ORIGINAL ARTICLE

Triple-fixed Combination of Dorzolamide/Timolol/Brimonidine: Efficacy Study in Bolivian Population

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Abstract

Aim and background: To assess the efficacy of 2% dorzolamide/0.5% timolol/0.2% brimonidine tartrate fixed combination (DTB-FC) eye drops in patients with intermediate glaucoma stage.

Materials and methods: A retrospective case series study was performed, including eyes diagnosed with primary open-angle (POAG) or chronic angle-closure glaucoma (CACG), which were at intermediate stage of the illness according to the Brusini grading system and were initially treated with 2% dorzolamide/0.5% timolol fixed combination (DT-FC), and switched at baseline to DTB-FC. Main outcome was intraocular pressure (IOP) baseline measured, as well as at weeks 1 and 2, months 1, 3, and 6, and 1 year after switching. IOP differences were analyzed using analysis of variance (ANOVA) repeated measures.

Results: A total of 36 eyes from 22 patients were included in the study. The median age of the participants was 61 years [interquartile range (IQR) 53–71], with 59.1% ($n = 13$) being female. At baseline, 1, 2 weeks, 1, 3, 6 months, and 1 year after switching to DTB-FC, the mean IOP values were 20.3 (95% CI, 19.5–21.1), 15.3 (95% CI, 14.5–16.1), 15.5 (95% CI, 14.7–16.2), 15.5 (95% CI, 14.8–16.0), 15.5 (95% CI, 14.9–16.2), 15.5 (95% CI, 14.8–16.2) and 15.3 (95% CI, 14.7–15.9) mm Hg, respectively ($p > 0.001$). The mean IOP reduction after 1 year of treatment was −5.0 ± (4.2–5.8) mm Hg. Treatment success rates were 86.1, 80.6, 80.6, 77.8, 72.2, and 66.7%, respectively. When stratified by diagnosis, there were no statistically significant differences in the treatment success rates between POAG and CACG ($p > 0.05$).

Conclusion: Therapy switching from DT-FC to DTB-FC was shown to be effective in reducing IOP of eyes with POAG or CACG during 6–12 months.

Clinical significance: The DTB-FC therapy improved the therapeutic management of POAG or CACG previously treated with DT-FC therapy, which may be relevant to prevent its progression in the future.

Keywords: Antiglaucomatous, Brimonidine, Dorzolamide, Fixed combination, Timolol, Topical therapy.

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Introduction

Glaucoma is the second leading cause of blindness worldwide after cataracts affecting an estimated 76 million people worldwide[1,2] and is expected to reach 111.8 million people by 2040.[3] This condition encompasses a range of disorders marked by the gradual degeneration of retinal ganglion cells and their fibers, which results in the atrophy of the optic nerve and the cupping of the optic disc, accompanied by defects in the visual field. If not addressed promptly, the damage can cause irreversible vision loss.[4]

Elevated intraocular pressure (IOP) is one of the main risk factors associated with this illness. Several studies provide strong evidence that IOP plays an important role in the optic neuropathy of glaucoma. Furthermore, studies demonstrated that reducing IOP decreases the risk of visual field progression in primary open-angle glaucoma (POAG).[5]

Therefore, glaucoma management aims to reduce IOP levels to delay progressive damage of optic nerves and, consequently, the visual field.[5] A decrease from baseline IOP of 20–30% has been recommended by American Academy of Ophthalmology.[6] In order to achieve the target IOP, topical antiglaucomatous eye drops remain the most common initial approach. Prostaglandins such as latanoprost, bimatoprost, or travoprost are the first choice for glaucoma treatment due to their better IOP-lowering ability than other antiglaucomatous drugs and their safety profile. Due to the chronic and progressive nature of glaucoma, after 5 years of treatment, 40% of patients need at least two medications to achieve a significant reduction in IOP.[7] At this point, ophthalmologists need to associate drugs with different mechanisms of action to reach target IOP. 2% dorzolamide/0.5% timolol fixed combination (DT-FC) is one of the most widely used combinations worldwide. In regulatory clinical trials, DT-FC has been shown to reduce IOP by approximately 9 mm Hg (32.7%) at peak and 7.7 mm Hg (27%) at trough.[8] When the combination of two drugs is insufficient, a third drug can be added. Maximal medical therapy involves using three or more classes of antiglaucoma medications to achieve the greatest possible reduction in IOP.[9]

Currently, in several South American countries, triple-fixed combinations are commercially available. 2% dorzolamide/0.5%

