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J Clin Pharmacol 2012 52: 1552 originally published online 22 November 2011
DOI: 10.1177/0091270011420254

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Circadian Intraocular Pressure and Blood Pressure Reduction With Timolol 0.5% Solution and Timogel 0.1% in Patients With Primary Open-Angle Glaucoma

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Purpose: To investigate the circadian and blood pressure (BP) reduction obtained with timolol maleate 0.5% solution administered twice daily versus timolol 0.1% in gel-forming carbomer administered in the morning in patients with primary open-angle glaucoma (POAG). **Methods:** This investigator-masked, crossover study prospectively enrolled naive POAG patients not receiving systemic cardiovascular medications. Following a baseline evaluation, they were randomized to receive a timolol 0.5% solution or timolol 0.1% hydrogel for 2 months and then switched to the alternative medication for a further 2 months. Intraocular pressure (IOP) phasing (sitting Goldmann tonometry at 10 AM, 2 PM, 6 PM, and 10 PM and supine Perkins tonometry at 2 AM and 6 AM) and ambulatory home BP monitoring were measured at baseline and after each treatment period. **Results:** On the basis of a prospective sample size estimate, 28 patients were analyzed. Mean

24-hour IOP decreased from 23.1 ± 0.7 mm Hg at baseline to 18.9 ± 0.6 mm Hg after timolol 0.5% and 18.9 ± 0.8 mm Hg after timolol 0.1% hydrogel ($P < .001$); both formulations also significantly decreased diurnal, nocturnal, and individual time point IOP in a statistically similar manner. Systolic and diastolic BP remained generally unaffected. The calculated diastolic ocular perfusion pressure was either unaffected or tended to increase with either medication. **Conclusion:** Both timolol formulations show similar and significant circadian efficacy and have minimal effects on BP and calculated diastolic ocular perfusion pressure.

Keywords: Timolol; Timogel; glaucoma; primary open-angle glaucoma

Journal of Clinical Pharmacology, 2012;52:1552-1557
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Lowering intraocular pressure (IOP) in patients with primary open-angle glaucoma (POAG) is still the only evidence-based management strategy.¹ For this purpose, the nonselective β -blocker timolol,

together with prostaglandin analogs, is licensed as a first-line therapy and remains one of the most popular topical medications in the treatment of glaucoma. Key advantages of timolol include its efficacy, low cost, extensive familiarity, and superior ocular tolerability.^{2,3} The major drawback with timolol remains the potential for cardiovascular systemic adverse events due to systemic absorption.⁴

Timolol is usually formulated as a 0.25% or 0.5% solution and is administered twice daily. However, more recently, a timolol 0.1% gel-forming carbomer (T-Gel 0.1%) has become available that can be administered only once a day. The potential advantage of a gel formulation is the extended precorneal residence time of the active medication. This may offer a larger proportion of timolol being absorbed in the eye and an extended duration of action, so that

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DOI: 10.1177/0091270011420254

T-Gel 0.1% may be used once daily.⁵⁻⁷ From a clinical viewpoint, the once-daily administration may be highly desirable, as evidence shows that patient compliance is better with once-a-day dosing schemes.⁸

Due to the prolonged ocular surface bioavailability of active ingredients with gel formulations, the amount of medication available for systemic absorption through the nasolacrimal apparatus is decreased, and the likelihood of systemic adverse events may be minimized. This potential advantage may be of clinical relevance, as systemic adverse events often pose a concern in patients treated with topical β -blockers. For instance, it has been found that topical β -blockers affect systemic hemodynamic parameters such as systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate.⁹⁻¹¹ Nonetheless, the effect of different timolol formulations on circadian IOP and blood pressure has not been adequately described.^{8,12,13}

Although it has been shown that both the timolol 0.5% solution and T-Gel 0.1% have comparable daytime efficacy,⁵⁻⁷ there is no published evidence on the circadian IOP efficacy and the effect upon 24-hour blood pressure of these 2 different formulations.

In this current study, we evaluated a T-Gel 0.1% formulation used once daily in the morning in newly diagnosed and previously untreated POAG patients and compared its effect on 24-hour IOP and blood pressure reduction with that of the commonly used timolol maleate 0.5% solution used twice daily.

METHODS

This prospective, randomized, investigator-masked, crossover study complied with the tenets of the Declaration of Helsinki, and its research protocol was approved by the Institutional Review Board of the Medical School of Aristotle University of Thessaloniki. Written informed consent was obtained from all patients before they were enrolled.

All newly diagnosed and previously untreated patients with mild-to-moderate POAG aged >45 years were offered the opportunity to participate in this study. The European Glaucoma Society criteria for the diagnosis of POAG were adhered to, and patients were enrolled if their morning (10:00 \pm 1 hour) untreated IOP was higher than 25 mm Hg.

