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The Effect of Unilateral Application of Timolol 0.5% on Systemic Cardiovascular Parameters and Intraocular Pressure and Perfusion

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Original article

Abstract

Aim: To study the effect of unilaterally applied timolol 0.5% on systemic blood pressure (BP), heart rate (HR), cerebrospinal fluid pressure (CSFP), intraocular pressure (IOP), ocular perfusion pressure (OPP) and translaminar pressure difference (TLPD).

Methods: This is an experimental clinical study of 14 healthy subjects. Ophthalmic examination included best corrected visual acuity (BCVA), slit lamp examination and autorefractometry. Systemic BP, HR and IOP were taken after the basic examination. Two drops of ophthalmic solution timolol 0.5% were instilled in the right eye (RE) of the subjects. Systemic BP and IOP were measured 30 minutes, one hour, one and a half hour and two hours after the local application. We evaluated the following parameters: systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), mean blood pressure (MBP) (mmHg), HR (bpm), estimated CSFP, IOP (mmHg), estimated TLPD (mmHg) and (OPP) (mmHg).

Results: After unilateral topical application of timolol 0.5%, there was a significant reduction of IOP and TLPD in both eyes (IOP RE $p<0.001$, IOP LE $p=0.006$; TLPD RE $p<0.001$, TLPD LE $p=0.006$) and a significant decrease of HR ($p=0.003$). OPP significantly increased only in the treated eye ($p=0.021$). There was a statistically significant correlation between IOP and HR in both eyes (RE $R=0.95$, $p=0.01$; LE $R=0.85$, $p=0.04$).

Conclusion: This report suggests that the systemic effect of topical unilateral administration of timolol 0.5% on heart rate is associated with the contralateral reduction of IOP in the untreated eye. However, this effect may not reach the full therapeutic potential of the drug, because of the insufficient increase of OPP in the contralateral untreated eye.

Keywords: timolol, intraocular pressure, systemic blood pressure, heart rate, ocular perfusion pressure

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1. Introduction

Glaucoma is among the leading causes of blindness in the world (Burton et al., 2020). Systemic and ocular risk factors for glaucoma have been identified, and biomechanical and vascular alterations were suggested, but the exact pathophysiology of this disease is still unknown (Weinreb et al., 2014). Increased intraocular pressure (IOP) is considered as the most significant risk factor for glaucoma and therapy is generally focused on medical, laser and surgical methods for IOP reduction. Topical beta blockers are among the oldest and most efficient medications for treatment of glaucoma. Timolol is a beta blocker that is widely used worldwide as a standard medication for IOP reduction, and its efficacy and safety have been proven (Silverstone et al., 1991; Brooks & Gilles, 1991). The mechanism behind the IOP lowering effect of timolol has not been elucidated yet, but it is generally accepted that timolol affects the production of aqueous humor by blocking the beta-adrenergic receptors of the ciliary epithelium (Barnes & Moshirfar, 2024). However, some reports suggest that the systemic effect of timolol on the cardio – vascular parameters may be the main mechanism of action of the drug (Kiyoga et al., 2024). Studies that report IOP reduction after oral administration of beta blockers may corroborate these suggestions (Duff et al., 1987). Installation of topical timolol in one eye is associated with a decrease in the IOP in the contralateral eye that is generally about one half of the IOP decrease of the treated eye (Dunhan et al., 1994). Topically instilled timolol can be absorbed by the systemic circulation and its non-selective beta-adrenergic receptor antagonist properties limit its uses in patients with pre-existing cardiovascular or respiratory disease (Zimmerman & Kaufman, 1977; Nelson et al. 1986). In addition to IOP, other risk factors have been identified for glaucoma, such as ocular perfusion pressure (OPP), (Seibold et al., 2017) as well as cerebro-spinal fluid pressure (CSFP) (Jonas & Wang, 2013) and trans-laminar pressure difference (TLPD) (Samuels et al., 2012). Previous studies that evaluated the topical and systemic effects of unilateral administration of timolol have not evaluated these risk factors. The aim of this report is to study the effect of unilaterally applied timolol 0.5% on systemic and ocular perfusion and pressure parameters. We also aimed to study the correlation of systemic cardiovascular parameters with ocular perfusion and pressure parameters in the treated and untreated eyes. To the best of our knowledge, this is the first study of the effects of unilateral administration of timolol 0.5% on ocular and systemic pressure and perfusion parameters, such as CSFP, OPP and TLPD.

