

Meta-analysis of timolol on diurnal and nighttime intraocular pressure and blood pressure

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PURPOSE. To evaluate the nighttime intraocular pressure (IOP) and blood pressure (BP) response to timolol treatment in patients with ocular hypertension or primary open-angle glaucoma.

METHODS. This was a meta-analysis of previously published studies that must have been randomized, prospective, crossover or parallel, single or double-masked trials. The treatment period must have been ≥ 2 weeks with ≥ 19 patients per treatment arm for a crossover, and ≥ 50 patients for a parallel designed trial. Studies must have included both baseline and treated 24-hour curves.

RESULTS. For the IOP analysis, we included 8 articles with 340 patients. A reduction from baseline was observed for timolol at each time point and for the 24-hour curve ($p \leq 0.009$). When 2 studies, in which timolol was used adjunctively, were removed, a similar difference was observed as above at each time point and for the 24-hour curve ($p \leq 0.003$). In 2 studies, there were small reductions from baseline for the mean diastolic and systolic BPs at most time points and for the 24-hour curve (3.9 and 4.2 mmHg, respectively) with timolol treatment. The ocular perfusion pressure did not show any difference between baseline and timolol treatment at any time point or for the 24-hour curve ($p > 0.05$).

CONCLUSIONS. This meta-analysis suggests that topical timolol therapy provides an ocular hypotensive effect over the 24-hour curve, including the nighttime hours, and while small reductions in the systolic and diastolic pressures occur, the ocular perfusion pressure is not altered over 24 hours.

KEY WORDS. Beta-blocker, Blood pressure, Intraocular pressure, Meta-analysis

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INTRODUCTION

Over the past several decades, beta-blockers have been a commonly used ocular hypotensive medication, showing effective diurnal pressure control in many studies and nighttime control by a number of authors (1-3). Many clinicians have expressed concern that beta-blockers demonstrate limited efficacy and reduced blood pressure (BP) at night. Specifically, Topper and Brubaker found that beta-blockers did not reduce aqueous production or intraocular pressure (IOP) at night (4). Liu and associates more recently showed

that patients in the supine position at night did not experience any pressure reduction with beta-blockers (5).

Hayreh and coworkers have noted that patients with normal tension glaucoma demonstrated lower BP and heart rates on timolol at night (6). Netland and associates showed that a greater percentage of patients on timolol had nocturnal heart rate dipping (< 60 beats/minute) (7). These findings have led to a concern that patients dosed with timolol, especially at night, may demonstrate reduced BP generally or episodic dips in BP that might decrease perfusion pressure and cause glaucomatous progression. Low

BP is believed by a number of investigators to be a risk factor for low normal-tension glaucoma (8-11). Unfortunately, there is little consensus regarding the effect of timolol at night on either IOP or the BP.

The purpose of this meta-analysis was to evaluate studies with IOP or BP data with ocular timolol at night in patients with ocular hypertension or primary open-angle glaucoma.

MATERIALS AND METHODS

Procedures

Articles evaluated in this meta-analysis were those that met the inclusion criteria and were found through the PubMed database (www.pubmed.gov) from its inception in 1966 to April 2008 or by the full articles in the personal file of one of the authors (W.C.S.). Search terms were glaucoma, ocular hypertension, primary open-angle glaucoma, nighttime, IOP, BP, ocular perfusion pressure, BP dipping, and specific glaucoma medicines including timolol and timolol gel forming solution. Generic names of single agent preparations, and these same medicines combined into fixed combinations, were used as search terms.

