:

This was a prospective therapeutic trial conducted at Al Ehsan Welfare Eye Hospital, Lahore from September, 2019 to September, 2020. The combination drops were launched in August, 2019 in Pakistan. We aimed to conduct this study to see the efficacy and side effects of brinzolamide plus brimonidine combination in our patients at Al Ehsan WelfareEye Hospital, Lahore. The patients were enrolled in end of September, 2019 and continued follow up for next 6 months. According to the standard medical ethics data was collected from patients fulfilling the inclusion criteria. Adults aged >40 years with primary open angle glaucoma, who had insufficient IOP control with one or two IOP lowering topical medications were included in the study. Exclusion criteria was angle closure glaucoma, pediatric glaucoma, diabetic retinopathy, uveitis and patients who lost follow up before 6 months. Total 45 patients, adult males and females, who fulfilled inclusion criteria were enrolled and 14 patients lost follow up before 6 months. Thirty-one (31) patients completed follow up of 6 months. The patient's sociodemographic details like age and gender were noted. History of all Patients was taken and all underwent a thorough clinical examination including best corrected visual acuity, IOP by Goldmann applanation tonometer, slit lamp examination, (cornea, iris/anterior chamber, lens, eyelids), dilated fundus examination by 90D lens (vitreous, retina, macula, optic nerve including cup-to-disc ratio), and gonioscopy. Optical coherence tomography (OCT) and visual field were performed for confirmation of glaucoma and the extent of damage. Patients self-administered eye drops at 8a.m ±30 and 8p.m ±30 minutes (12 hourly) in both eyes during study visits. Follow up was planned at 3 weeks, 3 month and 6 months. Follow up visit included intraocular pressure IOP, cup to disc CD ratio measurements and documentation of any adverse drug reactions,allergic reactions or systemic side effects.

Results:

The total number of patients enrolled were 45 fulfilling inclusion criteria but only 31 completed 6 months follow up, 20 (64.52%) females and 11 (35.48%) males (Figure1: pie chart showing gender distribution). The mean age of patients was 56.78 years. The CD ratio was 0.7 or below in 16 (51.62%) patients and above 0.8 in remaining 15 (48.39%). The mean IOP at presentation was 24.81 mm in patient right eye and 23.96mm in their left eye. The mean IOP measured at end of 6 months, while patient was using combination of Brinzolamide 1% and brimonidine 0.2%, was 13.78mm with standard deviation

10.14mm and14.26mm in left eye with standard deviation 9.50mm. Figure 2 shows the graphical presentation of IOP at presentation and at end of 6 months.

The ocular hyperemia was noted by 6 (18%) patients and 3 (9%) had complaint of blurred vision. Other known adverse effects like allergic conjunctivitis, irritation, dry mouth and somnolence were not seen in this study.

The t test reveals p value p <0.000 in IOP at presentation and at end of 6 months with 95% confidence interval that is highly significant. (Table 1)