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timolol/0.2% brimonidine tartrate (DTB-FC) is one of them. This therapeutical option combines a carbonic anhydrase inhibitor, a β-adrenergic blocking agent, and an α2-adrenergic agonist. The efficacy and safety of DTB-FC were previously evaluated, although clinical data is limited.[10,11] In those studies, the antiglaucomatous triple-fixed combination reduced IOP levels by 42.3% in naïve patients which represents an additional reduction of 13.9% from those treated with DT-FC.[10]

Polydrug regimens for glaucoma pose several important clinical challenges: worse medical treatment adherence, reduced efficacy through the wash-out of medication, and increased exposure to preservatives. All these aspects may be improved with the use of antiglaucomatous fixed combination eye drops.[12–14]

This study aims to assess the ocular hypotensive effectiveness of a newly available fixed combination ophthalmic solution containing 2.0% dorzolamide, 0.5% timolol and 0.2% brimonidine in a Bolivian population.

Materials and Methods

Study Design and Bioethics

A single-center open label retrospective study was designed. The Institutional Review Boards (IRB) of the Bolivian center evaluated the research protocol and considering that the confidentiality of the data of the participating patients was maintained and that the study design was observational, it was accepted without the need for any other type of evaluation or monitoring. The participating researchers carried out the present study in accordance with the Declaration of Helsinki and all the participating patients accepted through informed consent that their data would be used in a scientific study for academic purposes, safeguarding their confidentiality.

Study Population, Main Parameters, and Data Collection

A glaucoma specialist (JM) reviewed and included clinical records of patients with POAG or chronic angle-closure glaucoma (CACG), in an intermediate stage of the illness according to the Brusini grading stage (S2) who switched from the DT-FC to the dorzolamide/timolol/brimonidine fixed combination (DTB-FC). These patients were treated at Centro de Ojos del Norte in Santa Cruz, Bolivia, between September 2019 and March 2020. These patients had initially been treated with DT-FC but had uncontrolled IOP and subsequently switched to DTB-FC (Xegrex®, Lab. Poen, Argentina). Eligible patients were required to have complete medical records, including complete standard follow-up, and no history of previous drainage surgeries or valve implants. The standardized follow-up in this clinic for cases of glaucoma patients who make a switch in treatment is as follows: 1, 2 weeks, 1, 3, 6 months, and 1 year after switch. For each affected eye, the following data were collected: patient demographics (age and sex), type of glaucoma, IOP (mm Hg) at baseline (at the time of the medication switch), and during standardized follow-up for up to 1-year postswitch. Additionally, data from visual field assessments were reviewed to perform the baseline Brusini grade of each case. Visual field testing was conducted using a Humphrey field analyzer (HFA™3, Zeiss Inc.). IOP measurements were conducted following standard clinical practices using a calibrated Goldmann applanation tonometer (GAT) after applying topical anesthesia and fluorescein staining. Adverse events related to the study medication and any changes in medical or surgical treatments were documented for each eye under investigation.

Main Outcome Measures

The primary outcome was IOP achieved different time points: at baseline, 1 and 2 weeks, 1, 3, and 6 months, and 1 year of treatment with DTB-FC. Additionally, the IOP reduction over the time was assessed. Treatment failure was defined when IOP was higher than 20 mm Hg or surpassing the IOP target previously set by a glaucoma specialist. Both the intent-to-treat (ITT) population and the per-protocol (PP) population were included in the analysis.

Statistical Analysis

Statistics were performed using Statistical Package for the Social Sciences (SPSS) statistical software, version 21 (SPSS, IBM Inc). The IOP data were evaluated using repeated measures analysis of variance (ANOVA). For the ITT population, the last-observation-carried-forward (LOCF) method was applied. Categorical variables such as patient demographics and treatment success/failure rates were analyzed by the Chi-squared test or Fischer's exact test.

Results

The study included a total of 36 eyes from 22 patients with intermediate glaucoma who were treated with DTB-FC. Demographics for both ITT population ($n = 22$) and PP population ($n = 16$) are summarized in Table 1. No statistical differences were observed between both groups. In the ITT population, the median age was 61.0 years [with an interquartile range (IQR) of 53–71], and 59.1% of patients were female. Additionally, 59.1% of the patients were diagnosed with POAG. Among the eyes under analysis, 52.8% were left eyes, and 63.6% of the patients had bilateral disease.