After potentially relevant studies were identified and studies were excluded based on the inclusion/exclusion criteria, complete articles were retrieved for more details and studies then were excluded based on inclusion/exclusion criteria. Accepted articles for this study met the inclusion criteria of randomized, prospective, crossover or parallel, single or double-masked trial, evaluating a single preparation, with a treatment period of at least 2 weeks and at least 19 patients per treatment arm for a crossover, and 50 patients for a parallel, designed trial. This criterion limiting the sample size was used to assure that individual trials were large enough to have a minimum sufficient statistical power to draw clinically meaningful conclusions. Five of the articles had a sample size calculation. Only subjects with ocular hypertension, exfoliation, or open-angle glaucoma were included. Studies also must have had both baseline and treated 24-hour curves measured with only 1 product (monotherapy preparation or a fixed combination). Included articles also must have measured the IOP at least 3 times during the nocturnal period, from 18:00 to 06:00, and no more than 5 hours should have separated any 2

measurements. At least 3 time points should have been measured in the daytime for comparison. Intraocular pressures must have been measured with Goldmann applanation tonometry when in the sitting position. If nighttime pressures were measured in the supine position a Perkins or Tono-Pen tonometer must have been used. These methods were chosen because Goldmann tonometry is considered the gold standard for measuring the pressure in clinical practice while the Perkins emulates this method in the supine position (12).

In a similar fashion, if the article included BP data at least 3 daytime and 3 nighttime readings must have been provided to be included in the meta-analysis. The ocular perfusion pressure should have been made available in the article or the associated nighttime BP readings and the IOP measurements, ± 1 hour from the BP readings, so that the perfusion pressure could be calculated (see formula in Statistics). These data had to be available from the final active treatment visit and from baseline. Each article was evaluated independently to assure it met the inclusion criteria specified above (P.W.L. and C.J.K.). All articles meeting the above criteria were used in the meta-analysis. No specific exclusion criteria were defined for the study.

Potential articles were further evaluated independently (P.W.L.) for quality according to the Delphi criteria (13). These measures help assure the quality of an article used for a meta-analysis. Each included article did not meet all criteria. All articles met the level II criteria. Two articles by Konstas et al and Stewart et al (15, 18) did not meet all the level Ia and Ib criteria (Tab. I) (14-22). Specifically, in both articles timolol was not randomized, but in both articles the primary intent was not to evaluate timolol efficacy. The first of these studies compared primarily the effect of timolol in exfoliation versus primary open-angle glaucoma (15). The second of these studies evaluated primarily the timing of latanoprost dosing. In this study, patients were treated first with timolol and then randomized to latanoprost either dosed in the morning or evening (18). Since the primary purpose of these studies was not to compare timolol to another active control, we judged based on the Delphi criteria, that these articles should not be excluded.

Statistics

Mean IOP values for the 24-hour curve, and for individual time points, were analyzed for the reduction in pressure from baseline for each treatment arm. Baseline levels could

have been untreated or with prior treatment with one other medicine before timolol was added. Results were analyzed separately for timolol added as monotherapy as well as all monotherapy and adjunctive studies together. We also summarized the reduction in ocular pressure from the 3 nighttime time points (18:00-05:00) and the 3 daytime time points (06:00-17:00). A test of heterogeneity was performed on the 24-hour IOP (23).

The BP, IOP, and perfusion pressure were also analyzed for changes from baseline for timolol for the 24-hour curve, and for individual time points. The perfusion pressures were calculated as $2/3$ [diastolic BP + $1/3$ (systolic – diastolic BP)] – IOP (24).

Six individual time periods were utilized in the meta-analysis to describe mean changes in intraocular, blood, and perfusion pressures over the 24-hour curve. We summarized time points into the following time periods: 02:00-05:00, 06:00-09:00, 10:00-13:00, 14:00-17:00, 18:00-21:00, and 22:00-01:00 (example: a time point of 03:00 was used as a 02:00 time point). For studies that included 2 time points within an individual range described above, an average was taken for both measurements and this number was used as 1 time point (example: pressures taken at 02:00 and 04:00 were averaged and used as the 02:00-05:00

time point). The 24-hour curve was the mean of the 6 individual time points. Quaranta and associates measured only supine nighttime pressures during the nighttime hours (17). The reduction in intraocular pressure from baseline was within the range of the other studies and therefore the Quaranta article was included in this meta-analysis.

