Medicina (Kaunas) 2013;49(7):310–4

The Effect of Nebulized Dorzolamide/Timolol Fixed Combination Mist versus Drops on Retrobulbar Blood Flow and Intraocular Pressure in Glaucoma Patients

Ingrida Janulevičienė[1], Lina Šiaudvytytė[1], Rūta Baršauskaitė[1], Vaida Dilienė[1], Loreta Kuzmienė[1], Brent Siesky[2], Alon Harris[2]

[1]Department of Ophthalmology, Medical Academy, Lithuanian University of Health Sciences, Lithuania,
[2]Glaucoma Research and Diagnostic Center, Eugene and Marilyn Glick Eye Institute, Indiana University School of Medicine, USA

Key Words: *nebulized mist; dorzolamide/timolol fixed combination; retrobulbar blood flow; intraocular pressure; primary open-angle glaucoma.*

Summary. *Objective. The aim of this study was to evaluate intraocular pressure (IOP), retrobulbar blood flow (RBF), and ocular side effects after the application of topical dorzolamide/timolol fixed combination (DTFC) drops vs topical nebulized DTFC mist in patients with primary open-angle glaucoma.*

Material and Methods. A total of 15 POAG patients were enrolled in a prospective study. Retrobulbar blood flow was measured in the ophthalmic (OA) and central retinal (CRA) arteries using color Doppler imaging. DTFC mist or drops were applied to the experimental eye, and it was examined after 15 and 60 minutes. DTFC mist was applied 6 times for 30 seconds using a misting device.

Results. DTFC mist significantly increased peak-systolic (PSV) and end-diastolic (EDV) velocities after 15 and 60 minutes in both the arteries (OA: increase of 12.5% and 9.6% in PSV, P=0.01; increase of 25.8% and 23.1% in EDV, P=0.03; CRA: increase of 11.5% and 8.7% in PSV, increase of 32% and 21.6% in EDV, respectively, P<0.05). DTFC drops had a similar effect on PSV and EDV in the CRA after 15 and 60 minutes (increase of 8.1% and 9.6% in PSV; increase of 17.1% and 23% in EDV, respectively, P=0.03), but a significant effect on PSV and EDV in the OA was documented only after 15 minutes (increase of 9% and 21.4%, respectively, P=0.02). DTFC mist reduced the resistance index in the CRA after 15 and 60 minutes (decrease of 8.5% and 10.2%, respectively, P=0.04). Both methodologies showed a significant decrease in IOP after 15 and 60 minutes (P<0.05). All patients complained of ocular irritation after drop application, and 1 patient complained of general weakness after mist treatment.

Conclusions. Nebulized DTFC mist significantly reduced IOP and increased blood flow in the OA and the CRA, causing no ocular irritation as compared with traditional DTFC drop methodology.

Introduction

Primary open-angle glaucoma (POAG) is a progressive optic neuropathy that leads to the loss of retinal ganglion cells and optic nerve damage (1). Although glaucoma is a multifactorial disease, elevated intraocular pressure (IOP) remains the most important known risk factor (2). Clinical studies have demonstrated that certain patients with POAG suffer from reduced ocular blood flow (OBF), which may be primarily of vascular origin or secondary to IOP elevation (3, 4). Some authors have hypothesized that the death of retinal ganglion cells and the optic nerve head may be due to ischemia as a result of elevated IOP or reduced oxygen supply because of reduced blood flow (5–8).

Correspondence to I. Janulevičienė, Department of Ophthalmology, Medical Academy, Lithuanian University of Health Sciences, Eivenių 2, 50161 Kaunas, Lithuania
E-mail: ingrida.januleviciene@kaunoklinikos.lt

The conventional treatment of POAG is the topical application of IOP-lowering drugs. It is known that certain drugs, even formulated in an eye drop, may have an impact on OBF and its regulation. Some data support increased blood flow and the enhancement of OBF regulation with carbonic anhydrase inhibitors. These appear to exceed a pressure-lowering effect alone. Several studies have shown the capability of dorzolamide to increase various OBF parameters (9–14), although other studies have failed to show a similar effect (15–17). A vasodilatative effect of dorzolamide might be explained by induced acidosis in local tissues. Contrary to dorzolamide, timolol may cause vasoconstriction by blocking β-2 receptors. Some studies reported that a single instillation of timolol did not have a significant effect on retrobulbar blood flow (RBF) (18–21). It has been shown that the addition of dorzolamide to timolol monotherapy decreases IOP and increases retinal

blood flow in the superficial retinal vasculature in both healthy patients and patients with POAG (9).