Exclusion criteria for ophthalmic conditions were any type of glaucoma other than POAG, corneal or other anatomical conditions making applanation tonometry unreliable, central corneal thickness \leq 500

μm or \geq 600 μm , previous laser treatment or any ocular surgery, best corrected visual acuity (BCVA) less than Snellen 0.4, cup-to-disc ratio \geq 0.8, mean deviation worse than -15 dB in Humphrey 24-2 SITA standard perimetry, or the possibility of visual function deterioration and optic nerve damage as a result of study procedures according to the investigator's judgment. Exclusion criteria related to systemic conditions were inability to understand the study procedures and give informed consent and contraindications to β -blocker treatment (obstructive pulmonary disease, second- or third-degree atrioventricular block, bradycardia, and severe heart failure). Additionally, patients were excluded if they had a history of cardiovascular disease (eg, heart disease, arrhythmia, or arterial hypertension) and concomitant systemic treatment that could modify blood pressure (BP), such as β -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or diuretics.

Assessments

During an initial eligibility visit, all study patients underwent a detailed ophthalmic examination. Enrolled participants were admitted to the hospital for an untreated baseline 24-hour IOP assessment at habitual position, with Goldmann tonometry performed at 10:00, 14:00, 18:00, and 22:00 (\pm 1 hour) and Perkins tonometry with the patient supine in bed at 02:00 and 06:00 (\pm 1 hour).

Ambulatory BP was recorded using an automated portable device (TM-2430, A&D Co, Saitama, Japan), which indirectly determines BP by means of oscillometrically measuring the vibratory signals associated with blood flow in the brachial artery, and satisfies the SBP and DBP accuracy levels recommended by the British Hypertension Society and the Association for the Advancement of Medical Instrumentation.¹⁴ An appropriately sized cuff was placed on the participant's nondominant arm, and BP was measured automatically every 15 minutes between 08:00 and 22:00 and every 30 minutes between 22:00 and 08:00. If a reading was not obtained properly, the device was programmed to repeat it. The BP values recorded throughout the 24-hour period were subsequently recovered from the recording chip and stored in a personal computer.

The hospital IOP measurements and home BP monitoring were made on consecutive days in order to prevent any influence of the former on the latter.¹⁵ The first IOP measurements were made every 4 hours from 10 AM on day 1 to 6 AM on day 2, after which the patients were fitted with the dynamic BP

measuring device and were discharged. The device was kept in place for 24 hours (until 7 AM on day 3), during which the patients were asked to follow their usual routine as much as possible. Subsequently, the patients were randomly assigned to 2 months' topical treatment with a timolol 0.5% solution (Timoptol 0.5%, Merck Sharp & Dohme, Rome, Italy) administered twice daily (08:00 and 20:00) or Timogel 0.1% (Laboratoires THEA SA, Clermont-Ferrand, France) once in the morning (08:00). At the end of this period, the patients were again admitted to the clinic to repeat the 24-hour IOP and ambulatory BP assessments in the same way as at baseline. The morning after the assessment, the patients were switched to the opposite medication for a period of another 2 months, after which they were once again admitted to the clinic to repeat the 24-hour IOP and ambulatory BP evaluation.

Patients were instructed to instill the medication by the study nurse (one single drop into the lower conjunctival sac, and nasolacrimal occlusion for at least 1 minute). Patients were asked to give back the bottles of study medications every 3 weeks, and the use of T-Gel 0.1% and timolol 0.5% was verified by the study nurse. In all cases, utilization of medications appeared to be in keeping with the study duration. A detailed clinical examination was performed during all of the periods of hospitalization, and investigator-observed adverse events and patient-reported symptoms or complaints concerning the medication were recorded. The IOP was always measured by 2 well-trained investigators who were unaware of the treatment regimen. The same calibrated Goldmann and Perkins tonometers were used throughout the study.

Endpoints

The primary study endpoints were mean nocturnal and 24-hour IOP. Nocturnal IOP was calculated at baseline and at the end of each treatment period as the mean of the assessments at 2 AM and 6 AM. The secondary endpoints were IOP at each time point, 24-hour SBP, DBP, and diastolic ocular perfusion pressure (DOPP, calculated at each time point as the difference between DBP and IOP). Study drug-related adverse events were also assessed.

Statistical Methods

One eye per patient was analyzed (if both eyes fulfilled the eligibility criteria, the eye with the higher IOP was used). An intent-to-treat approach was used, and in case of missing data, the last observation

Table I Patient Demographics

| | |
|--|-------------------|
| Patients, n | 28 |
| White, n (%) | 28 (100) |
| Age, mean (SD), minimum-maximum, y | 62 (10), 45-78 |
| Male, n (%) | 15 (53) |
| Central corneal thickness, mean (SD), minimum-maximum, μm | 538 (22), 507-579 |

available was carried forward. The safety population included all patients who received at least one treatment. Patients were assigned to treatment groups based on what they actually received. In each patient, for each endpoint, the difference of pressure values at the end of each treatment period versus baseline was calculated and compared by means of a paired *t* test. Incidence of adverse events was analyzed by means of the McNemar test.