Statistical analysis between baseline and timolol treatment for BP, IOP, and ocular perfusion pressure were performed using a random effects model (25).

RESULTS

Patients

The articles used in this meta-analysis are shown in Table I. Originally, from the searched databases, 77 articles were believed to potentially meet the guidelines for the meta-analysis and were obtained for a complete review. Of these, 8 met the inclusion and exclusion criteria, including 8 timolol treatment arms and 340 patients, for the IOP portion of the analysis. Two articles received some level of financial support (14, 21).

TABLE I - ARTICLES INCLUDED IN THIS ANALYSIS

Reference	Abbreviated citation	Article use	Position	Baseline	Treatment	No. patients	Weeks
14	Konstas et al, Arch Ophthalmol 2006; 124: 1553-7	IOP	Sitting	None	Timolol	33	8
					LTFC	33	8
15	Konstas et al, Arch Ophthalmol 1997; 115: 975-9	IOP	Sitting	None	Timolol-POAG	38	26
					Timolol-EXG	38	26
16	Orzalesi et al, Invest Ophthalmol Vis Sci 2000; 41: 2566-73	IOP	Sitting	None	Timolol	20	4
					Latanoprost	20	4
17	Quaranta et al, Invest Ophthalmol Vis Sci 2006; 47: 2917-23	IOP	Sitting and supine	None	Timolol	27	6
					Latanoprost	27	6
18	Konstas et al, Am J Ophthalmol 1999; 120: 15-20	IOP and BP	Sitting	None	Timolol	34	8
					Latanoprost AM	34	4
					Latanoprost PM	34	4
19	Konstas et al, Arch Ophthalmol 2005; 123: 898-902	IOP	Sitting	None	Latanoprost PM	37	8
					LTFC	37	8
20	Tamer and Oksuz, Ophthalmic Res 2007; 39: 24-31	IOP	Sitting	Latanoprost	Timolol	36	4
21	Feldman et al, Curr Med Res Opin 2008; 24: 2403-12	IOP	Sitting	None	Timolol	115	8
					DTFC	117	8
22	Costagliola et al, Graefes Arch Clin Exp Ophthalmol 2008; 246: 389-96	BP	Sitting	None	Timolol	30	4
					Latanoprost	30	4

BP = blood pressure; DTFC = dorzolamide/timolol fixed combination; EXG = exfoliation glaucoma; IOP = intraocular pressure; LTFC = latanoprost/timolol fixed combination; POAG = primary open-angle glaucoma.

We excluded the other articles (n = 69) if they did not isolate the effect of timolol (n = 16), there were not enough IOP measurements (n = 14), there were no comparative non-timolol measurements (baseline or parallel placebo arm, n = 10), subjects were not qualified for this analysis (n = 10), there was insufficient sample size (n = 6), required data for inclusion were not available (n = 4), the article was a review article (n = 4), the article was of insufficient study design (n = 4), or the article was in a foreign language (Japanese, n = 1).

One of these 8 articles, as well as 1 additional article, met the BP analyses inclusion criteria which included 2 timolol treatment arms and 57 patients (18, 22). The 7 other articles, included in the IOP evaluation, were excluded from this portion of the analysis because they did not measure the BP.

Intraocular pressure

The results of the IOP analyses are shown in Table II and Figure 1. A statistical reduction in IOP from baseline for timolol was observed at each time point, and for the 24-hour curve pressure (p≤0.009). When the 2 studies, in which timolol was used adjunctively, were removed, a similar statistical difference was observed, as above, at each time point and for the 24-hour pressure curve (p≤0.003). The mean reduction of pressure from baseline at night (3.6 mmHg) was lower than during the day (5.1 mmHg, p=0.144). Without the one article that measured the pressure at night in the supine position, the results were a 5.0 mmHg reduction

