OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2018.

Research Article
Efficacy and Safety of Intraocular Pressure-Lowering Agents Bimatoprost and Timolol Maleate in Glaucoma

Lin Chen, Xiaoli Zeng and Xuewen Huang

Department of Ophthalmology, Nanchong Central Hospital, Second Clinical College of North Sichuan Medical College, Nanchong, 637000 Sichuan, China

Ist and 2nd authors contributed this work equally

Abstract

Background and Objective: Intraocular pressure (IOP) elevation is a major risk associated with glaucoma. Timolol is the most frequently used drug in the management of open-angle glaucoma (OG). The objective of this study was to compare the IOP-lowering effects of bimatoprost (BM) with timolol in a Chinese population with OG. **Methodology:** A total of 480 eyes of indoor patients suffering from OG (study group) and 50 normal eyes of indoor patients not suffering from OG (non-study group) were included in the study. The eyes of the treatment, control and non-study groups were treated with one drop of 0.03% w/v BM once daily, 0.5% w/v timolol maleate (TM) twice daily and water injection twice daily for 3 months, respectively. The IOP was measured at baseline and at 2, 6 weeks and 3 months of treatment. Conjunctival hyperemia, eye irritation, ocular hyperemia, foreign body sensation in eyes, corneal staining, heart rate and systolic and diastolic blood pressures were determined for the study group between baseline and 3 months of treatment. SPSS was use to analyze the data. Analysis of covariance was used to show better efficacy of BM compared with TM. One-way analysis of variance (ANOVA) and the Wilcoxon test were used for insignificant differences of ocular and systematic adverse effects. **Results:** There was a significant difference in IOP at baseline compared with the end of 3 months of BM ($p = 0.00041$) and TM ($p = 0.0091$) treatments. There was no significant difference between conjunctival hyperemia, eye irritation, ocular hyperemia, foreign body sensations in eyes, corneal staining, heart rate and systolic and diastolic blood pressures between baseline and at the end of 3 months of patients treated with BM. There was a significant difference for eyes reaching and maintaining an IOP$\leq$18 mmHg between the control group and the treatment group ($p = 0.0478$). **Conclusion:** The BM was more effective than timolol in lowering IOP over 3 months of treatment in open-angle glaucoma patients.

Key words: Evidence-based medicine, hyperemia, ocular hypertension, prostaglandin analog, prostamide

Received: Accepted: Published:

Citation: Lin Chen, Xiaoli Zeng and Xuewen Huang, 2018. Efficacy and safety of intraocular pressure-lowering agents bimatoprost and timolol maleate in glaucoma. Int. J. Pharmacol., CC: CC-CC.

Corresponding Author: Xuewen Huang, Department of Ophthalmology, Nanchong Central Hospital, Second Clinical College of North Sichuan Medical College, Nanchong, 637000 Sichuan, China Tel/Fax: 0086-18181112109

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The occurrence of open-angle glaucoma (OG) is second only to cataracts and is the leading cause of irreversible blindness[1]. Intraocular pressure (IOP) elevation is one of the major risk factors associated with OG and a reduction in IOP decreases the risk of OG[2]. IOP management is based on a patient's profile[3], with a lower limit of IOP or ''target pressure'' (generally≤18 mmHg) associated with no visual damage[4].

Management of OG involves a different class of drugs (Table 1)[5]. Bimatoprost (BM) is a synthetic analog of prostamide F2-α and is a potent ocular hypotensive agent[6]. "Prostaglandin" is more commonly used than "prostamide." However, timolol maleate (TM) is the most frequently used drug in the management of OG. BM treatment is more inexpensive than TM treatment for IOP reduction in the management of OG[5]. BM reduces the IOP without significant changes in hyperemia, heart rate, blood pressure, or other systematic adverse effects[7]. However, TM significantly ($p \leq 0.05$) decreases the heart rate and blood pressure and also causes hyperemia during long-term use[8]. Moreover, other IOP lowering agents, such as latanoprostene are associated with significant hyperemia, coronary artery disease, cholelithiasis and subdural hemorrhage[9]. However, acetazolamide is used for short-term IOP elevation only[10].