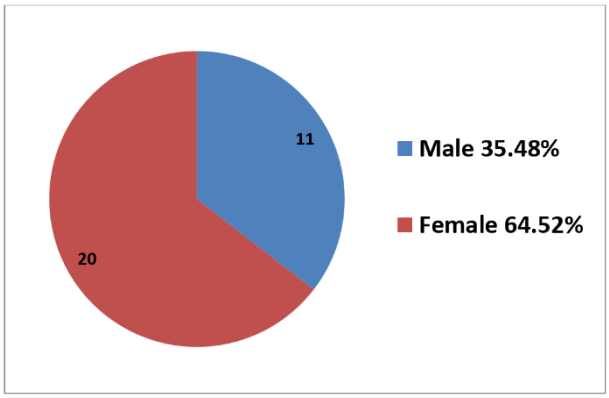

Fig - 1 Gender Distribution

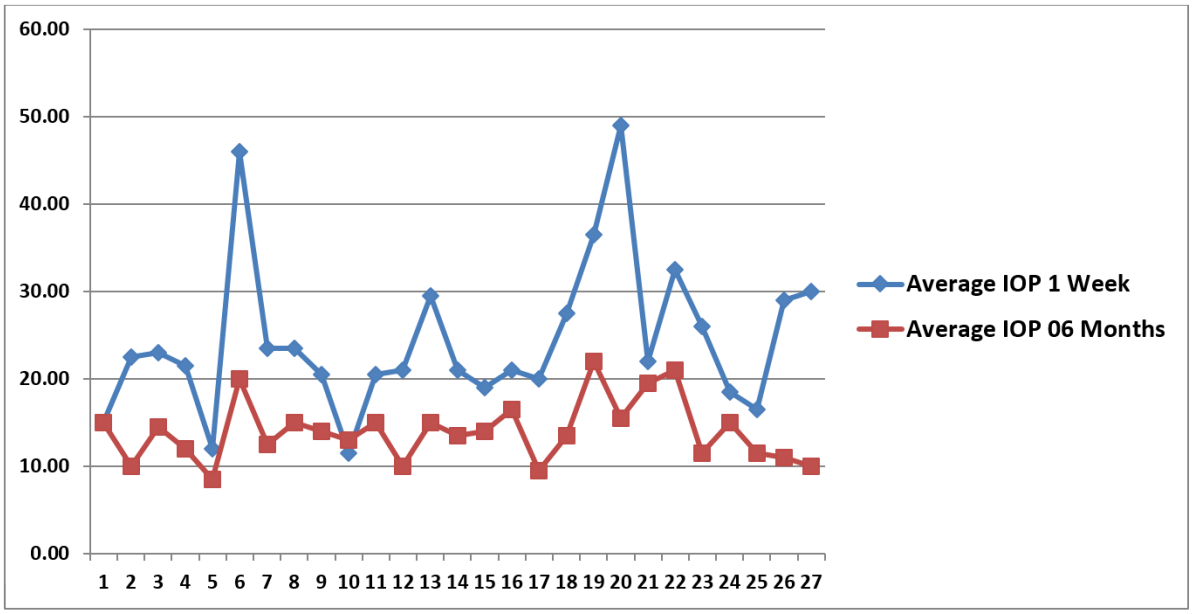

Fig – 2 IOP reduction at six months from initial

	T	Df	Sig (2tailed)	Mean difference	Lower	Upper
IOP at presentation	12.714	26	0.000	24.81481	20.8030	28.8266
IOP at end of 6 months	17.756	26	0.000	13.7778	12.1828	15.3728

Table – 1 One sample Test: 95% confidence interval of the difference

Discussion:

In open angle glaucoma usually mono-therapy is started as a first line treatment. The ocular hypertensive treatment study reported that at 5 years, about 40% of patients required two medications to achieve a 20% IOP reduction from baseline, while an additional 9% needed more than three medications [4-6,].

Each anti-glaucoma medication if used separately will expose the eye to large number of preservatives causing side-effects and eventually non-compliance. Secondly, using multiple drops is cumbersome for patients. In addition, exposure to preservatives of glaucoma drops may lead to conjunctival congestion and ocular surface damage. Therefore, fixed combinations are preferred because of their relative cost and low side effects profile [7].

In April 2013, the US Food and Drug Administration (FDA) approved a new fixed-combination anti-glaucoma containing brinzolamide 1% and brimonidine 0.2% (BBFC). It is available as eye drops for patient use since August, 2019 in Pakistan.

The results of our study confirm the IOP lowering efficacy of BBFC and its safety profile in our patients over six months time period. The most common ocular adverse effects in our study were ocular hyperemia and blurred vision. Although other local side effects like corneal erosions, photophobia, and conjunctivitis mentioned in different studies [8,9] were not observed in our study. Systemic adverse effects like alter taste sensation, oral dryness, fatigue, somnolence and decreased alertness were also not observed in our patients[10-12].

The drops contain two active ingredients: a carbonic anhydrase inhibitor (brinzolamide) and α2-agonist (brimonidine). It exerts its IOP-lowering effect via two mechanisms. Brimonidine decreases aqueous production and brinzolamide decreases aqueous production along with increases aqueous trabecular outflow. The mechanism of action of these two drugs in lowering IOP complement each other. It is combination of two hypotensive anti glaucoma agents in a single bottle thus increasing the compliance and decreasing the total amount of eye exposure to deleterious preservatives of eye drops.

The combination is recommended in cases where beta blockers and prostaglandin analogues are contraindicated as they are reported to cause a number of side effects including conjunctival hyperemia, eyelash growth, hyper-pigmentationof the iris and periocular skin. Beta blockers are generally well tolerated but are contraindicated in patients with conditions, like heart block, asthma, bradycardia, chronic obstructive pulmonary disease and depression [13-18].