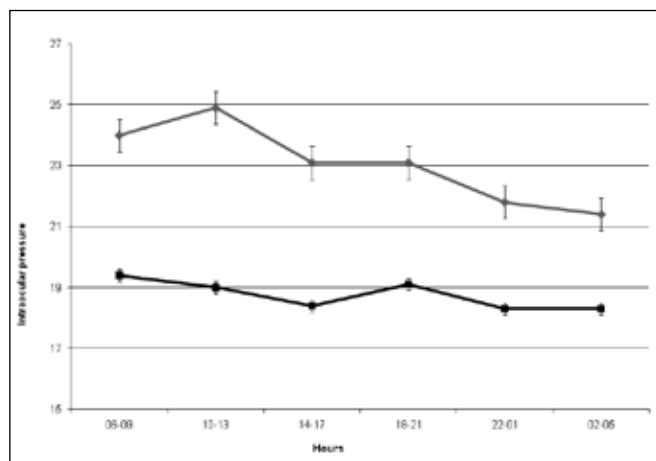


Fig. 1 - The mean intraocular pressure measurements of the 8 utilized articles at each time point at baseline (grey, diamonds) and with treatment (black, squares).

during the day and a 3.6 mmHg decrease during the night. A test of heterogeneity showed the 8 articles were not significantly heterogeneous (p=0.55).

Blood pressure

In 2 studies, there were small reductions from baseline for the mean diastolic and systolic BPs at most time points (p≤0.288) and for the 24-hour curve (p=0.019) for both diastolic and systolic pressures with timolol treatment. The ocular perfusion pressure did not show any difference between baseline and timolol treatment at any time point

TABLE II - BASELINE, TREATMENT, AND 24-HOUR AVERAGE INTRAOCULAR PRESSURES FOR EACH ARTICLE (mmHg)

Reference	06:00-09:00		10:00-13:00		14:00-17:00		18:00-21:00*		22:00-01:00*		02:00-05:00*		24-hour	
	B	T	B	T	B	T	B	T	B	T	B	T	B	T
14	25.7	20.0	27.2	19.8	25.3	18.9	24.8	19.4	24.0	18.8	23.1	18.5	25.0	19.2
15	21.1	18.9	24.0	18.1	21.1	18.2	21.2	18.5	20.1	17.7	19.7	17.8	21.2	18.2
16	23.0	19.5	23.1	20.3	22.0	18.0	22.5	18.8	20.4	18.0	19.0	17.7	21.7	18.7
17	26.4	20.9	26.5	19.2	22.7	17.4	21.7	17.9	21.4	18.6	23.5	19.9	23.7	19.0
18	23.2	20.1	26.4	19.7	22.6	18.8	23.3	19.6	22.1	18.5	20.8	18.0	23.1	19.1
19	25.0	16.2	26.5	16.4	24.5	17.1	23.8	17.4	22.7	16.5	22.9	16.5	24.2	16.7
20	22.6	19.6	21.4	18.8	22.0	19.0	22.7	20.2	21.2	19.3	19.8	18.9	21.6	19.3
21	24.7	19.9	24.3	19.3	24.6	19.7	25.1	20.7	22.8	18.7	22.1	19.0	23.9	19.6
p value	0.0004		<0.0001		0.0001		0.001		0.001		0.009		<0.0001	

*Nighttime hours.
B = baseline; T = treatment.

or for the 24-hour pressure curve ($p \geq 0.537$).

DISCUSSION

Low nighttime BP remains a concern in glaucoma treatment because it potentially may compromise ocular perfusion pressure, which theoretically could lead to progressive optic disc damage. Several prior studies have indicated that patients with normal-tension glaucoma or progressed primary open-angle glaucoma may have an increased incidence of nocturnal BP dipping or reduced 24-hour mean BP (8-10, 26, 27), although these findings have not been completely consistent (11).