The objective of this research was to compare the IOP-lowering effect of once-a-day (OD) BM eye drops and twice-a-day BD-TM ophthalmic solution in a Chinese population with OG. The secondary endpoint of the study was to check ocular and systematic adverse effects of both the treatments.

MATERIALS AND METHODS

The patients admitted to Nanchong Central Hospital between December 1, 2012 and January 1, 2016 were considered for the study.

The BM (0.03% LUMIGAN®) was purchased from Allergen (Irvine, CA, USA) and TM (0.5% TIMOPTIC®) ophthalmic solution was purchased from Shandong Bausch and Lomb-Freda Pharmaceutical (Jinan, China). Dexamethasone sodium phosphate (0.1% w/v Dexan) eye drops and water for injection (WFI) were purchased from Wuhan Wujing Medicine (Wuhan, China).

Subjects: The ethics committee of ophthalmology of the Nanchong Central Hospital and the 2nd clinical college of North Sichuan Medical College approved the experimental protocol, the ethical guidelines for biomedical research on human participants were followed in accordance with Chinese law[11].

Inclusion criteria: A total of 480 eyes of 319 indoor patients suffering from OG (study group) and 50 normal eyes of patients not suffering from OG (non-study group) were included in the study. Patients of both sexes were ≥18 years of age, with advanced, mild, or moderate OG. The included eyes had no visual potentials. An informed consent form regarding reduction in the IOP was signed by each patient prior to the study. The patients were then randomly divided into three groups (Table 2).

Exclusion criteria: Patients who had difficulty understanding the informed consent form, who refused to sign the informed consent form, who did not return for the study follow-up, or who were <18 years of age were excluded from the study. Patients who had a corneal abnormality, evidence of visual potential, ocular inflammation, ocular infection, cardiac diseases, asthma, or intraocular surgery were also excluded from the study.

Prior sample size calculations: The sample size was calculated using Epi 3.0.1 open software (Epidemiologic Statistics for Public Health) to be 214 subjects for the treatment and control groups from the enrolled patients in the study group. The parameters used for calculations were as follows: An α-error probability of 0.05, a hypothesized percentage frequency of an outcome factor in the population of 95±5% and a

Table 1: Agents used for the management of open-angle glaucoma

Class	Drugs	Preferred route of administration
Muscarinic cholinergic agonist	Pilocarpine and Carbachol	Topical
Carbonic anhydrous inhibitors	Acetazolamide, Dichlorophenamide and Methazolamide	Systematic and oral
	Dorzolamide and Brinzolamide	Topical
Prostamide or prostaglandin analogs	Bimatoprost, latanoprostene and Travoprost	Topical
β1-adrenergic antagonist	Timolol, Carteolol, Levobunolol, Metipranolol and Betaxolol	Topical
α-2 adrenergic agonists	Epinephrine, Dipivefrin, Apraclonidine and Brimonidine	Topical

Table 2: Age and sex of subjects randomized for the study

Groups		Drug	Total number of eyes (n)%	Eyes of male patients (n)%	Eyes of female patients (n)%	Age (years)			Number of patients
						Mean	Age 65 and over	Age less than 65	
Study groups	Treatment group	BM	216(100)	149(69)	67(31)	59.34±9.8	85(39)	131(61)	155
	Control group	TM	214(100)	139(65)	75(35)	61.13±10.1	78(36)	136(64)	135
Non-study group		WFI	50(100)	30(60)	20(40)	57.21±8.2	22(44)	28(56)	29

Data are expressed as a number (percent). Age is expressed as the Mean±SD. All patients were from China. BM: Bimatoprost, TM: Timolol maleate, WFI: Water for injection. Advanced open-angle glaucoma eyes were also included in the study

confidence level of 5%. The Consolidated Standards of Reporting Trials (CONSORT) chart of the enrolled glaucoma eyes is shown in Fig. 1.