IOP-lowering eye drops pose several problems of drug delivery. First, the exposed anterior ocular surface has limited permeability and is continuously washed by tear fluid. Due to the limited permeability of the ocular surface and natural clearance and drainage, eye drops usually contain large amounts of active ingredients, which are potentially wasted. To resolve permeability problems in the eye, penetration enhancers are often added to topical pharmaceutical compositions, which are known as irritants potentially causing severe ocular irritation (22). Due to an unpleasant nature and difficulty of the instillation process, patients show lower compliance with treatment regimens. The topical administration of medications in a drop form also increases the possibility of causing corneal abrasion due to an inadvertent contact of the bottle tip with the cornea.

Attempting to overcome the current disadvantages of eye drops and to improve the administration of eye drugs, research on the application of misting has been started. The application of medications to the eyes using nebulized mist may have an advantage of accurate dosing, economical use of active ingredients with increased bioavailability of active compounds, increased patient compliance, and reduced risk of corneal abrasion as compared with the current drop methods.

The aim of our study was to compare the effects of topical DTFC drops and topical nebulized topical dorzolamide/timolol fixed combination (DTFC) mist on IOP and RBF and evaluate complaints in POAG patients.

Material and Methods

A total of 15 POAG (30 eyes) patients were enrolled into a prospective, open-label, cross-over clinical trial. The study procedures were carried out according to the Declaration of Helsinki, and the study protocol was approved by the Medicine Review Board, Lithuanian University of Health Sciences (BE2.9). The Department of Ophthalmology, Indiana University School of Medicine, provided services as the data analysis center for RBF images. The study objectives and methods were explained to all patients before the examination. All the patients signed an informed consent form.

The inclusion criteria were as follows: 1) adult patients aged more than 18 years with a diagnosis of POAG or ocular hypertension; 2) willingness to sign informed consent before the study; and 3) best-corrected visual acuity of Snellen equivalent of 20/40 or better.

The exclusion criteria were as follows: 1) mean deviation lower than or equal to –12 dB in Humphrey Visual Fields central 24-2 SITA Standard; 2) the cup-to-disc ratio equal or greater than 0.9; 3) previous eye diseases other than refractive error; 4) previous orbital or ocular trauma; 5) previous renal, hepatic, or respiratory diseases and asthma; 6) previous allergy to either of the study medications; 7) pregnancy or breastfeeding; and 8) contraindications to DTFC.

The color Doppler imaging (CDI; Accuvix, Korea) system was used for RBF measurements in the ophthalmic (OA) and central retinal (CRA) arteries. In each vessel, peak systolic velocity (PSV) and end-diastolic velocity (EDV) were determined, and the resistive index (RI) was calculated.

The patients attended the Clinic of Ophthalmology, Hospital of Lithuanian University of Health Sciences, for 2 study visits, each lasting about 1 hour. At enrollment, all the patients received timolol maleate monotherapy in both eyes. After baseline timolol measurements (IOP and RBF), the patients were randomly assigned for the application of DTFC drops or mist for the first treatment (right eye) and were crossed-over to the alternative arm during the second visit (left eye). After the DTFC drop/mist application, the patients were laid down for 15 minutes; IOP was measured in the supine position using a Tonopen applanation tonometer (Reichter, USA), and RBF was examined. After 1-hour rest, all the measurements were repeated. The patients' eyes were washed out with timolol maleate for 1 week, and a second set of baseline measurements were performed. After the baseline measurements, DTFC mist or drops were applied to another eye (left eye), and the same examinations as during the first visit were carried out after 15 and 60 minutes (Fig.). Nebulized DTFC mist was applied 6 times for 30 seconds using a misting device. Topical DTFC drops (Cosopt, Merck&Co; INC, Whitehouse station, USA) were given from a traditional bottle.

Statistical data analysis was performed by using the SPSS 17.0 program for Windows. All variables were described by descriptive statistics. The analysis of the quantitative variables included calculation of the mean (SD). Continuous data were compared by the Student *t* test for independent samples. The nonparametric Mann-Whitney test was used when the assumption of normal data distribution was rejected. The paired *t* test was used to evaluate the difference between the two variables for each case to see if the average difference is significantly different from zero. The level of significance was set at $P<0.05$.

