A Comparison of 0.1% Timolol Eye Gel and 0.5% Timolol Eye Drop in Patients with Chronic Angle-Closure Glaucoma

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***Background**: Primary angle-closure glaucoma has been reported with higher prevalence in Asian populations. There is no significant data of different response of topical medication between angle- closure and open angle eyes.*
***Objective**: The present study investigates ocular hypotensive effect and systemic side effects of 0.1% timolol eye gel once daily compared with 0.5% timolol eye drop twice daily in patients with chronic angle-closure glaucoma.*
***Material and Method**: The present study was a prospective, randomized, investigator-masked, two-period crossover study in chronic angle-closure glaucoma patients with each drug tested for a six-week period.*
***Results**: Twenty five eyes were included. Timolol 0.1% eye gel and 0.5% timolol eye drop significantly reduced IOP at 9 am, 11 am and 3 pm compared with baseline ($p < 0.001$). At week 6, the mean IOP reduction from baseline of 0.5% timolol eye drop group was higher than that of 0.1% timolol eye gel group at 9 am (3.68 mmHg, 2.51 mmHg respectively) and at 11 am (4.21 mmHg, 2.51 mmHg respectively). These differences were not statistically significant ($p = 0.421$, $p = 0.157$ respectively). At 3 pm of week 6, the mean IOP change from baseline of 0.1% timolol eye gel group (3.03 mmHg) was more than that of 0.5% timolol eye drop group (2.84 mmHg). There was also statistically insignificant difference ($p = 0.873$). The highest IOP reduction of 0.5% timolol eye drop was 4.21 mmHg (19.82%) at 11 am of week 6 and that of 0.1% timolol eye gel was 3.03 mmHg (14.38%) at 3 pm of the same week. There was no significant ocular side effect. Systolic blood pressure after treatment with 0.1% timolol eye gel and diastolic blood pressure after treatment with 0.5% timolol eye drop were significantly decreased from baseline ($p = 0.006$ and $p = 0.026$ respectively). But there was no clinical significance.*
***Conclusion**: Timolol 0.5% eye drop and 0.1% timolol eye gel effectively reduced IOP in chronic angle-closure glaucoma patients. There was no statistically significant difference in the ocular hypotensive effect of both drugs over a 24-hour period. There was no ocular side effect. Systemic side effect was clinically insignificant difference in both groups.*

***Keywords**: Timolol eye drop, Timolol eye gel, Chronic angle-closure glaucoma*

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Primary angle-closure glaucoma has been reported with higher prevalence in Asian compared to Caucasian populations[1, 2]. Angle closure is at least as common as open-angle glaucoma in South and East Asia[2]. Medical and surgical treatment are not significantly different to those of open angle glaucoma. Iridotomy has been proven to eliminate pupillary block and prevent acute angle-closure[3, 4]. There is no significant data of different response of topical medication between angle-closure and open angle eyes. Timolol is a non-selective beta-blocker that is commonly prescribed as treatment of elevated intraocular pressure in glaucoma and ocular hypertension[5]. Satisfactory pressure control has been achieved. It has been approved for reduction of intraocular pressure in concentration of 0.1%, 0.25% and 0.5%. Ocular and systemic side effect has been reported, especially in a higher concentration. Timolol 0.1% in hydrogel formulation has been developed to reduce concentration, increase contact time, consequently reduce frequency of application and risk of systemic and ocular side effects[6,7]. The present study investigates ocular hypotensive effect and systemic side effects of 0.1% timolol eye gel once daily compared to 0.5% timolol eye drop twice daily in patients with chronic angle-closure glaucoma.

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Material and Method

The present study was a prospective, randomized, investigator-masked, two period-crossover study in chronic angle-closure glaucoma patients with each drug tested for a six-week period. The Siriraj Institutional Review Board approved the present study in accordance with principle articulated in the Declaration of Helsinki. Each patient provided written informed consent prior to participation.

Inclusion Criteria

The enrolled patients were 18 years or older diagnosed with unilateral or bilateral primary angle-closure glaucoma. Angle-closure glaucoma was defined as either visual field defect or glaucomatous optic neuropathy in association with elevated intraocular pressure and anterior chamber angle grade 0-1 by Shaffer grading system for at least 180 degrees on gonioscopy. Iridotomy was done prior to the present study at least 4 weeks. Best corrected visual acuity was 20/200 or better. Intraocular pressure (IOP) was between 21-30 mmHg in patients without treatment and after a washout period of topical antiglaucoma medication.