Treatments: All eyes of the non-study, treatment and control groups were treated with one drop of WFI BD, 0.03% w/v BM eye drops (OD) and 0.5% w/v TM ophthalmic solution BD, respectively, for 3 months.

IOP measurements: Dexamethasone eye drops were instilled in all enrolled eyes 3 times a day for 5 days. The IOP was then measured using an ocular tonometer (ic100, Icare®, Vantaa, Finland) 1 h after the last installation. This IOP was defined as the baseline (BL)[12]. At the end of 2 and 6 weeks of treatment, or at the end of 3 months of treatment (ET), the IOP was measured at 7:30 am, 12 noon and 4:30 pm (local time)[6].

Evaluation of adverse effects: Ocular and systemic adverse effects were compared for eyes enrolled for study with eyes not enrolled in the study for every patient at BL and at ET. Ocular adverse effects were recorded by asking questions, visual inspections and using the appropriate instruments as applicable. Systematic adverse effects were evaluated by measuring systolic and diastolic blood pressures and the heart rate[1]. Normal values of systolic and diastolic blood pressures were considered as 160 and 90 mmHg, respectively[13]. The normal heart rate was considered to be 80 beats min^{-1} [14].

Statistical analysis: The IOP was expressed as the mean±standard deviation (SD) from three independent observations at 7:30 am, 12 noon and 4:30 pm. The data were analyzed using SPSS Statistics software for Windows, version 22.0.0.0 (IBM Corp., Armonk, NY, USA). Analysis of covariance (ANCOVA) was used for non-uniformity of dose regimens and to determine the superiority of the IOP reading after BM treatment compared with the TM treatment[1]. One-way analysis of variance (ANOVA) and the Wilcoxon test were used for insignificant differences of ocular and systematic adverse effects between and within groups, respectively. One-way ANOVA was used for eyes reaching and maintaining an IOP $\leq$18 mmHg between the control group and the treatment group[15]. The difference was considered statistically significant at a 95% level of confidence ($p \leq 0.05$).