Additional concern has existed that timolol, a common ocular hypotensive medicine (2), might aggravate nocturnal ocular perfusion pressure because it may decrease BP without potentially reducing the nocturnal IOP (17). Netland and associates found in patients with primary open-angle glaucoma that timolol reduced the nocturnal heart rate, and increased episodes of bradycardia, compared to controls (7). Hayreh and coworkers found that timolol-treated patients with normal tension glaucoma had a lower nocturnal minimum heart rate, a greater drop in diastolic BP, and an increased incidence in glaucomatous progression than untreated patients (6).

Gherghel and coworkers showed that, in patients with glaucoma with excessive BP dipping, no differences existed in this parameter between patients treated with or without a beta-blocker (28). Quaranta and associates recently found no change from untreated levels in ocular perfusion pressure with timolol while noting an increase in this parameter with latanoprost (17). In a similarly designed 24-hour study, Konstas and coworkers demonstrated that neither the latanoprost/timolol fixed combination nor timolol reduced nocturnal BP or perfusion pressure (29).

In a review of beta-blocker studies, Lama suggested that the maximum systemic impact from a single drop of timolol may not produce a clinically important BP effect (30). This medicine may be relatively short-acting, with a peak plasma level approximately 10 minutes after instillation (31). Controversy remains regarding timolol's effect upon nighttime BP and ocular perfusion pressure, especially when dosed at night.

The purpose of this meta-analysis was to evaluate studies with IOP or BP data with ocular timolol at night in patients with ocular hypertension or primary open-angle glaucoma.

This meta-analysis showed that in studies evaluating the effect of timolol on the IOP over 24 hours a statistical reduction was observed over the 24-hour day, including the nighttime hours. These data are clinically important because it helps confirm the ocular hypotensive effect of timolol at night.

The extent of the decrease of the nocturnal IOP was not as great as that observed in the daytime hours (3.6 and 5.1 mmHg, respectively), although the difference was not statistically significant. The reason for this trend to a lower pressure decrease at night is not known exactly but it may have resulted from the fact that the baseline pressures at night were less than daytime readings. Therefore, the lower baseline pressures, probably resulting from diminished aqueous production as noted above, may have limited the percent reduction derived from timolol during the nighttime hours (4).

It must be noted that the nighttime pressures in this trial were measured in the sitting position after being moved from a sleeping state and supine position. Although Goldmann applanation tonometry is the gold standard for measuring the pressure clinically, a change to the sitting position may reduce pressure. Also, the sympathetic activation upon awakening potentially could have increased aqueous flow and influenced the pressure (32). The most accurate way to measure the pressure clinically at night remains unknown.

Several historical concerns exist about using timolol at night, including a lack of an ocular hypotensive effect and an adverse influence on ocular perfusion. Although not a direct measure of IOP, Topper and associates were unable to detect an aqueous suppressant effect from timolol during the night (4). The reason why no reduction in aqueous production at night might be observed in spite of a number of clinical trials showing an ocular hypotensive effect is not clear by the studies evaluated in this meta-analysis.

Both the systolic and diastolic pressures were statistically decreased at most time points and over the 24-hour pressure curve, from baseline with timolol treatment, including at night. The extent of these reductions was small and consistent with prior studies evaluating data on IOP effects with timolol (32). The calculated ocular perfusion pressure remained unaltered from baseline over the 24-hour pressure curve and at each individual time point with timolol treatment. Our results are fairly consistent with additional internal data by Konstas and Stewart evaluating the 24-hour data of timolol which also demonstrated that timolol

did not affect blood or ocular perfusion pressure (29).

The results of this meta-analysis potentially differ from the results found by Netland and associates, who found a greater percentage of patients dipping to a heart rate of less than 60 beats/minute when treated with timolol (7). This parameter was not specifically evaluated in the current study. Our results potentially differ from those of Hayreh and associates, who indicated that patients demonstrated lower BPs and heart rates at night (6). However, this study did not contain baseline measures and included patients with normal tension glaucoma, which makes comparisons to the current meta-analysis difficult.

This meta-analysis suggests that topical timolol therapy provides an ocular hypotensive effect over the 24-hour pressure curve, including the nighttime hours. While small reductions in the systolic and diastolic pressures occur the ocular perfusion pressure is not altered over 24-hours including the nighttime hours.