2. Subjects and methods

This is an experimental clinical study of 14 healthy subjects. Demographic and clinical characteristics of the subjects are presented on Table 1.

Table 1. Clinical Characteristics of Subjects

Clinical characteristics	*Mean (SD)*	*Standard deviation*
Age (years)	44.64	± 9.24
BMI	25.05	± 4.23
SE OD (D)	(-) 0.84	± 2.67
SE OS (D)	(-) 0.64	± 2.63
BCVA OD	1.00	± 0.09
BCVA OS	1.00	± 0.09

Note: *BMI- body mass index, SE- spherical equivalence, BCVA- best corrected visual acuity, RE- right eye, LE- left eye*

Approval for this experimental clinical study was obtained before initial enrollment, from the ethics committee of our hospital (Approval number 3845/2). The study was performed according to the tenets of The Declaration of Helsinki. Informed consent was obtained from all subjects. Exclusion criteria were any acute or chronic ocular pathology, previous ocular surgery (including cataract and ocular refraction surgery), spherical equivalence ≥6D and presence of any systemic disease. Ophthalmic examination included best corrected visual acuity (BCVA), slit lamp examination and autorefractometry. Systemic BP and HR were taken using an automatic brachial sphygmomanometer (Omron Healthcare M3 Comfort, Kyoto, Japan). Body mass index (BMI) was calculated using the formula: weight (kg)/height ^{2} (meters). IOP was measured using an air puff tonometer (Keeler Pulsair, USA). Three measurements were taken for systemic BP, HR and IOP and mean values were calculated. Systemic BP, HR and IOP were taken after the basic examination. Two drops of ophthalmic solution timolol 0.5% were instilled in the right eye (RE) of the subjects. Systemic BP, HR and IOP were measured 30 minutes, one hour, one and a half hour and two hours after the local application. We evaluated the following parameters: systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), mean blood pressure (MBP) (mmHg), HR (bpm), estimated CSFP, IOP (mmHg), estimated TLPD (mmHg) and OPP (mmHg) at each point of measurement.

Mean BP was calculated using the formula:

1. MBP=1/3 SBP+2/3 DBP

CSFP was calculated using the formula:

2. CSFP=0.44*BMI+0.16*DBP-0.18*age-1.91 (Kasahara et al., 2018)

TLPD was calculated using the formula:

3. TLPD=IOP-CSFP

OPP was calculated using the formula:

4. OPP=2/3MBP-IOP

Paired t-test was used to analyse the parameters before and two hours after instillation of topical timolol 0.5%. The mean value of SBP, DBP, HR and IOP of all patients at each point of measurement was taken and Pearson's coefficient of correlation was used to study associations between IOP of each eye and the systemic parameters.

3. Results

Table 2 shows the results from the initial and the last measurements.

Table 2. Systemic and Ocular Pressure and Perfusion Mean (SD) Values of Patients at Initial Presentation and 2 Hours after Instillation of Timolol 0.5%

Systemic and Ocular Pressure and Perfusion Parameters	***Initial***		***After 2 hours***		***P value***
	Mean	***SD***	***Mean***	***SD***	
SBP (mmHg)	113.36 (10.29)	± 10.29	112.21	± 14.91	0.684
DBP (mmHg)	79.71 (8.39)	± 8.39	80.64	± 10.56	0.635
MBP (mmHg)	90.93 (8.16)	± 8.16	91.17	± 11.61	0.911
CSFP (mmHg)	13.83 (2.98)	± 2.98	13.98	± 3.48	0.635
HR (b/min)	78.43 (8.10)	± 8.10	69.07	± 7.36	**0.003**
TLPD RE (mmHg)	1.6 (4.03)	± 4.03	(-)1.92	± 2.57	**<0.001**
TLPD LE (mmHg)	1.98 (4.09)	± 4.09	0.53	± 2.95	**0.006**
OPP RE (mmHg)	45.19	± 5.27	48.87	± 7.11	**0.021**
OPP LE (mmHg)	44.81	± 5.73	46.42	± 7.09	0.241
IOP RE (mmHg)	15.43	± 2.65	11.90	± 1.88	**<0.001**
IOP LE (mmHg)	15.81	± 2.91	14.36	± 2.86	**0.006**
P value IOP RE:LE	0.357		**<0.001**		