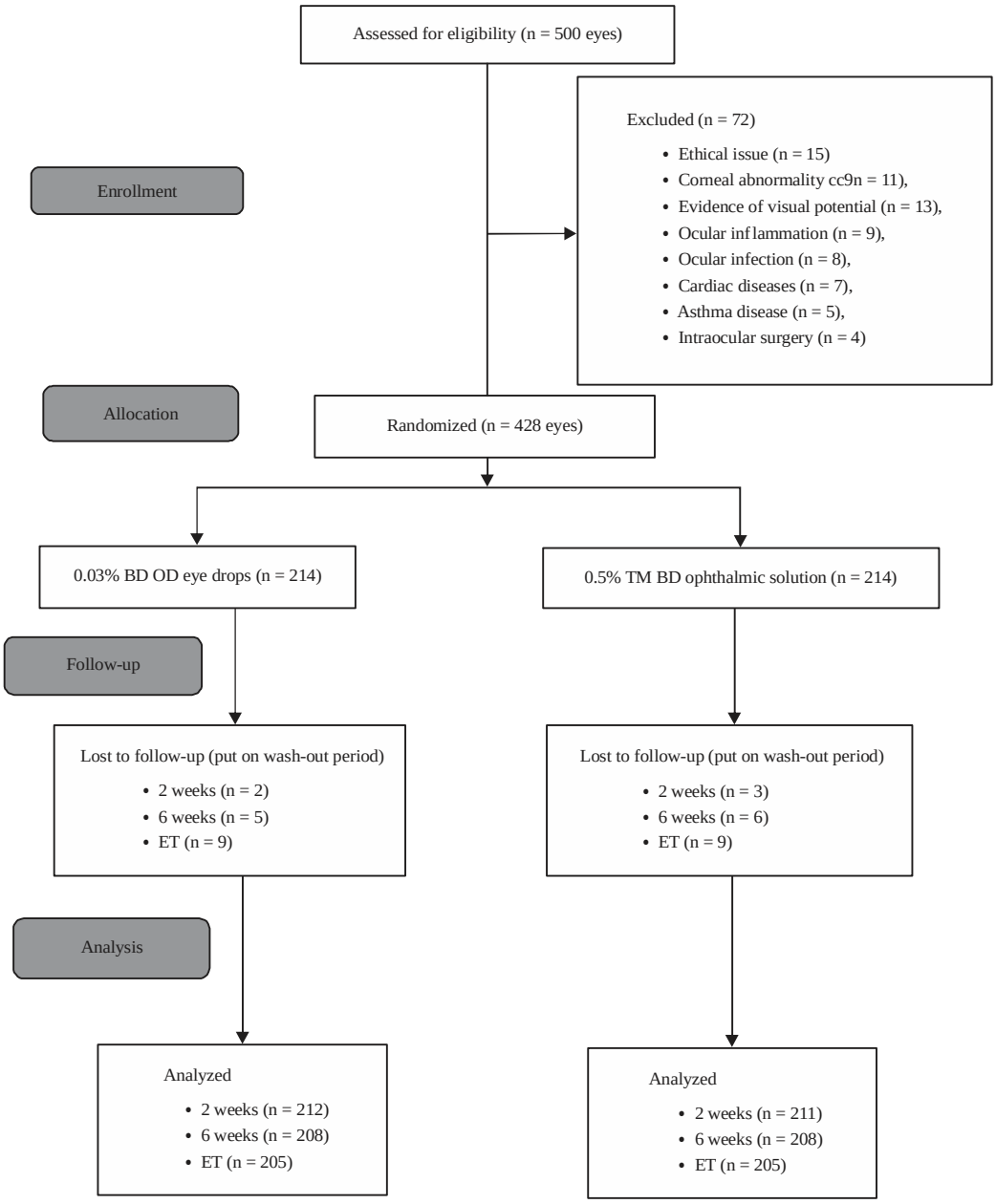

Fig. 1: Consolidated standards of reporting trials flow diagram of the study. BL: Baseline, BM: Bimatoprost, TM: Timolol maleate, OD: Once a day, BD: Twice a day and ET: At the end of 3 months of treatment

RESULTS

Twelve patients involving 18 eyes (9 control and 9 treatment) were excluded from the study and placed in the washout period.

The ANCOVA showed that the IOP was significantly reduced between BL and ET using 0.03% w/v BM eye drops OD and 0.5% w/v TM ophthalmic solution BD (both, $p \leq 0.05$).

The IOP was also significantly reduced at ET when comparing 0.03% w/v BM eye drops OD and 0.5% w/v TM ophthalmic solution BD ($p \leq 0.05$, Table 3).

Table 4 shows that there was no significant adverse ocular effect of treatment at ET ($p = 0.061$). Moreover, Fig. 2 shows that there was no significant change in ocular parameters between BL and at the ET for treatments of all groups.

Table 3: Effects of treatments on the intraocular pressure of eyes

	Mean IOP (mm Hg)											
	BL			2 weeks			6 weeks			ET		
Groups	7:30 am	12 noon	4:30 pm	7:30 am	12 noon	4:30 pm	7:30 am	12 noon	4:30 pm	7:30 am	12 noon	4:30 pm	p-value*
Treatment group	27.1±2.6	27.0±2.5	27.2±2.7	18.1±2.1	17.9±1.9	17.8±1.8	16.8±1.8	16.7±1.7	16.6±1.6	14.1±1.3	13.9±1.3	13.7±1.3	0.00041
n_1	214	214	214	212	212	212	209	209	209	205	205	205	N/A
Control group	26.5±2.4	26.6±2.5	26.7±2.6	20.1±2.2	19.9±2.1	19.8±2	18.1±1.9	18±1.9	17.9±1.9	16.5±1.8	16.1±1.6	15.9±1.4	0.0091
n_2	214	214	214	211	211	211	208	208	208	205	205	205	NA
p-value	0.45	0.46	0.47	0.049	0.048	0.041	0.04	0.039	0.038	0.037	0.036	0.02	N/A

n_1: Number of eyes in the treatment group, n_2: Number of eyes in the control group. The intraocular pressure (IOP) was expressed as the Mean±SD. BL: Baseline and ET: At the end of 3 months of treatment
*Between BL and the ET, between the treatment and the control groups

There was also no significant systematic adverse effect at the ET between the treatment group and non-study group ($p = 0.12$). Moreover, Table 5 shows that there was no significant difference for the parameters of systematic adverse effects between BL and at the ET for treatments of all groups ($p \leq 0.05$).