Out of the 36 eyes in the study, 24 (66.7%) completed the 1-year follow-up with DTB-FC (PP). Specifically, 7 eyes (19.4%) were categorized as stage S2, 11 eyes (30.6%) as stage S3, 14 eyes (38.9%) as stage S4, and 4 eyes (11.1%) as stage S5.

A total of 12 eyes (33.3%) required additional pharmacological or surgical interventions to achieve IOP target. During follow-up period, only six (16.7%) eyes required the addition of a prostaglandin analog to complete pharmacological treatment. Notably, all the eyes requiring the addition of a prostaglandin were diagnosed with POAG. Furthermore, six eyes (16.7%) underwent glaucoma surgery for the control of IOP, including two eyes (5.6%) that received phacoemulsification with Kahook Dual Blade goniotomy, one eye (2.8%) underwent high-frequency deep sclerotomy, and three eyes (8.3%) underwent trabeculectomy. Only one adverse event

Table 1: Patients demographics and characteristics at baseline

Characteristic	*ITT (n = 22)*	*PP (n = 16)*
Age, median (IQR)	61.0 (53–71)	61.0 (53–71)
Gender, *n* (%)		
Female	13 (59.1)	9 (56.3)
Male	9 (40.9)	7 (43.8)
Diagnosis, *n* (%)		
POAG	13 (59.1)	8 (50.0)
CCAG	9 (40.9)	8 (50.0)
Bilateral disease, *n* (%)		
Yes	14 (63.6)	8 (50.0)
No	8 (36.4)	8 (50.0)

IQR, interquartile range

was reported: conjunctival hyperemia in three eyes (8.3%), two of which received selective laser trabeculoplasty (SLT).

The mean IOP values at baseline, 1, 2 weeks, 1, 3, 6 months, and 1 year were: 20.3 (95% CI, 19.5–21.1), 15.3 (95% CI, 14.5–16.1), 15.5 (95% CI, 14.7–16.2), 15.4 (95% CI, 14.8–16.0), 15.5 (95% CI, 14.9–16.2), 15.5 (95% CI, 14.9–16.2), and 15.3 (95% CI, 14.7–15.9) mm Hg, respectively ($p > 0.001$) for the PP population (Table 2 and Fig. 1). The analysis of the ITT population showed similar responses to the PP population (Table 2). Mean IOP values at baseline, 1, 2 weeks, 1, 3, 6 months, and 1 year were 21.1 (95% CI, 20.3–22.0), 16.2 (95% CI, 15.3–17.2), 16.7 (95% CI, 15.7–17.7), 16.9 (95% CI, 15.8–17.9), 16.8 (95% CI, 15.7–17.9), 16.9 (95% CI, 15.8–18.8), and 16.7 (95% CI, 15.6–17.8) mm Hg, respectively ($p > 0.001$).

The mean IOP reduction for the PP population after 1, 2 weeks, 1, 3, and 6 months, and 1 year of treatment from baseline were −5.0 (95% CI, −5.8 to −4.2), −4.8 (95% CI, −5.7 to −4.0), −4.8 (95% CI, −5.7 to −3.9), −4.8 (95% CI, −5.6 to −3.9), −4.8 (95% CI, −5.6 to −3.9), and −5.0 (95% CI, −5.8 to −4.2) mm Hg, respectively ($p < 0.001$) (Table 3). Similar results were observed in the ITT population (Table 3).

After 6 months of treatment, a 23.6% reduction in IOP was achieved with DTB-FC compared to baseline values obtained with DT-FC. After 1 year, a 24.6% reduction in IOP was achieved. The rate of treatment success of the DTB-FC treatment for the overall population after 6 months of treatment was 72.2% (26 eyes) and after 1 year it was 66.7% (24 eyes). No statistically significant differences were observed between the groups when stratified by diagnosis throughout the study period ($p > 0.05$) (Table 4).

Discussion

Glaucoma is a chronic and irreversible eye disease that stands as a global health challenge, especially in developing countries. Patients in these regions often face a higher incidence, more

Table 2: Comparison of the mean intraocular pressure at each assessment visit in the PP and ITT population