Exclusion Criteria

Exclusion criteria consisted of an open anterior chamber angle, previous intraocular surgery and laser therapy other than laser iridotomy, advanced glaucomatous optic neuropathy or visual field defect, ocular inflammation or infection within 3 months of the present study, previous hypersensitivity to benzalkonium chloride or timolol and other abnormal ocular conditions. Patients with a history of asthma, chronic obstructive pulmonary disease, congestive heart failure, use of systemic medication which affected IOP including adrenergic agonists, calcium channel blockers, carbonic anhydrase inhibitors, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers were excluded. Pregnant and childbearing women were also excluded.

Procedures

All patients had a screening visit to assess eligibility prior to the baseline visit. All current ocular hypotensive therapy was discontinued. Washout period consisted of 4 weeks for prostaglandins, 3 weeks for β antagonists, and 2 weeks for adrenergic drugs, cholinergic drugs and topical carbonic anhydrase inhibitors. The baseline examination and the follow up assessment were carried out by the masked examination doctor (A.M. and P.L.). The allocation code was opened by the research nurse who scheduled the patient to each drug group. At the baseline visit, patients were randomized by random number table into groups receiving 0.5% timolol eye drop twice daily or 0.1% timolol eye gel in the morning in the first treatment period. After three-week washout period, patients were evaluated for baseline prior to reversal of treatment in the second treatment period. Patients previously received 0.5% timolol eye drop were switched to 0.1% timolol eye gel and patients previously received 0.1% timolol eye gel were switched to 0.5% timolol eye drop. Patients were asked to bring the present study medication on visiting date and instil it after IOP measurement at 9 am.

The present study comprised of seven visits: pre-study visit, baseline visit for period 1, second and sixth week visit of treatment period 1, baseline visit for period 2, second and sixth week visit of treatment period 2. Deviation of up to one week for baseline visits and four days for the remaining visits was accepted. Pre-study visit included ocular and medical history, visual acuity tested by Snellen chart, intraocular pressure measurement by Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy, dilated fundus examination, resting pulse and blood pressure measurement. Automated perimetry was performed with a Humphrey Field Analyzer (30-2; Humphrey Instruments, Inc, San Leandro, California), if not performed within 6 months.

Examination for every study visit included intraocular pressure measurement by Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland) at 9 am before instilling the study medication, 11 am and 3 pm, visual acuity, slit-lamp biomicroscopy, resting pulse rate and blood pressure measurement. Deviation of half an hour was accepted for tonometry at 9 am, 11 am and 3 pm. Any changes in ocular finding, systemic medication and adverse events were recorded at the end of each treatment period (Fig. 1).

The present study timolol eye drop was timolol maleate 0.5% (Timoptol, Merck, West point, PA, USA), administered twice daily at 9 am and 9 pm. The present study timolol eye gel was 0.1% timolol eye gel (Nyolol eye gel, Novartis, Duluth, GA, USA), administered at 9 am.

Statistical Analysis

T-test or Mann-Whitney U test for period effect and carry-over effect was used to test mean IOP, mean IOP change from baseline, blood pressure change and heart rate change. IOP change from baseline was

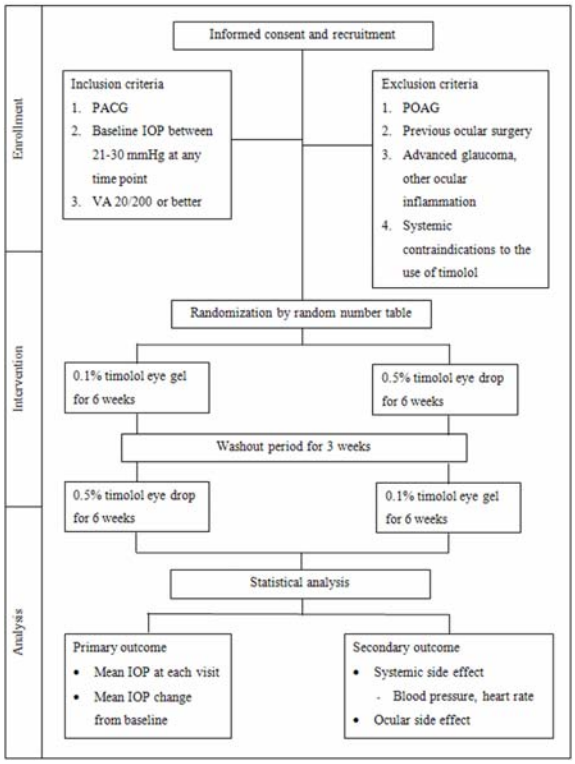

Fig. 1 Flow plan of the study protocal

defined as mean IOP at second and sixth week minus mean IOP baseline of the same treatment period. A p-value of 0.05 or less was considered statistically significant.