There were significantly greater numbers of eyes reaching and maintaining an IOP $\leq$18 mmHg for the treatment group, compared with the control group ($p = 0.0478$, Fig. 3).

DISCUSSION

This study showed an increased efficacy and safety of 0.03% w/v BM eye drops in OD dosing at the ET. To date, there has been no study that reported increased efficacy and safety of BM at the ET of OG patients[16].

The study compared the efficacy and safety of BM using ANCOVA, one-way ANOVA and the Wilcoxon test. The efficacy and safety of 0.5% w/v TM ophthalmic solution BD in OG patients has been reported[17], but there has not yet been a report that compared 0.03% w/v BM eye drops OD and 0.5% w/v TM ophthalmic solution BD due to a lack of uniformity of doses[18].

This study also included advanced OG patients with mild and moderate OG. However, the study excluded advanced OG eyes from the study, but included the results for mild or moderate OG patients, to better assess the drug efficacy[19]. Regarding the disease conditions selected for the study, BM was effective for all OG patients.

Most of the patients in the treatment group showed IOP reductions at the ET, compared with the control group. A reduction in 1 mmHg of the IOP results in a 20% reduction in the risk of visual field progression[20]. A BM-a prostaglandin analog was effective in IOP reduction[21]. The efficacy of 0.03% w/v BM eye drops OD was measured by IOP reduction responses and evaluated by the number of eyes that showed an IOP reduction that was lower than the BL value at 2 and 6 weeks and at the ET. BM is well-tolerated by humans[22] and the results of the present study showed that BM was effective in the treatment of OG patients.

Unlike the control group, the treatment group included five eyes with conjunctival hyperemia and six eyes with eye irritations at the ET. This was reported because BM involves conjunctival hyperemia[23,24] and eye irritation[25] as side effects. The number of human patients with conjunctival hyperemia was high,

Table 4: Adverse effects of the ocular treatments

	Treatment group		Control group		Non-study group	
Parameters	At BL (n = 214) N%	At ET (n = 205) N%	At BL (n = 214) N%	At ET (n = 205) N%	At BL (n = 50) N%	At ET (n = 50) N%
Conjunctival hyperemia	2(1)	5(2.5)	2(1)	2(1)	0(0)	0(0)
Eye irritation	0(0)	6(3)	1(0.5)	1(0.5)	0(0)	1(2)
Eye pain	1(0.5)	1(0.5)	1(0.5)	1(0.5)	0(0)	1(2)
Ocular hyperemia	0(0)	1(0.5)	0(0)	1(0.5)	0(0)	0(0)
Blurred vision	0(0)	1(0.5)	0(0)	1(0.5)	0(0)	1(2)
Eye pruritis	0(0)	1(0.5)	0(0)	0(0)	0(0)	0(0)
Asthenopia	0(0)	1(0.5)	0(0)	0(0)	0(0)	0(0)
Dry eye	0(0)	1(0.5)	0(0)	1(0.5)	0(0)	1(2)
Punctate keratitis	0(0)	0(0)	0(0)	1(0.5)	0(0)	0(0)
Foreign body sensation in eyes	0(0)	1(0.5)	0(0)	1(0.5)	0(0)	0(0)
Inflamed administration site	0(0)	1(0.5)	0(0)	1(0.5)	0(0)	1(2)
Instillation site pain	0(0)	1(0.5)	0(0)	1(0.5)	0(0)	1(2)
Corneal staining investigations	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)