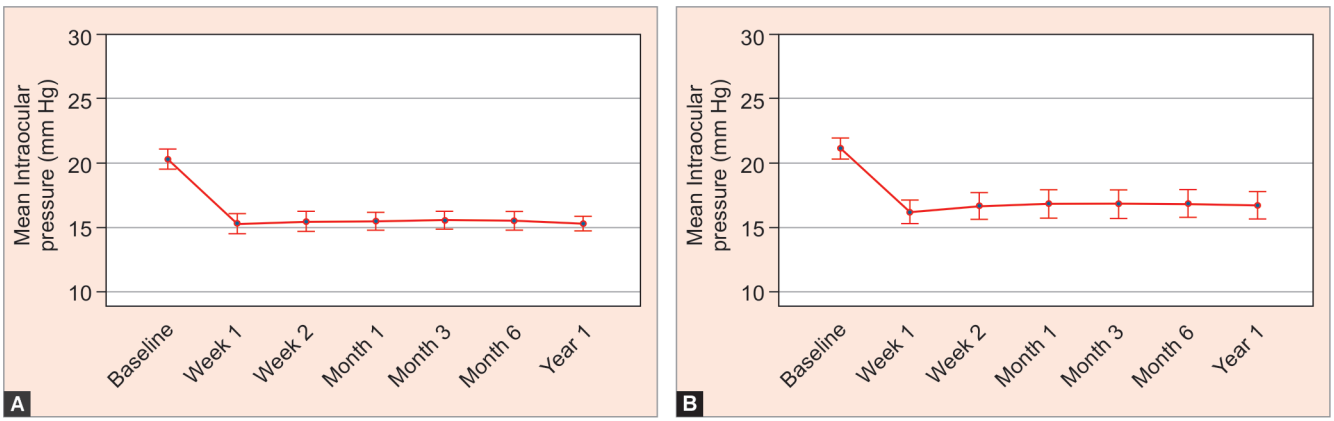
Mean IOP (95% CI) mm Hg								
Baseline	*Week 1*	*Week 2*	*Month 1*	*Month 3*	*Month 6*	*Year 1*	*n*	*p-value**
Per-protocol population (PP)								
20.3 (19.5–21.1)	15.3 (14.5–16.1)	15.5 (14.7–16.2)	15.5 (14.8–16.0)	15.5 (14.9–16.2)	15.5 (14.8–16.2)	15.3 (14.7–15.9)	24	<0.001
Intent-to-treat population (ITT)								
21.1 (20.3–22.0)	16.2 (15.3–17.2)	16.7 (15.7–17.7)	16.9 (15.8–17.9)	16.8 (15.7–17.9)	16.9 (15.8–18.0)	16.7 (15.6–17.8)	36	<0.001

*ANOVA repeated measure

Table 3: Intraocular pressure reduction at each assessment visit from baseline in the PP and ITT population

	Per-protocol population (PP)			*Intent-to-treat population (ITT)*		
	Mean IOP 95% CI	*n*	*p-value**	*Mean IOP 95% CI*	*n*	*p-value**
Week 1	−5.0 (−5.8 to −4.2)	24	<0.001	−4.9 (−5.7 to −4.0)	36	<0.001
Week 2	−4.8 (−5.7 to −4.0)	24	<0.001	−4.4 (−5.3 to −3.5)	36	<0.001
Month 1	−4.8 (−5.7 to −3.9)	24	<0.001	−4.7 (−5.8 to −3.6)	32	<0.001
Month 3	−4.8 (−5.6 to −3.9)	24	<0.001	−5.2 (−6.3 to −4.1)	29	<0.001
Month 6	−4.8 (−5.6 to −3.9)	24	<0.001	−5.4 (−6.4 to −4.4)	28	<0.001
Year 1	−5.0 (−5.8 to −4.2)	24	<0.001	−5.0 (−5.8 to −4.2)	24	<0.001

*Paired *t*-test from baseline (DT treatment)



Figs 1A and B: Effect of switching to 2% dorzolamide/0.5% timolol/0.2% brimonidine tartrate triple fixed combination ophthalmic solution twice daily in patients with glaucoma who had been receiving at baseline 2% dorzolamide/0.5% timolol fixed combination ophthalmic solution twice daily. Each value represents mean IOP (95% CI). ANOVA repeated measures was used in statistical analysis. (A) Mean IOP at baseline, 1, 2 weeks, 1, 3, 6 months, and 1 year in the per protocol (PP) population ($n = 24$). $p < 0.001$ correspond to ANOVA repeated measures analysis. (B) Mean IOP at baseline, 1, 2 weeks, 1, 3, 6 months, and 1 year in the intention to treat (ITT) population ($n = 36$). $p < 0.001$ corresponds to ANOVA repeated measures analysis

Table 4: Treatment success/failure for the overall population and the stratified population