Results

Twenty two patients (30 eyes) were enrolled in the present study. Of the 5 patients who were excluded, three patients were lost to follow-up from the first visit, one patient had IOP less than 21 mmHg after washout period and one patient in 0.5% timolol eye drop first treatment group required cessation of treatment due to bradycardia after starting medication. Seventeen patients (25 eyes) completed the 15-week study of the two periods. Demographic data including age, sex and previous ocular medication are shown in Table 1. Twenty-five eyes were included in statistical analysis for IOP.

Intraocular Pressure

Mean baseline IOP of 0.5% timolol eye drop group was greater than 0.1% timolol eye gel group at 9 am and 11 am and lower at 3 pm but there was no statistically significant difference (p>0.05) (Table 2). Diurnal IOP measured at baseline, week 2 and week 6 are shown

Table 1. Demographic data of enrolled 17 patients (25 eyes)

Characteristics	
Age (years)	
Mean $\pm$ SD	62.8 $\pm$ 8.6
Range	42-78
Gender	
Male	2 (11.8%)
Female	15 (88.2%)
Side (eye)	
Right	13 (52%)
Left	12 (48%)
Previous ocular medication (eyes)	
Beta-blocker	22
Beta-blocker and sympathomimetic	2
Alpha-agonist	1

in Fig. 2 and 3. Both medication significantly reduced IOP at all time point compared with baseline ($p < 0.001$). From Table 2, 0.5% timolol eye drop reduced IOP greater than 0.1% timolol eye gel at 9 am and 11 am of week 2 and week 6. In contrast with the lowering effect at 3 pm, 0.1% Timolol eye gel lowered IOP more than 0.5% timolol eye drop at both weeks.

The mean IOP change from baseline of week 2 and 6 at 9 am, 11 am and 3 pm are shown in Table 2. At 9 am (trough) the mean IOP change ranged from 1.93 to 2.51 mmHg in 0.1% timolol eye gel group compared to the mean IOP reduction of 3.27 to 3.68 mmHg in 0.5% timolol eye drop group. There was no statistically significant difference between the two groups. ($p = 0.390$, 0.421, p-for carry-over effect=0.615, 0.704 respectively). At 11 am (2 hours after instillation in which the peak effect was expected) the mean IOP decrease were 1.91 to 2.51 mmHg for 0.1% timolol eye gel group and 3.60 to 4.21 mmHg in 0.5% timolol eye drop group and there was also statistically insignificant difference. However, at 3 pm of both weeks, the mean IOP change of 2.73 to 3.03 mmHg in 0.1% timolol eye gel group was higher than the mean change of 2.47 to 2.84 mmHg in 0.5% timolol eye drop group but there was no statistically significant difference ($p = 0.845$, 0.873, p for carry-over effect = 0.891, 0.829 respectively). The percentage of IOP reduction of 0.5% timolol eye drop was 17.42% (SD = 10.46) and that of 0.1% timolol eye gel was 12.33% (SD = 12.48) at trough. However, the highest IOP reduction of 0.1% timolol eye gel was 14.38% (SD = 7.63) at 3 pm of week 6 and the maximum IOP reduction of 0.5% timolol eye drop was 19.82% (SD = 12.45) at 11 am of the same week.

Ocular Side Effects

There was no significant ocular side effect.