Results

A total of 15 POAG patients (73.3% of women and 26.7% of men) with a mean age of 62.4 (SD, 11.3) years were enrolled into the study. The char-

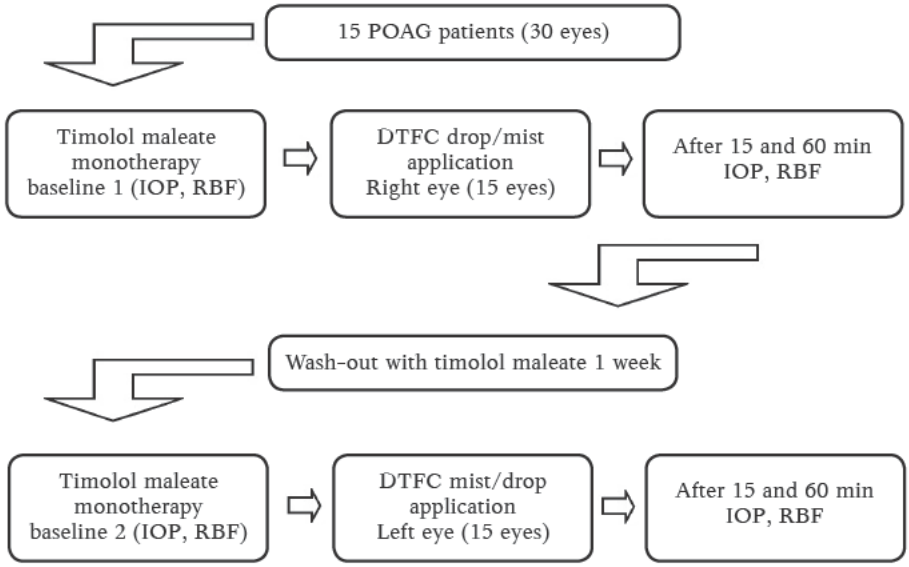

Fig. Study design

acteristics of patients are shown in Table 1. The mean duration of glaucoma treatment was 3.3 years (SD, 3.9). The mean best-corrected logMar visual acuity was 0.26 (SD, 0.2), and no significant differences in visual acuity measured during both the visits were documented. Moreover, there were no significant differences in IOP and RBF measured at the baseline between the eyes ($P>0.05$).

Both treatment methodologies showed a significant decrease in IOP after 15 and 60 minutes. IOP decreased by 5.7% ($P=0.01$) after 15 minutes and by 10.2% ($P=0.002$) after 60 minutes using DTFC mist, and by 4% ($P=0.01$) and 9.3% ($P<0.001$), respectively, using DTFC drops.

Changes in RBF velocities and the RI after the application of different DTFC methodologies are shown in Table 2. The application of DTFC mist showed a significant increase in velocities in the CRA and the OA as compared with the baseline measurement after the application of timolol ($P<0.05$). DTFC mist also reduced the RI in both vessels, but a significant effect was seen just in the CRA after 15 (a decrease by 8.5%, $P=0.01$) and 60 minutes (a decrease by 10.2%, $P=0.04$).

The application of DTFC drops had a similar effect on PSV and EDV in the CRA after 15 and 60 minutes ($P<0.05$) (Table 2). However, a significant effect PSV and EDV in the OA was seen only after 15 minutes (an increase in PSV and EDV by 9%

Table 1. Patients' Characteristics

Characteristic	Value
Sex	
Male	4 (26.7)
Female	11 (73.3)
Age, mean (SD) [range], years	62.4 (11.3) [38–76]
Glaucoma treatment, mean (SD), years	3.3 (3.9)
Systemic medications	
Beta blockers	6 (40)
ACE inhibitors	4 (26.7)
Angiotensin II inhibitors	1 (6.7)
Aspirin	4 (26.7)
Other drugs	8 (53.3)

Values number (percentage) unless otherwise stated.
ACE, angiotensin-converting-enzyme.