All of the studies present in the literature demonstrated mean diurnal IOP to be significantly lower in the patients group using brimonidine/brinzolamide as compared to control and non-inferior to that with the concomitant group using two separate bottles. A large, multi-center study demonstrated significantly superior 24-hour IOP-lowering efficacy of BBCF versus multiple topical anti glaucoma drops. There are many studies conducted in Turkey, Korea, China and UK showing effective role of BBCF[19-22].

To our knowledge, there is no published

study in Pakistan about efficacy of this combination drug as it is introduced here 4 years ago. A study conducted in Peshawar, Pakistan in 2015 has shown the effect of combination of Travoprost and Timolol, found to be effective in patients of POAG [23]. But these are not suitable for patients of heart block, respiratory distress, asthmatics and diabetics and combination of BBFC can be given to these safely.

Conclusion:

The combination of 1% Brinzolamide and 0.2% Brimonidine used twice daily is effective treatment for treatment of Primary open angle glaucoma. It is effective in lowering of intra ocular pressure (IOP) and well tolerated by patients. It is safe and effective treatment option for patients with POAG in whom IOP is not controlled with mono-therapy and in whom beta-blockers or prostaglandin analogues are contraindicated. The authors have not received any funding and no conflict of interest to be disclosed. The limitation of study is small sample size.

References:

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014 Nov;121(11):2081-90. doi: 10.1016/j.ophtha.2014.05.013.
2. Allison K, Patel D, Alabi O. Epidemiology of Glaucoma: The Past, Present, and Predictions for the Future. Cureus. 2020 Nov 24;12(11): e11686. doi: 10.7759/cureus.11686. PMID: 33391921.
3. Evangelho K, Mogilevskaya M, Losada-Barragan M, Vargas-Sanchez JK. Pathophysiology of primary open-angle glaucoma from a neuroinflammatory and neurotoxicity perspective: a review of the literature. Int Ophthalmol. 2019 Jan;39(1):259-271. doi: 10.1007/s10792-017-0795-9.
4. Zhang, N., Wang, J., Li, Y. et al. Prevalence of primary open angle glaucoma in the last 20 years: a meta-analysis and systematic review. Sci Rep 11, 13762 (2021). https://doi.org/10.1038/s41598-021-92971-w
5. Jain K, Rastogi PS, 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(1):112-117.
6. Aihara M, Adachi M, Matsuo H, Togano T, Fukuchi T, and NS. Additive effects and safety of fixed combination therapy with 1% brinzolamide and 0.5% timolol versus 1% dorzolamide and 0.5% timolol in prostaglandin-treated glaucoma patients. Acta Ophthalmol. 2017;95(8): e720–6. doi:10.1111/aos.13401.
7. Agarwal P, Tayal S, Gautum A. Comparative study to assess efficacy of safety of brinzolamide 1% and timolol 0.5% fixed combination eye drops versus dorzolamide 2%af timolol 0.5% fixed combination in management of open angle glaucoma. J Family Med Prim Care. 2022 May;11(5): 2167-2171.doi: 10.4103/jfmpc.jfmpc_1578_21.
8. Nguyen QH, McMenemy MG, Realini T, Whitson JT, Goode SM. Phase 3 Randomized 3-Month Trial with an Ongoing 3-Month Safety Extension of

Fixed-Combination Brinzolamide 1%/Brimonidine 0.2%. J Ocul Pharmacol Ther. 2013;29(3):290–7. doi:10.1089/jop.2012.0235.