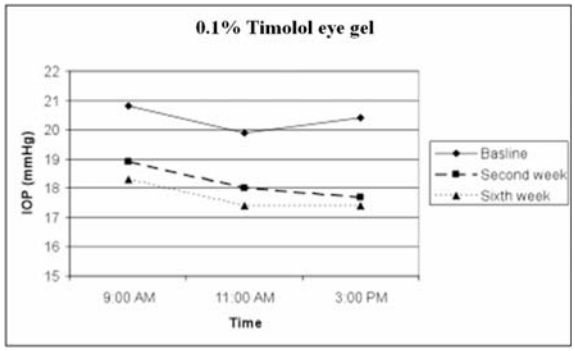

Fig. 2 Diurnal IOP at baseline, second week and sixth week of 0.1% timolol eye gel group

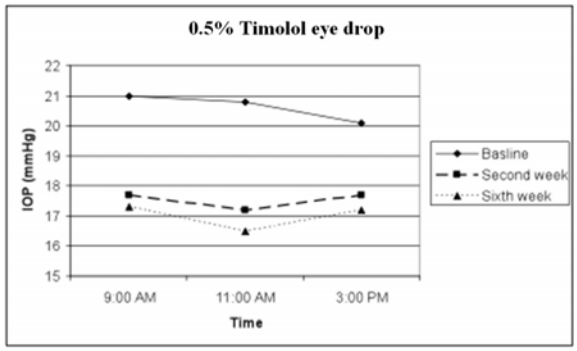

Fig. 3 Diurnal IOP at baseline, second week and sixth week of 0.5% timolol eye drop group

Systemic Side Effects

Mean blood pressure and mean heart rate at 9 am of baseline and 9 am of sixth week are shown in Table 3. Systolic blood pressure after treatment with timolol eye gel and diastolic blood pressure after treatment with timolol eye drop were significantly decreased from baseline ($p = 0.006$ and $p = 0.026$ respectively). But it was clinically insignificant. Mean blood pressure and mean heart rate before and after instillation of both drugs at sixth week are shown in Table 3. There was no significant change of blood pressure and heart rate after treatment in both groups.

Discussion

The present study demonstrated that both medications significantly reduced IOP comparing with baseline IOP at all time point of second and sixth week. Timolol 0.5% eye drop reduced IOP greater than 0.1% timolol eye gel at 9 am and 11 am of week 2 and 6. The highest mean IOP change of 0.5% timolol eye drop group was at 11 am of both weeks. This supported the IOP-lowering effect of timolol eye drop which peaks at 2 hours after instillation and lasts for at least 12-24 hours[9,12]. While 0.1% timolol eye gel may require a longer time to develop the peak response as the authors found in the present study, the IOP-lowering effect of 0.1% timolol eye gel at 3 pm was higher than that at 11 am. The present study observed the trough of the time-response curve by measuring IOP at 9 am, 12 hours after the last dose of timolol eye drop and 24 hours after the last dose of timolol eye gel and the peak of the

Table 2. Comparison between mean intraocular pressure (IOP) and mean IOP change from baseline at 9 am., 11 am. and 3 pm. of week 2 and week 6 in mmHg. (n=25)

	Timolol eye gel		Timolol eye drop		p-value*
	mean (SD)	mean change (SD)	mean (SD)	mean change (SD)	
9 am. (trough)					
baseline	20.81 (3.22)		20.97 (2.42)		
week 2	18.88 (2.29)	-1.93 (2.61)	17.71 (3.10)	-3.27 (3.36)	0.390
week 6	18.31 (3.00)	-2.51 (2.09)	17.31 (2.62)	-3.68 (2.37)	0.421
11 am. (peak)					
baseline	19.87 (3.48)		20.76 (2.31)		
week 2	17.96 (2.09)	-1.91 (2.55)	17.16 (2.90)	-3.60 (3.58)	0.294
week 6	17.36 (2.47)	-2.51 (2.66)	16.55 (2.65)	-4.21 (2.75)	0.157
3 pm.					
baseline	20.41 (2.75)		20.13 (2.41)		
week 2	17.68 (3.22)	-2.73 (2.34)	17.67 (2.44)	-2.47(2.98)	0.845
week 6	17.39 (2.01)	-3.03 (1.79)	17.29 (2.59)	-2.84 (2.71)	0.873

* p-value for the period effect of mean IOP change

Table 3. Comparison of blood pressure and heart rate at 9 am baseline to 9 am of week 6 and 9 am of week 6 (preinstillation) to 3 pm of week 6 (6 hours postinstillation) (n=17)