Table 2. Changes in Color Doppler Imaging Parameters Applying Different Treatment Methodologies

Parameter	Mist Application, %		Drop Application, %	
	After 15 min	After 60 min	After 15 min	After 60 min
OA				
PSV, cm/s	↑ 12.5*	↑ 9.6*	↑ 9.0*	↑ 7.4
EDV, cm/s	↑ 25.8*	↑ 23.1*	↑ 21.4*	↑ 14.2
RI	↓ 2.3	↓ 3.1	↓ 3.7*	↓ 1.4
CRA				
PSV, cm/s	↑ 11.5*	↑ 8.7*	↑ 8.1*	↑ 9.6*
EDV, cm/s	↑ 32.0*	↑ 21.6*	↑ 17.1*	↑ 23.0*
RI	↓ 8.5*	↓ 10.2*	↓ 3.5	↓ 5.1

OA, ophthalmic artery; CRA, central retinal artery; PSV, peak systolic velocity; EDV, end diastolic velocity; RI, resistive index.
*$P<0.05$, a significant change comparing the timolol baseline values and those after 15 or 60 minutes (paired-sample t test).

[P=0.02] and 21.4% [P=0.004], respectively). All patients reported ocular irritation experienced after the DTFC drop application, and only 1 patient (6.7%) complained of general weakness after the mist treatment.

Discussion

Dorzolamide and timolol have been formulated as a combination product to provide a more convenient dosing regimen for patients requiring multiple medications. The disadvantage of the fixed combination is that it exposes patients to the risk of side effects from both components. The most commonly reported ocular adverse events are burning and stinging. Combination drugs, however, may also offer a potential advantage of decreased toxicity from preservatives as both drugs are preserved with a single agent in the same bottle (23). Our study showed that all patients felt discomfort after the application of DTFC drops, while the mist of the same medication did not cause any unpleasant feelings. Mist is defined as a cloud of particles grouped together and formed by a nebulizer, which is commonly used in pulmonary diseases and is known for good distribution on the surface. Probably, this property had a positive impact on the increased RBF after mist application.

The results of our study showed a better effect on RBF using DTFC mist than DTFC drops. DTFC drops increased CRA hemodynamics, while a significant increase in OA blood flow was transient. Mist application not only increased blood flow velocities in both the arteries but also reduced the RI in the CRA. Our previous studies showed similar changes in RBF using ocular irritants in healthy patients (24).

Our pilot study shows a vast therapeutic potential for improved noninvasive delivery methods of glaucoma medications to ocular tissues. This advancement in drug delivery holds the potential to increase patient compliance and more important an increase in retrobulbar circulation, also avoiding unpleasant ocular irritation.

Conclusions

Nebulized topical dorzolamide/timolol fixed combination mist significantly reduced intraocular pressure and increased blood flow in the ophthalmic and central retinal arteries, causing no ocular irritation as compared with the traditional topical dorzolamide/timolol fixed combination drop methodology.

Acknowledgments

The device for misting was sponsored by Pharmalight.

Conflict of Interest

I.J. receives research grants from MSD, Santen, Pharmalight and serves as a lecturer and consultant for Alcon, Allergan, MSD, Santen.

A.H. received remuneration from MSD and Alcon for serving as a lecturer and Merck, Pharmalight, Sucampo Pharmaceuticals, XLVision, Nanoretina and ONO Pharmaceuticals, for serving as a consultant. The investigator also holds an ownership interest Adom (which all relationships above are pursuant to IU's policy on outside activities).

No competing financial interests exist.