This meta-analysis was limited by the number of articles that met the inclusion and exclusion criteria, especially

for BP parameters. The effects upon perfusion pressure might differ according to the cardiovascular condition of the patient, which was not evaluated in this analysis. More well-controlled prospective 24-hour studies are needed that would further confirm or disprove this meta-analysis in regards to the effect of timolol on BP parameters and ocular perfusion pressure, especially at nighttime. In addition, this article did not address other physiologic properties of some beta-blockers that might limit glaucomatous progression apart from ocular hypertensive effect, such as betaxolol and its positive blood flow characteristics (3, 33).

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REFERENCES

1. Stewart WC, Konstas AGP, Nelson LA, Kruff B. Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines. *Ophthalmology* 2008; 115: 1117-22.
2. Stewart WC. *Clinical Practice of Glaucoma*. Thorofare: SLACK Inc.; 1990: 255-97.
3. Ritch R. *The Glaucomas*. St. Louis: Mosby-Year Book, Inc.; 1996: 1426-30.
4. Topper JE, Brubaker RF. Effects of timolol, epinephrine, and acetazolamide on aqueous flow during sleep. *Invest Ophthalmol Vis Sci* 1985; 26: 1315-9.
5. Liu JH, Kripke DF, Weinreb RN. Comparison of the nocturnal effects of once-daily timolol and latanoprost on intraocular pressure. *Am J Ophthalmol* 2004; 138: 389-95.
6. Hayreh SS, Podhajsky P, Zimmerman MB. Beta-blocker eye-drops and nocturnal arterial hypotension. *Am J Ophthalmol* 1999; 128: 301-9.
7. Netland PA, Weiss HS, Stewart WC, Cohen JS, Nussbaum LL. Cardiovascular effects of topical carteolol hydrochloride and timolol maleate in patients with ocular hypertension and primary open-angle glaucoma. *Am J Ophthalmol* 1997; 123: 465-77.
8. Meyer JH, Brandi-Dohrn J, Funk J. Twenty four hour blood pressure monitoring in normal tension glaucoma. *Br J Ophthalmol* 1996; 80: 864-7.
9. Muzyka M, Nizankowska MH, Kozirowska M, Zajac-Pytrus H. Occurrence of nocturnal arterial hypotension in patients with primary open-angle glaucoma and normal tension glaucoma. *Klin Oczna* 1997; 99: 109-13.
10. Yazici B, Usta E, Erturk H, Dilek K. Comparison of ambulatory blood pressure values in patients with glaucoma and ocular hypertension. *Eye* 2003; 17: 593-8.
11. Plange N, Kaup M, Daneljan L, Predel HG, Remky A, Arend O. 24-hour blood pressure monitoring in normal tension glaucoma: night time blood pressure variability. *J Hum Hypertens* 2006; 20: 137-42.
12. Quaranta L, Konstas AGP, Rossetti L, et al. Untreated 24-hour intraocular pressures measured with Goldmann applanation tonometry versus nighttime supine pressures with Perkins applanation tonometry. *Eye* (in press 2010).
13. Verhagen AP, de Vet HC, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998; 51: 1235-41.
14. Konstas AG, Lake S, Economou AI, Kaltsos K, Jenkins JN, Stewart WC. 24-Hour control with a latanoprost-timolol fixed combination vs timolol alone. *Arch Ophthalmol* 2006; 124: 1553-7.
15. Konstas AG, Mantziris DA, Cate EA, Stewart WC. Effect of timolol on the diurnal intraocular pressure in exfoliation and primary open-angle glaucoma. *Arch Ophthalmol* 1997; 115: 975-9.