Note: *BMI- body mass index, SE-spherical equivalence, BCVA-best corrected visual acuity, RE-right eye, LE-left eye, SBP-systolic blood pressure, DBP-diastolic blood pressure, MBP-mean blood pressure, CSFP-cerebrospinal fluid pressure, HR-heart rate, TLDP-translaminar fluid pressure, OPP-ocular perfusion pressure, IOP-intraocular pressure. Statistically significant values are shown in bold.*

There was a significant reduction (p=0.003) of the HR two hours after unilateral application of timolol 0.5%. IOP significantly decreased in both eyes (RE IOP p<0.001, LE IOP p=0.006). The mean IOP in both eyes during the different time points of measurement is presented in Figure 1.

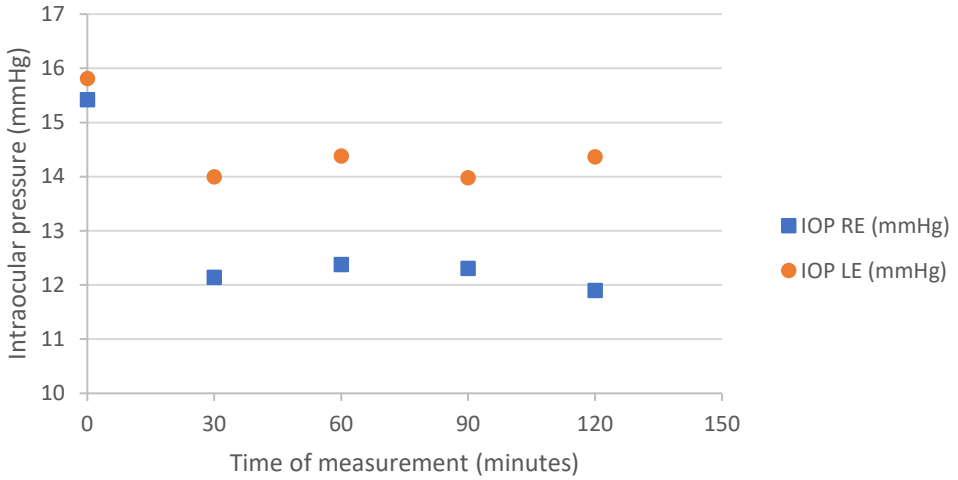

Fig. 1. Intraocular Pressure Values during Five Measurement Points in the Right and Left Eye after Unilateral Application of Timolol 0.5%.
Legend: IOP- Intraocular Pressure, RE – Right Treated Eye, LE – Left Untreated Eye

There was no significant difference between RE and LE IOP at the first measurement before timolol 0.5% application, but two hours after application of timolol 0.5%, the RE IOP was significantly lower than the LE IOP (Table 2).
The TLPD of both eyes also decreased after unilateral application of timolol 0.5% (RE TLPD p<0.001; LE TLPD p=0.006). The OPP significantly increased only in the treated RE (p=0.021). Table 3 shows the coefficients of correlation between mean values of IOP and systemic BP and HR at each measurement point.

Table 3: Coefficients of Correlation R between Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate and Right Eye and Left Eye Intraocular Pressure

Systemic Cardiovascular Parameters	***RE IOP***	***LE IOP***
SBP	0.60	0.80
DBP	0.18	0.40
HR	0.95*	0.85*

Note: *RE-right eye, LE-left eye, SBP-systolic blood pressure, DBP-diastolic blood pressure, HR-heart rate.*
** - statistically significant*

There was a statistically significant correlation between mean IOP and mean HR in both eyes at the five measurement points (RE R=0.95, p=0.01; LE R=0.85, p=0.04). Figure 2 presents the correlation plots between mean HR and mean IOP in the treated right eye and untreated left eye.