BL: Baseline, ET: At the end of 3 months of treatment. Data are expressed as the number of eyes (percent). The value of p = 0.061 for one-way ANOVA between groups at the ET. The p-values using the Wilcoxon test were 0.95 and 0.89 for the treatment and control groups, respectively

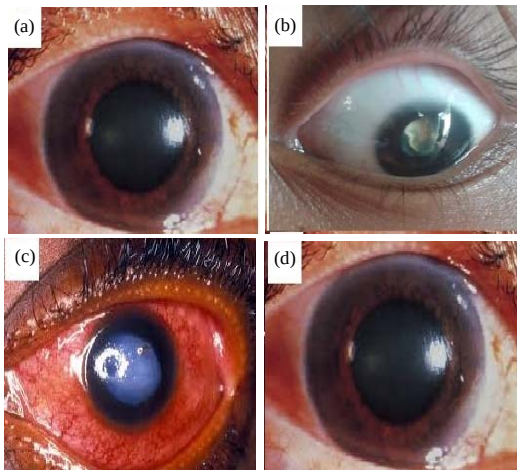

Fig. 2(a-d): Photographs of eyes enrolled in the study, (a) Treatment-group eye at BL, (b) Treatment-group eye at the ET, (c) Control-group eye at BL and (d) Control-group eye at the ET

BL: Baseline, ET: At the end of 3 months of treatment

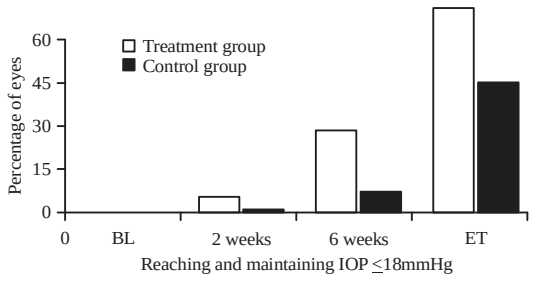

Fig. 3: Eyes reaching and maintaining an IOP ≤18 mmHg at the ET. Advanced open-angle glaucoma eyes were also included in the study. A p-value of 0.0478 for one-way ANOVA between the treatment and control groups. At the ET, 72.46 and 46.34% of treatment and control group eyes, respectively, reached and maintained an IOP ≤18 mmHg

ET: At the end of 3 months of treatment. IOP: Intraocular pressure

because the eyes enrolled for the study already had symptoms of this disorder. The control group included two patients with abnormal systolic blood pressure, 4 patients with abnormal diastolic blood pressure and 6 patients with abnormal heart rates, because long-term treatment with TM decreases the heart rate and blood pressure[8]. With respect to the results of adverse effects, BM was safer than TM.

At the ET, 72.46 and 46.34% of the treatment and control groups, respectively, reached and maintained an IOP ≤18 mmHg. OG patients reaching and maintaining an IOP of ≤18 mmHg have a significant ($p \leq 0.05$) reduction in the risk of visual field progression[4]. The results of the present study therefore concluded that BM was a successful treatment for reaching and maintaining the target IOP.

Table 5: Comparison of systematic adverse events

Parameters of systematic adverse effects	Treatment group		Control group		Non-study group	
	At BL (n = 115) N%	At ET (n = 150) N%	At BL (n = 135) N%	At ET (n = 130) N%	At BL (n = 29) N%	At ET (n = 27) N%
Chest discomfort	0(0)	1(0.7)	0(0)	0(0)	0(0)	0(0)
Dysgeusia	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Headache	0(0)	1(0.7)	0(0)	1(0)	0(0)	0(0)
Dyspnea	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Dizziness	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Somnolence	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Abnormal systolic blood pressure	0(0)	1(0.7)	0(0)	2(1.5)	0(0)	0(0)
Abnormal diastolic blood pressure	0(0)	1(0.7)	0(0)	4(3)	0(0)	0(0)
Abnormal heart rate	0(0)	0(0)	0(0)	6(5)*	0(0)	0(0)