	9 am baseline mean (SD)	9 am of week 6 mean (SD)	p-value*	3 pm of week 6 mean (SD)	p-value#
Syslolic blood pressure					
Timolol eye gel	138.82 (19.00)	128.82 (15.76)	0.006	123.53 (9.96)	0.095
Timolol eye drop	131.76 (15.10)	127.29 (34.12)	0.284	132.94 (15.32)	0.531
Diastolic blood pressure					
Timolol eye gel	81.76 (10.15)	78.82 (8.57)	0.461	77.06 (6.86)	0.422
Timolol eye drop	81.18 (6.97)	78.82 (7.81)	0.026	79.41 (8.27)	0.791
Heart rate					
Timolol eye gel	77.06 (7.22)	76.41 (4.89)	0.423	75.53 (6.76)	0.608
Timolol eye drop	78.00 (9.19)	75.18 (7.38)	0.567	76.24 (6.89)	0.438

P* = p-value for comparison 9 am baseline to 9 am of week 6
P# = p-value for comparison 9 am of week 6 to 3 pm of week 6

time-response curve was observed at 11 am. At week 2 and 6, diurnal IOP postinstillation of 0.1% timolol eye gel was around 1 mmHg reduction from pre-instillation IOP at 9 am, while diurnal IOP of 0.5% timolol eye drop was less than 1 mmHg changed. This supported the prolonged half-life of timolol, which was reported about 35 hours[12].

The IOP reduction of timolol solution is about 20-25% from baseline [12]. In the present study, the IOP reduction of 0.5% timolol eye drop was 19.82% but the IOP reduction of 0.1% timolol eye gel was 14.38%. These results may be due to the carry-over effect of the previous medication used if the washout period was not long enough since the present study was designed to be a two-period cross-over study. For this reason, the authors tested the carry-over effect at all time point and found that there was no statistically significant difference. The present study demonstrated that timolol eye gel and eye drop had a similar IOP lowering effect in chronic angle closure glaucoma patients, in the same way as in primary open angle glaucoma and ocular hypertension patient[8]. The present study also confirmed the previous study that timolol eye drop administerd twice daily and timolol eye gel administerd once daily are comparable in lowering IOP over a 24-hour period[11].

Timolol maleate is a nonselective β-adrenergic receptor antagonist and well known for its ocular hypotensive efficacy by reducing aqueous humor production[10,12]. Timolol 0.5% solution was the first clinically available topical beta-blocker and has remained a mainstay of glaucoma therapy. Twice-daily dosing is the recommended regimen. Timolol maleate ophthalmic gel forming solution was introduced later which combines timolol maleate with a unique hydrogel vehicle, a highly purified heteropolysaccharide[11]. This bioadhesive gel extends precorneal contact time, increases local ocular absorption, decreases risk of benzalkonium chloride, decreases amount of timolol available for systemic absorption via nasolacrimal duct and allows once-daily dosing[8]. Timolol eye gel had more preference than timolol solution from its once-daily dosing in one study[11].

Ocular toxicity of timolol are usually mild such as burning, conjunctival hyperemia and superficial punctate keratopathy[11,12]. The authors observed no ocular toxicity in both groups. While systemic toxicity of timolol includes slow pulse rate, decrease blood pressure and syncope[11,12]. The authors found decreased systolic blood pressure after week 6 of timolol eye gel use and decreased diastolic blood pressure after week 6 of timolol eye drop use, but there was no clinical significance.

The major limitations of the study were the small sample size, short duration of the follow up time and probably short duration of washout period. These make it difficult to conclude that 0.1% timolol eye gel is comparable to 0.5% timolol eye drop in lowering IOP over a 24-hour period. However, on the basis of the result of the present study, further study about an equivalence or non-inferiority of the ocular hypotensive efficacy should be done.

Conclusion

Timolol 0.5% eye drop and 0.1% timolol eye gel effectively reduced IOP in chronic angle-closure

glaucoma patients. There was no statistically significant difference in the ocular hypotensive effect of both drugs. Ocular side effect was not found in the present study. Systemic side effect, the blood pressure change, was clinically insignificant.

Potential conflicts of interest

None.