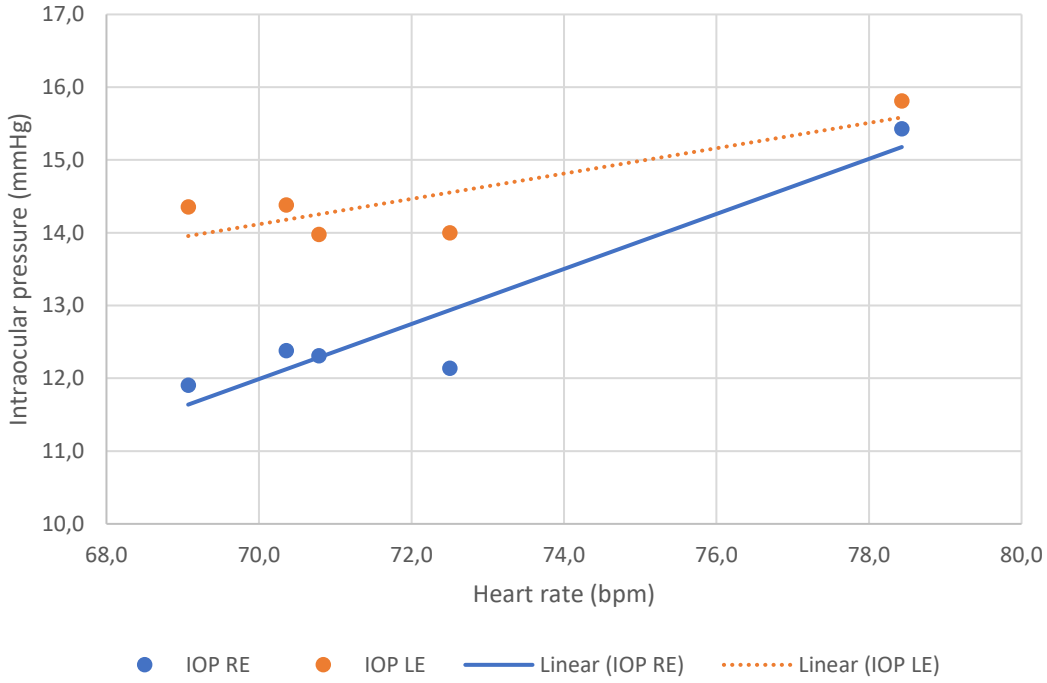

Fig. 2. Correlation between the Mean Values of Heart Rate and Mean Values of Intraocular Pressure at each measurement point in the Right and Left Eye.
Legend: IOP- Intraocular Pressure, Orange Dotted Line – Trend Line of Left Eye, Blue Line – Trend Line of Right Eye

4. Discussion

The results from this study demonstrate that unilateral topical application of timolol 0.5% significantly affects HR in our group of healthy participants. The effect of decreasing HR after topical application of beta blockers has been reported before (Duff et al., 1987).
Some studies even suggested that this may be the primary method of IOP lowering (Duff et al., 1987; Dunham et al. 1994, Seibold et al., 2017) and that the bradycardic effect of beta blockers may in itself have the therapeutic effect on optic nerve circulation and slowing of glaucoma progression (Kiyota et al., 2024).
Unilateral application of timolol 0.5% decreased the IOP of the contralateral untreated eye of our subjects. This has also been demonstrated in previous studies (Dunham et al., 1994). The reason for this effect is not clarified. It may be unlikely that the active