BL: baseline; ET: At the end of 3 months of treatment. Data are expressed as the number of patients (percent). p = 0.12 using one-way ANOVA between the treatment and control groups at the ET. The p-values using the Wilcoxon test were 0.65 and 0.12 for the treatment and control groups, respectively. *Both eyes of each patient were enrolled in the study

CONCLUSION

It was concluded that the treatment with 0.03% w/v BM OD effectively and safely lowered the IOP compared with 0.5% w/v TM ophthalmic solution BD over 3 months of treatment in human subjects with OG. BM safely maintained the IOP of glaucoma eyes at $\leq$18 mmHg.

SIGNIFICANCE STATEMENT

This study discovers the superior intraocular pressure lowering effect of bimatoprost that can be beneficial for open-angle glaucoma. This study will help the ophthalmologists to uncover the critical areas of analog of prostamide that many researchers were not able to explore.

ACKNOWLEDGMENT

The authors thank all the individuals who took part in this study and the healthcare providers, technicians and administrative staff who enabled this study to be carried out. The authors especially thankful to management, medical and non-medical staff of Nanchong Central Hospital, the Second Clinical College of North Sichuan Medical College, Nanchong, Sichuan, China for their help and allow to access facilities to do research and Grammarly Inc., the USA for access to Grammarly software.

REFERENCES

1. Weinreb, R.N., B.S. Sforzolini, J. Vittitow and J. Liebmann, 2016. Latanoprostene bunod 0.024% versus Timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: The APOLLO study. Ophthalmology, 123: 965-973.
2. Kawase, K., J.L. Vittitow, R.N. Weinreb and M. Araie, 2016. Long-term safety and efficacy of latanoprostene bunod 0.024% in Japanese subjects with open-angle glaucoma or ocular hypertension: The JUPITER study. Adv. Ther., 33: 1612-1627.
3. Cheng, J., M. Xiao, H. Xu, S. Fang, X. Chen, X. Kong and X. Sun, 2016. Seasonal changes of 24-hour intraocular pressure rhythm in healthy Shanghai population. Medicine (Baltimore), Vol. 95, No. 31. 10.1097/MD.0000000000004453.
4. Foster, P.J. and A.P. Khawaja, 2017. The association of systemic medication and disease with intraocular pressure. JAMA Ophthalmol., 135: 203-204.
5. El-Khamery, A.A.E., A.I. Mohamed, H.E.H. Swify and A.I. Mohamed, 2017. Cost-effectiveness of glaucoma management with monotherapy medications in Egypt. J. Adv. Pharm. Technol. Res., 8: 25-28.
6. Vyas, P., U. Naik and J.B. Gangaiah, 2011. Efficacy of bimatoprost 0.03% in reducing intraocular pressure in patients with 360° synechial angle-closure glaucoma: a preliminary study. Indian J. Ophthalmol., 59: 13-16.
7. Chen, Y.Y., T.H. Wang, C. Liu, K.Y. Wu, S.L. Chiu, S. Simonyi and D.W. Lu, 2016. Tolerability and efficacy of bimatoprost 0.01% in patients with open-angle glaucoma or ocular hypertension evaluated in the Taiwanese clinical setting: The Asia Pacific Patterns from Early Access of Lumigan 0.01% (APPEAL Taiwan) study. BMC Ophthalmol., Vol. 16. 10.1186/s12886-016-0338-6.
8. Gunther-Harrington, C.T., E.S. Ontiveros, T.E. Hodge, L.C. Visser and J.A. Stern, 2016. Effects of 0.5% timolol maleate ophthalmic solution on heart rate and selected echocardiographic indices in apparently healthy cats. J. Vet. Internal Med., 30: 733-734.
9. Medeiros F.A., R.M. Keith, P. James, S.S. Baldo, J.L. Vittitow and R.N. Weinreb, 2016. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: The LUNAR study. Am. J. Ophthalmol., 168: 250-259.