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การศึกษาเปรียบเทียบผลของ 0.1% ทิโมลอลชนิดเจลและ 0.5% ทิโมลอลชนิดหยอดในการรักษาต้อหินมุมปิดเรื้อรัง

อังคณา เมธีไตรรัตน์, ปณิธี เลื่อมสำราญ, ศุภมาส โรจนนินทร์, นริศ กิจณรงค์

***ภูมิหลัง**: โรคต้อหินมุมปิดเป็นโรคที่พบบ่อยในชาวเอเชียปัจจุบันยังไม่มีข้อมูลเพียงพอในการเปรียบเทียบผลของยาหยอดระหว่างผู้ป่วยที่มีมุมตาปิดและเปิด*

***วัตถุประสงค์**: เพื่อรายงานผลการลดความดันตาและผลข้างเคียงของร่างกายของ 0.1% ทิโมลอลชนิดเจลใช้วันละครั้งเปรียบเทียบกับ 0.5% ทิโมลอลชนิดหยอดใช้วันละสองครั้ง ในการรักษาผู้ป่วยต้อหินมุมปิดเรื้อรัง*

***วิธีการศึกษา**: การวิจัยแบบสุ่มไปข้างหน้าและบดบังผู้ทำการวิจัย มีสองช่วงในการวิจัยและสลับการรักษาในผู้ป่วยโรคต้อหินมุมปิดเรื้อรัง โดยศึกษายาแต่ละชนิดเป็นเวลาหกสัปดาห์*

***ผลการศึกษา**: จากการศึกษาทั้งหมด 25 ตา ความดันตาเฉลี่ยหลังการรักษาของกลุ่ม 0.1% ทิโมลอลชนิดเจลและ 0.5% ทิโมลอลชนิดหยอดลดลงจากความดันตาเฉลี่ยก่อนการรักษาอย่างมีนัยสำคัญในเวลา 9, 11 และ 15 นาฬิกา ($p < 0.001$) ค่าเฉลี่ยของความดันตาเปลี่ยนแปลงจากก่อนการรักษาของกลุ่ม 0.5% ทิโมลอลชนิดหยอดที่สัปดาห์ที่ 6 ลดลงมากกว่า ค่าเฉลี่ยความดันตาเปลี่ยนแปลง ของกลุ่ม 0.1% ทิโมลอลชนิดเจลที่เวลา 9 นาฬิกา (3.68 มม.ปรอท, 2.51 มม.ปรอท ตามลำดับ) และที่เวลา 11 นาฬิกา (4.21 มม.ปรอท, 2.51 มม.ปรอท ตามลำดับ) แต่ไม่มีนัยสำคัญทางสถิติ ($p = 0.421$, $p = 0.157$ ตามลำดับ) ที่เวลา 15 นาฬิกาของสัปดาห์ที่ 6 ค่าเฉลี่ยของความดันตาเปลี่ยนแปลงของกลุ่ม 0.1% ทิโมลอลชนิดเจล (3.03 มม.ปรอท) ลดลงมากกว่าค่าเฉลี่ย ของความดันตาเปลี่ยนแปลงของกลุ่ม 0.5% ทิโมลอลชนิดหยอด (2.84 มม.ปรอท) ความดันตา ที่ลดลงต่างกัน ไม่มีนัยสำคัญทางสถิติ ($p = 0.873$) 0.5% ทิโมลอลชนิดหยอดลดความดันตาได้สูงสุด (19.82%) ที่เวลา 11 นาฬิกาของสัปดาห์ที่ 6 และ 0.1% ทิโมลอลชนิดเจลลดความดันตาได้มากที่สุด (14.38%) ที่เวลา 15 นาฬิกาสัปดาห์เดียวกัน ยาทั้งสองชนิดไม่มีผลข้างเคียงทางตา ความดันโลหิตซิสโทลิกหลังจากรักษาด้วยทิโมลอลชนิดเจล และความดันโลหิตไดแอสโทลิกหลังจากรักษาด้วยทิโมลอลชนิดหยอด ลดลงอย่างมีนัยสำคัญในสัปดาห์ที่หกเทียบกับก่อนการรักษา ($p = 0.006$ และ $p = 0.026$ ตามลำดับ) โดยไม่มีความสำคัญทางคลินิก*

***สรุป**: 0.5% ทิโมลอลชนิดหยอดและ 0.1% ทิโมลอลชนิดเจลสามารถลดความดันตาได้อย่างมีประสิทธิภาพในผู้ป่วยต้อหินมุมปิดเรื้อรัง โดยไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติในการลดความดันตา ในช่วง 24 ชั่วโมง ไม่พบมีผลข้างเคียงทางตาและผลข้างเคียงทางร่างกายในทั้งสองกลุ่ม*