components of the drug reach the contralateral eye by transmission through the nasolacrimal system.
Another suggested mechanism is the "ophthalmotonic consensual effect" that has been disproved in some studies (Newman et al., 2010). Finally, the beta blocker may be absorbed in the systemic blood stream through the conjunctival or nasal blood vessels, which is also suggested by the altered cardio-vascular parameters of our patients. Systemic absorption of the active component after topical instillation of timolol 0.5% solution has been reported (Uuistalo et al., 2005). Therefore the IOP reduction in the contralateral eye could be attributed to the decrease of the HR, as suggested in previous studies (Duff et al., 1987; Dunham et al., 1994; Seibold et al., 2017).
However, the IOP in the treated eye was significantly lower than in the untreated eye at the last measurement following timolol 0.5% application suggesting that the local effect of the agent to the adrenergic receptors in the ciliary epithelium may be the predominant mechanism of action for the IOP hypotensive effect of timolol.
The other formula derived parameters indicated that OPP increased only in the treated eye and TLPD decreased in both eyes. OPP is considered as an indicator of the blood flow perfusion of the eye and optic nerve (Leske, 2009). It was found decreased in both normal tension glaucoma and high-tension glaucoma (Kurysheva et al., 2018). The fact that OPP increased only in the treated eye suggests that timolol 0.5% may increase ocular blood perfusion only when administered topically. It also suggests that the bradycardic effect of beta blockers may be insufficient to achieve the therapeutic effect on optic nerve circulation and slowing of glaucoma progression.
TLPD is the difference between the IOP and the CSFP. Increased TLPD has also been discussed as a possible mechanism for optic nerve damage in glaucoma (Jonas et al., 2015).
Patients with normal tension glaucoma were reported to have lower CSFP than patients with primary open-angle glaucoma and control subjects (Jonas et al., 2015). The pressure gradient between the IOP and the retrobulbar CSFP at the level of lamina cribrosa will increase when CSFP is decreasing. TLPD positively correlated with visual-field loss in patients with open-angle glaucoma (Jonas & Wang, 2013).
In the present study TLPD decreased significantly in both treated and untreated eyes suggesting a possible bilateral effect of timolol on the pressure difference at the region of lamina cribrosa.

4.1 Limitations of the study

Our study was limited by a small number of subjects that may have influenced the significance of some results.
Furthermore, the systemic pressure-related parameters, such as – CSFP, as well as ocular pressure parameters, such as TLPD and OPP were based on calculations, not direct measurements. Estimated CSFP was reported to be a satisfactory surrogate for direct lumbar puncture measurement of CSFP, (Kasahara et al., 2018) and we chose this method because direct measurement is not ethically acceptable.
Nevertheless, we were able to confirm that timolol 0.5% decreases IOP in both treated and untreated eyes. HR significantly decreased two hours after topical unilateral instillation of timolol 0.5% and was significantly associated with IOP. These results corroborate previous reports on the bradycardic effect of timolol 0.5% drops.
We suggest that the ocular hypotensive effect of timolol 0.5% on IOP is based on two mechanisms – the topical effect of the drug to the adrenergic receptors of the ciliary epithelium that is dominant effect and the systemic effect of reduction of the HR that causes additional IOP decrease. TLPD significantly decreased in both eyes, but OPP was significantly increased only in the treated eye.

4.2 Future directions

This study supports the data suggesting the effect of HR on IOP (Duff et al., 1987; Dunham et al., 1994; Seibold et al., 2017; Kiyota et al., 2024). Systemic hypertension and hypotension have been discussed as risk factors for glaucoma, however the effect of altered HR has not been investigated to the same extent as a possible pathogenic mechanism in ocular hypertension and glaucoma. It may be also interesting to study the therapeutic effect of reduction of HR on glaucoma.
A meta-analysis reported that slow deep breathing reduces the HR (Garg et al., 2023). Therefore techniques such as slow deep breathing may be investigated for possible effect on both HR and IOP in patients with glaucoma. We suggest randomised controlled studies involving larger patient groups for future investigation of the effect of HR on IOP.

5. Conclusion

In conclusion, unilateral application of timolol 0.5% decreases IOP and TLPD in both the treated and untreated contralateral eye. HR reduction after unilateral timolol 0.5% application was significantly associated with IOP reduction in both treated and untreated eyes.
However, the IOP hypotension following the bradycardic effect of timolol 0.5% is insufficient to achieve a full therapeutic effect because the OPP was significantly increased only in the treated eye, hence the importance of topical application of the drug.

Ethical approval

Received from the ethics committee of our hospital (Approval number 3845/2).

Conflict of interests

Authors declare no conflict of interests.

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