10. Hayashi, K., M. Yoshida, S.I. Manabe and K. Yoshimura, 2017. Prophylactic effect of oral acetazolamide against intraocular pressure elevation after cataract surgery in eyes with glaucoma. Ophthalmology, 124: 701-708.
11. Karlberg, J.P.E. and M.A. Speers, 2010. Reviewing Clinical Trials: A Guide for the Ethics Committee; Clinical Trial Center. The University of Hong Kong, Hong Kong, ISBN: 9789881904119.
12. Karimian, F., A. Faramarzi, S. Fekri, H. Mohammad-Rabie and D. Najdi *et al*., 2017. Comparison of loteprednol with fluorometholone after myopic photorefractive keratectomy. J. Ophthalm. Vis. Res., 12: 11-16.
13. Pinto, E., 2007. Blood pressure and ageing. Postgrad. Med. J., 83: 109-114.
14. Maksuti, E., N. Westerhof, B.E. Westerhof, M. Broome and N. Stergiopulos, 2016. Contribution of the arterial system and the heart to blood pressure during normal aging – a simulation study. PLoS One, 10.1371/journal.pone.0157493.
15. Zhong, Y., M. Xiang, W. Ye, Y. Cheng and Y. Jiang, 2010. Visual field protective effect of *Erigeron breviscapus* (Vant.) Hand. Mazz. extract on glaucoma with controlled intraocular pressure: A randomized, double-blind, clinical trial. Drugs R&D., 10: 75-82.
16. Garcia, G.A., P. Ngai, M. Mosaed and K.Y. Lin, 2012. Critical evaluation of latanoprostene bunod in the treatment of glaucoma. Clin. Ophthalm., 10: 2035-2050.
17. Stewart, W.C., J.C. Oehler, N.T. Choplin, J.I. Markoff, M.R. Moster, P. Ichhpujani and L.A. Nelson, 2013. A comfort survey of timolol hemihydrate 0.5% solution once or twice daily vs timolol maleate in sorbate. J. Curr. Glaucoma. Pract., 7: 11-16.
18. Orme, M., S. Collins, H. Dakin, S. Kelly and J. Loftus, 2010. Mixed treatment comparison and meta-regression of the efficacy and safety of prostaglandin analogues and comparators for primary open-angle glaucoma and ocular hypertension. Curr. Med. Res. Opin., 26: 511-528.
19. Garway-Heath, D.F., D.P. Crabb, C. Bunce, G. Lascaratos and F. Amalfitano *et al*, 2015. Latanoprost for open-angle glaucoma (UKGTS): A randomised, multicentre, placebo-controlled trial. Lancet, 385: 1295-1304.
20. Heijl, A., 2015. Glaucoma treatment: by the highest level of evidence. Lancet, 385: 1264-1266.
21. Weinreb, R.N., T. Ong, B.S. Sforzolini, J.L. Vittitow, K. Singh and P.L. Kaufman, 2015. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. Br. J. Ophthalmol., 99: 738-745.
22. Tsumura, T., K. Yoshikawa, H. Suzumura, T. Kimura, S. Sasaki, I. Kimura and R. Takeda, 2012. Bimatoprost ophthalmic solution 0.03% lowered intraocular pressure of normal-tension glaucoma with minimal adverse events. Clin. Ophthalmol., 6: 1547-1552.
23. Weinreb, R.N., S.B. Scassellati, J. Vittitow and J. Liebmann, 2016. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the apollo study. Ophthalmology, 123: 965-973.
24. Daka, Q. and V. Trkulja, 2014. Efficacy and tolerability of mono-compound topical treatments for reduction of intraocular pressure in patients with primary open angle glaucoma or ocular hypertension: an overview of reviews. Croat Med. J., 55: 468-480.
25. Li, X., F. He, B.T. Gabelt, Y. Wang and S. Cai *et al*., 2017. Effects of latanoprost and bimatoprost on the expression of molecules relevant to ocular inflow and outflow pathways. PLoS ONE, Vol. 11, No. 3. 10.1371/journal.pone.0151644.