	Overall population	
Follow-up	*Success, n (%)*	*Failure, n (%)*
Week 1	31 (86.1)	5 (13.9)
Week 2	29 (80.6)	7 (19.4)
Month 1	29 (80.6)	7 (19.4)
Month 3	28 (77.8)	8 (22.2)
Month 6	26 (72.2)	10 (27.8)
Year 1	24 (66.7)	12 (33.3)

	Stratified population				
	POAG (n = 21)		CCAG (n = 15)		
Follow-up	Success, *n* (%)	Failure, *n* (%)	Success, *n* (%)	Failure, *n* (%)	*p*-value
Week 1	19 (90.5)	2 (9.5)	12 (80.0)	3 (20.0)	0.630*
Week 2	19 (90.5)	2 (9.5)	10 (66.7)	5 (33.3)	0.103*
Month 1	17 (81.0)	4 (19.0)	12 (80.0)	3 (20.0)	1.000*
Month 3	17 (81.0)	4 (19.0)	11 (73.3)	4 (26.7)	0.694*
Month 6	15 (71.4)	6 (28.6)	11 (73.3)	4 (26.7)	0.900**
Year 1	13 (61.9)	8 (38.1)	11 (73.3)	4 (26.7)	0.473**

*Fischer's exact test; **Chi-squared test

advanced disease, and an increased risk of progressing to blindness due to inadequate early detection and limited treatment options. Several factors, including progressive visual field loss, advanced age, and noncompliance with treatment regimes, contribute to the risk of blindness from glaucoma.[15] Achieving target IOP levels is crucial for managing the disease effectively. However, single medications may not always achieve the target IOP, potentially leading to poor adherence due to complex regimens involving multiple eye drops.[11] Triple fixed combination eye drops offer a solution by simplifying treatment regimens, minimizing bottle and drop use, and reducing preservative exposure, thus decreasing the risk of ocular surface diseases.[11] In developing countries, surgery is occasionally recommended as an initial treatment for glaucoma due to the expense of glaucoma medications and poor adherence to topical treatments. However, it's essential to recognize that postsurgical follow-up and complications can lead to increased indirect costs. Therefore, optimizing glaucoma management with eye drops, including triple combinations of antiglaucoma agents, can postpone the necessity for surgery and reduce the progression of nerve damage.[16]

This retrospective study assessed the efficacy of a newly available commercial antiglaucoma treatment combining three drugs with distinct mechanisms of action: dorzolamide, a carbonic anhydrase inhibitor that decreases aqueous humor production; timolol, a β-adrenergic blocker that also reduces aqueous humor production; and brimonidine tartrate, an α2-adrenergic agonist that decreases aqueous humor production and enhances uveoscleral outflow. Patients with uncontrolled IOP levels while on DT-FC were switched to DTB-FC. It is interesting to note that not many papers have studied this fixed triple combination.[10,11] For example, there are two works of Baiza-Durán et al., who evaluated a similar product, with the same drugs, but from another laboratory (Sophia; Mexico) versus DT-FC and brimonidine tartrate and timolol fixed combination (BT-FC).[10,11] Although these studies were also conducted in a Latin population, we consider that it is not a similar population to that of Bolivia, and therefore they are not completely comparable studies.

Our study revealed that after 1 year of switching to DTB-FC, 66.7% of patients achieved IOP control, resulting in a significant reduction in IOP of approximately 24%. This finding aligns with previous studies comparing DT-FC to DTB-FC, showing that DTB-FC provides a substantial additional reduction in IOP.[10] Notably, when compared to BT-FC, DTB-FC resulted in a 10% additional IOP reduction after 90 days of treatment.[11]

To explore the effectiveness of DTB-FC across different glaucoma subtypes, we stratified the population into POAG and CACG groups. Interestingly, we found that DTB-FC demonstrated similar effectiveness in both types of glaucoma, and that is an original finding that is therapeutically important to highlight. It's worth noting that all participants who required the addition of a prostaglandin analog were diagnosed with POAG, indicating that this combination therapy may be particularly beneficial for this subgroup.

Furthermore, our study reported only one adverse event, conjunctival hyperemia was observed in two patients. This suggests that DTB-FC has a favorable safety profile, which is crucial for long-term glaucoma management.

We recognize the limitations of our study, stemming from its retrospective design and the small number of cases. However, we highlight the relevance and originality of providing information on a population that has potentially different characteristics from others, having studied the therapeutic response to a novel therapeutic option. Likewise, we hope that the present work can stimulate further studies in Latin America, which will allow a better knowledge of the form of expression of pathologies as relevant as glaucoma and, at the same time, to understand and describe the therapeutic responses and their population differences at regional and global level.