9. Lo, Jonathan S et al. "Efficacy and tolerability of brinzolamide/brimonidine suspension and prostaglandin analogs in patients previously treated with dorzolamide/timolol solution and prostaglandin analogs." Clinical Ophthalmology (Auckland, N.Z.) 10 (2016): 583 - 586.
10. Anne J Lee & Peter McCluskey (2008) Fixed combination of topical brimonidine 0.2% and timolol 0.5% for glaucoma and uncontrolled intraocular pressure, Clinical Ophthalmology, 2:3, 545-555, DOI: 10.2147/opth.s3840
11. Kim, J. A.and H. Lee. Effectiveness and Safety Verification of Brinzolamide Combination Therapy on Primary Open-angle Glaucoma or Ocular Hypertension: A Systematic Review and Meta-analysis Study. The Korean College of Clinical Pharmacy, Sept. 2021, doi:10.24304/kjcp.2021.31.3.205.
12. Tekeli O, Köse HC. Evaluation of the Use of Brinzolamide-Brimonidine Fixed Combination in Maximum Medical Therapy. Turk J Ophthalmol 2022; 52:262-269. DOI: 10.4274/tjo.galenos.2021.25488
13. Kóthy P, Holló G. Real-life experience of using brinzolamide/brimonidine fixed drop combination in a tertiary glaucoma centre. Int Ophthalmol. 2020; 40:377-383.
14. . Wang N, Lu DW, Pan Y, Astakhov Y, Iureva T, Adewale A, Walker TM. Comparison of the Intraocular Pressure-Lowering Efficacy and Safety of the Brinzolamide/Brimonidine Fixed-Dose Combination versus Concomitant Use of Brinzolamide and Brimonidine for Management of Open-Angle Glaucoma or Ocular Hypertension. Clin Ophthalmol. 2020; 14:221-230.
15. Wy S, Kim YK, Jeoung JW, Park KH, Ha A. Comparison of Two Combinations of Maximum Medical Therapy for Lowering Intraocular Pressure in Primary Open-angle Glaucoma. Korean J Ophthalmol. 2020; 34:19-26.
16. Onoe H, Hirooka K, Nagayama M, Hirota A, Mochizuki H, Sagara T, Suzuki K, Okumichi H, Kiuchi Y. The Efficacy, Safety and Satisfaction Associated with Switching from Brinzolamide 1% and Brimonidine 0.1% to a Fixed Combination of Brinzolamide 1% and Brimonidine 0.1% in Glaucoma Patients. J Clin Med. 2021 Nov 10;10(22):5228. doi: 10.3390/jcm10225228.
17. Topouzis F., Goldberg I., Bell K., Tatham A.J., Ridolfi A., Hubatsch D., Nicolela M., Denis P., Lerner S.F. Brinzolamide/brimonidine fixed-dose combination bid as an adjunct to a prostaglandin analog for open-angle glaucoma/ocular hypertension. Eur. J. Ophthalmol. 2021; 31:103–111. doi: 10.1177/1120672119878044
18. Aoki R, Terao E, Dote S, Shiraishi M, Oogi S, Ueda K, Kimura Y, Nagata Y, Nakakura S. Efficacy and safety of a fixed combination of 1% brinzolamide and 0.1% brimonidine as treatment for glaucoma: a retrospective study focusing on the number of ingredients. BMJ Open Ophthalmol. 2022 Dec;7(1): e001200. doi: 10.1136/bmjophth-2022-001200.
19. Tekeli, O., & Köse, H. C. (2022). Evaluation of the Use of Brinzolamide-Brimonidine Fixed Combination in Maximum Medical Therapy. Turkish journal of ophthalmology, 52(4), 262–

269. https://doi.org/10.4274/tjo.galenos.2021.25488
20. Inoue K, Kunimatsu-Sanuki S, Ishida K, et al. Intraocular pressure-lowering effects and safety of brimonidine/brinzolamide fixed combination after switching from other medications. Jpn J Ophthalmol 2022; 66:440–6. 10.1007/s10384-022-00930-3
21. Kozobolis V, Panos GD, Konstantinidis A, et al. Comparison of dorzolamide/timolol vs brinzolamide/brimonidine fixed combination therapy in the management of primary open-angle glaucoma. Eur J Ophthalmol 2017; 27:160–3. 10.5301/ejo.5000826.
22. Ningli Wang, Da-Wen Lu, Yingzi Pan, Yury Astakhov, Tatyana Iureva, Adeniyi Adewale and Thomas M Walker, 'Comparison of the Intraocular Pressure-Lowering Efficacy and Safety of the Brinzolamide/Brimonidine Fixed-Dose Combination versus Concomitant Use of Brinzolamide and Brimonidine for Management of Open-Angle Glaucoma or Ocular Hypertension' Clinical Ophthalmology 2020:14 221–23.
23. Khan F, Rehman M, Ilyas O, Zeeshan T, Ahmad I. Comparison of intraocular pressure lowering effect of Travoprost and Timolol/Dorzolamide combination in primary open angle glaucoma. Pak J Ophthalmol 2015, vol. 31, no. 4, Oct-Dec, 2015.

Authors Contribution

Concept and Design: Norin Iftikhar Bano
Data Collection / Assembly: Muhammad Tariq Khan
Drafting: Dr. Tariq Mehmood Qureshi, Umair Tariq Mirza
Statistical expertise: Amna Iftikhar Arshad
Critical Revision: Sidrah Riaz