References

1. Siesky B, Harris A, Cantor LB, Kagemann L, Weitzman Y, McCranon, et al. A comparative study of the effects of brizolamide and dorzolamide on retinal oxygen saturation and ocular microcirculation in patients with primary open-angle glaucoma. Br J Ophthalmol 2008;92:500-4.
2. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z; EMGT Group. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmol 2007;114: 1965-72.
3. Rojanapongpun P, Drance SM, Morrison BJ. Ophthalmic artery flow velocity in glaucomatous and normal subjects. Br J Ophthalmol 1993;77:25-9.
4. Butt Z, McKillop G, O'Brien C, Allan P, Aspinall P. Measurement of ocular blood flow velocity using colour Doppler imaging in low tension glaucoma. Eye (Lond) 1995;9: 29-33.
5. Kuehn MH, Fingert FH, Kwon YH. Retinal ganglion cell death in glaucoma: mechanisms and neuroprotective strategies. Ophthalmol Clin North Am 2005;18:383-95.
6. Rokicki W, Dorecka M, Romaniuk W. Retinal ganglion cells death in glaucoma - mechanism and potential treatment. Part I. Klin Oczna 2007;109:349-52.
7. Harris A, Chung HS, Ciulla TA, Kagemann L. Progress in measurement of ocular blood flow and relevance to our understanding of glaucoma and age-related macular degeneration. Prog Retin Eye Res 1999;18:669-87.
8. Yoshida Y, Sugiyama T, Utsunomiya K, Ogura Y, Ikeda T. A pilot study for the effects of donepezil therapy on cerebral and optic nerve head blood flow, visual field defect in normal-tension glaucoma. J Ocul Pharmacol Ther 2010;26: 187-92.
9. Siesky B, Harris A, Kagemann L, Stefansson E, McCranor L, Miller B, et al. Ocular blood flow and oxygen delivery to the retina in primary open-angle glaucoma patients: The addition of dorzolamide to timolol monotherapy. Acta Ophthalmol 2010;88:142-9.
10. Harris A, Arend O, Arend S, Martin B. Effects of topical dorzolamide on retinal and retrobulbar hemodynamics. Acta Ophthalmol Scand 1996;74(6):569-72.
11. Martinez A, Gonzalez F, Capeans C, Perez R, Sanchez-Salorio M. Dorzolamide effect on ocular blood flow. Invest Ophthalmol Vis Sci 1999;40:1270-5.
12. Moss AM, Harris A, Siesky B, Rusia D, Williamson KM, Shoshani Y. Update and critical appraisal of combined timolol and carbonic anhydrase inhibitors and the effect on ocular blood flow in glaucoma patients. Clin Ophthalmol 2010;4:233-41.
13. Siesky B, Harris A, Brizendine E. Margues C, Loh J, Mackey J, et al. Literature review and meta-analysis of topical carbonic anhydrase inhibitors and ocular blood flow. Surv

Ophthalmol 2009;54:33-46.
14. Harris A, Jonescu-Cuypers CP, Kagemann L, Nowacki EA, Garzozi H, Cole C, et al. Effect of dorzolamide timolol combination versus timolol 0.5% on ocular blood flow in patients with primary open-angle glaucoma. Am J Ophthalmol 2001;132:490-5.
15. Bernd AS, Pillunat LE, Böhm AG, Schmidt KG, Richard G. Ocular hemodynamics and visual field in glaucoma treated with dorzolamide. Ophthalmologe 2001;98:451-5.
16. Pillunat LE, Bohm AG, Koller AU, Schimdt KG, Klemm M, Richard G. Effect of topical dorzolamide on optic nerve head blood flow. Graefes Arch Clin Exp Ophthalmol 1999; 237:495-500.
17. Bergstrand IC, Heijl A, Harris A. Dorzolamide and ocular blood flow in previously untreated glaucoma patients: a controlled double-masked study. Acta Ophthalmol Scand 2002;80:176-82.
18. Nicolela MT, Buckley AR, Walman BE, Drance SM. A comparative study of the effects of timolol and latanoprost on blood flow velocity of the retrobulbar vessels. Am J Ophthalmol 1996;122:784-9.
19. Evans DW, Harris A, Cantor LB. Primary open-angle glaucoma patients characterized by ocular vasospasm demonstrate a different ocular vascular response to timolol versus betaxolol. J Ocul Pharmacol Ther 1999;15:479-87.
20. Galassi F, Sodi A, Renieri G, Ucci F, Pieri B, Harris A, et al. Effects of timolol and dorzolamide on retrobulbar hemodynamics in patients with newly diagnosed primary open-angle glaucoma. Ophthalmologica 2002;216:123-8.
21. Harris A, Spaeth GL, Sergott RC, Katz LJ, Cantor LB, Martin BJ. Retrobulbar arterial hemodynamic effects of betaxolol and timolol in normal-tension glaucoma. Am J Ophthalmol 1995;120:168-75.
22. Morgan RV, Huntzicker MA. Delivery of systemic regular insulin via the ocular route in dogs. J Ocul Pharmacol Ther 1996;12:515-26.
23. Clineschmidt CM, Williams RD, Snyder E, Adamson IA. A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. Ophthalmology 1999;106:17-24.
24. Primus S, Januleviciene I, Siesky B, Gerber A, Egan P, Amireskandari A, et al. The effect of diluted penetration enhancer in nebulized mist versus liquid drop preparation forms on retrobulbar blood flow in healthy human subjects. Pharmaceutics 2012;4:377-84.

Received 4 January 2013, accepted 30 July 2013