Conclusion

The fixed combination of DTB-FC offers an effective option for patients with uncontrolled IOP levels under DT-FC therapy, helping them achieve their target IOP and thereby delaying progressive optic nerve damage. The synergistic effect of

this combination of three antiglaucomatous drugs makes it a valuable addition to the treatment armamentarium for glaucoma. Nonetheless, individualized patient care remains essential, and some patients may still require additional interventions to reach their target IOP levels. Additional research and long-term studies are required to validate these findings and evaluate the long-term effectiveness of DTB-FC in managing glaucoma.

Clinical Significance

This study showed the hypotensive efficacy of a DTB-FC (dorzolamide, timolol, brimonidine) in Bolivian patients previously treated with a double-fixed combination (dorzolamide, timolol). The hypotensive efficacy was similar for both POAG and CACG, and was maintained for 12 months in most cases.

References

1. Quigley H, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90(3):262–267. DOI: 10.1136/bjo.2005.081224
2. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 2014;121(11):2081–2090. DOI: 10.1016/j.ophtha.2014.05.013
3. Allison K, Patel D, Alabi O. Epidemiology of glaucoma: the past, present, and predictions for the future. Cureus 2020;12(11):e11686. DOI: 10.7759/cureus.11686
4. Gedde S, Vinod K, Wright MM, et al. Primary open-angle glaucoma preferred practice pattern®. 2020.
5. Gedde SJ, Vinod K, Wright MM, et al. Primary open-angle glaucoma preferred practice pattern®. Ophthalmology 2021;128(1):71–150. DOI: 10.1016/j.ophtha.2020.10.022
6. Ambrus A, Lum FC, Garratt S. Primary open-angle glaucoma preferred practice pattern®.
7. Justiniano MJ. Líneas de tratamiento en glaucoma en ángulo abierto. In: Mundi I, (ed). Glaucoma Tips, Consejos y Experiencias. Santa Cruz de la Sierra; 2022; pp. 172–179.
8. Konstas AG, Schmetterer L, Katsanos A, et al. Dorzolamide/timolol fixed combination: learning from the past and looking toward the future. Adv Ther 2021;38(1):24–51. DOI: 10.1007/s12325-020-01525-5
9. Lerner SF, Oddone F, Lu DW, et al. Maximum medical therapy: brinzolamide/brimonidine and travoprost/timolol fixed-dose combinations in glaucoma and ocular hypertension. Clin Ophthalmol 2019;13:2411–2419. DOI: 10.2147/OPTH.S228777
10. Baiza-Durán LM, Alvarez-Delgado J, Contreras-Rubio AY, et al. The efficacy and safety of two fixed combinations: timolol-dorzolamide-brimonidine versus timolol-dorzolamide. A prospective, randomized, double-masked, multi-center, 6-month clinical trial. Ann Ophthalmol 2009;41(3–4):174–178. PMID: 20214051.
11. Baiza-Durán L, Llamas-Moreno J, Ayala-Barajas C. Comparison of timolol 0.5%+brimonidine 0.2%+dorzolamide 2% versus timolol 0.5%+brimonidine 0.2% in a Mexican population with primary open-angle glaucoma or ocular hypertension. Clin Ophthalmol 2012;6:1051–1055. DOI: 10.2147/OPTH.S33578
12. Webers CAB, Beckers HJM, Nuijts RMMA, et al. Pharmacological management of primary open-angle glaucoma: second-line options and beyond. Drugs and Aging 2008;25(9):729–759. DOI: 10.2165/00002512-200825090-00002
13. Woodward DF, Chen J. Fixed-combination and emerging glaucoma therapy. Exp Opin Emerg Drugs 2007;12(2):313–328. DOI: 10.1517/14728214.12.2.313
14. Khouri AS, Realini T, Fechtner RD. Use of fixed-dose combination drugs for the treatment of glaucoma. Drugs and Aging 2007;24(12):1007–1016. DOI: 10.2165/00002512-200724120-00004
15. Chen PP. Risk and risk factors for blindness from glaucoma. Curr Opin Ophthalmol 2004;15(2):107–111. DOI: 10.1097/00055735-200404000-00009
16. Delgado MF, Abdelrahman AM, Terahi M, et al. Management of glaucoma in developing countries: challenges and opportunities for improvement. Clin Outcomes Res 2019;11:591–604. DOI: 10.2147/CEOR.S218277