16. Orzalesi N, Rossetti L, Invernizzi T, Bottoli A, Autelitano A. Effect of timolol, latanoprost, and dorzolamide on circadian IOP in glaucoma or ocular hypertension. *Invest Ophthalmol Vis Sci* 2000; 41: 2566-73.
17. Quaranta L, Gandolfo F, Turano R, et al. Effects of topical hypotensive drugs on circadian IOP, blood pressure, and calculated diastolic ocular perfusion pressure in patients with glaucoma. *Invest Ophthalmol Vis Sci* 2006; 47: 2917-23.
18. Konstas AG, Maltezos AC, Gandi S, Hudgins AC, Stewart WC. Comparison of 24-hour intraocular pressure reduction with two dosing regimens of latanoprost and timolol maleate in patients with primary open-angle glaucoma. *Am J Ophthalmol* 1999; 128: 15-20.
19. Konstas AG, Boboridis K, Tzetzis D, Kallinderis K, Jenkins JN, Stewart WC. Twenty-four-hour control with latanoprost-timolol-fixed combination therapy vs latanoprost therapy. *Arch Ophthalmol* 2005; 123: 898-902.
20. Tamer C, Oksuz H. Circadian intraocular pressure control with dorzolamide versus timolol maleate add-on treatments in primary open-angle glaucoma patients using latanoprost. *Ophthalmic Res* 2007; 39: 24-31.
21. Feldman RM, Stewart RH, Stewart WC, Jia G, Smugar SS, Galet VA. 24-Hour control of intraocular pressure with 2% dorzolamide/0.5% timolol fixed-combination ophthalmic solution in open-angle glaucoma. *Curr Med Res Opin* 2008; 24: 2403-12.
22. Costagliola C, Parmeggiani F, Virgili G, et al. Circadian changes of intraocular pressure and ocular perfusion pressure after timolol or latanoprost in Caucasians with normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol* 2008; 246: 389-96.
23. Wolf FM. *Meta Analysis: Quantitative Methods for Research Synthesis*. Newbury Park: Sage Publications, Inc.; 1986: 44-5.
24. Sehi M, Flanagan JG, Zeng L, Cook RJ, Trope GE. Relative change in diurnal mean ocular perfusion pressure: a risk factor for the diagnosis of primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 2005; 46: 561-7.
25. JMP. *Statistics and Graphics Guide, Version 5*. Cary, NC: SAS Institute Inc.; 2002: 251-64.
26. Graham SL, Drance SM, Wijsman K, Douglas GR, Mikelberg FS. Ambulatory blood pressure monitoring in glaucoma: the nocturnal dip. *Ophthalmology* 1995; 102: 61-9.
27. Kaiser HJ, Flammer J, Graf T, Stumpf D. Systemic blood pressure in glaucoma patients. *Graefes Arch Clin Exp Ophthalmol* 1993; 231: 677-80.
28. Gherghel D, Orgul S, Gugleta K, Flammer J. Retrobulbar blood flow in glaucoma patients with nocturnal over-dipping in systemic blood pressure. *Am J Ophthalmol* 2001; 132: 641-7.
29. Konstas AGB, Pikilidou MI, Tsironi S, et al. 24-hour intraocular pressure and blood pressure levels with latanoprost/timolol fixed combination versus timolol. *Curr Eye Res* 2009; 34: 369-77.
30. Lama PJ. Systemic adverse effects of beta-adrenergic blockers: an evidence based assessment. *Am J Ophthalmol* 2002; 134: 749-60.
31. Nilsson SF, Mäepea O, Samuelsson M, Bill A. Effects of timolol on terbutaline- and VIP-stimulated aqueous humor flow in the cynomolgus monkey. *Curr Eye Res* 1990; 9: 863-72.
32. Stewart WC, Garrison PM. -blocker-induced complications and the glaucoma patient: newer treatments to help reduce systemic side effects. *Arch Intern Med* 1998; 158: 221-6.
33. Stewart WC, Feldman R, Mychaskiw MA. Ocular blood flow in glaucoma: the need for further clinical evidence and patient outcomes research. *Br J Ophthalmol* 2007; 91: 1363-4.