The sample size estimate was based on the difference from baseline of IOP after 2 months of treatment with the timolol 0.5% solution or T-Gel 0.1%, with a mean difference of ≥ 1 mm Hg (and a standard difference of 1.5 mm Hg) being considered relevant. At a significance level of .05 for a 2-sided test and a power of .80, it was calculated that 28 patients were required.

Data are presented as mean (standard deviation [SD]) or absolute frequency and percentage. Statistical significance was set at .05. No adjustment for multiple testing was performed. Therefore, all the analyses other than that of the primary endpoint are to be considered as hypothesis generating. The analyses were made using SAS software (Statistical Analysis System, version 9.1, SAS Institute Inc, Cary, North Carolina).

RESULTS

Twenty-eight POAG patients completed the study (Table I). There were no serious systemic adverse effects; all of the reported adverse events were local: timolol 0.5%– and T-Gel 0.1%–related adverse events (the number of patients reporting or being observed having an adverse event, McNemar test): ocular foreign body sensation: 9 (32%) versus 7 (25%), $P = .558$; conjunctival hyperemia: 11 (39%) versus 8 (28%), $P = .401$; ocular itching: 6 (21%) versus 3 (10%), $P = .279$; ocular stinging: 6 (21%) versus 5 (17%), $P = .739$; punctate corneal epitheliopathy: 2 (7%) versus 1 (3%), $P = .556$. None of the patients showed a decrease in BCVA or any signs of glaucoma progression during the study.

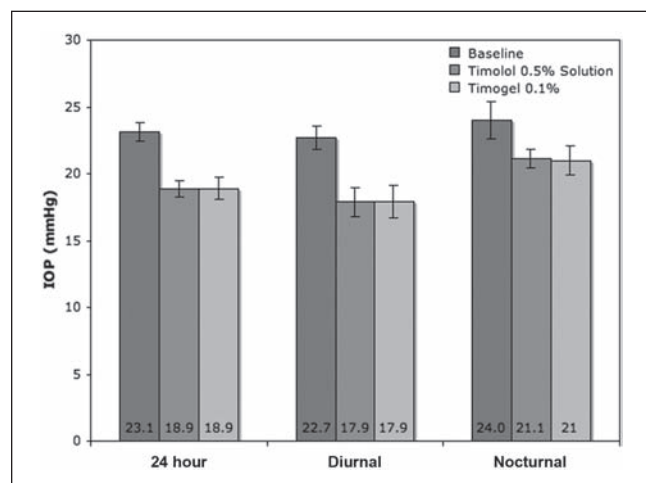


Figure 1. Twenty-four-hour, diurnal, and nocturnal mean intraocular pressure (IOP) curves for the patients at baseline and after treatment with timolol 0.5% solution and T-gel 0.1%. The error bars represent one standard deviation.

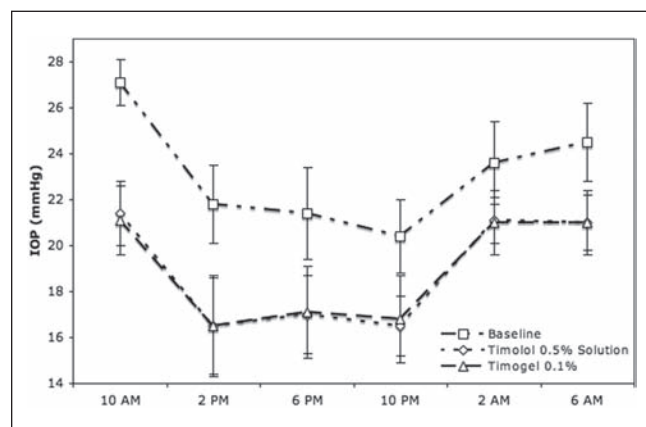


Figure 2. Intraocular pressure (IOP) curves at each time point at baseline and after treatment with timolol 0.5% solution and T-gel 0.1%. The error bars represent one standard deviation.

The trends over time at baseline and after 2 months of treatment with either T-Gel 0.1% or timolol 0.5% of IOP are shown in Figures 1 and 2, while the nocturnal IOP, the IOP at each time point, as well as 24-hour IOP, BP, and calculated DOPP values are described in Table II.

Although each medication significantly reduced IOP with reference to baseline values, the comparison of these decreases between drugs did not show any statistically significant difference for nocturnal IOP, 24-hour IOP, and for each single IOP time point.

DISCUSSION

We examined the 24-hour ocular hypotensive effects and tolerability of a timolol 0.5% solution administered twice daily and T-Gel 0.1% administered in the morning in naive POAG patients not receiving systemic cardiovascular medication. We also investigated the effects of the formulations on SBP and DBP and calculated DOPP throughout the 24-hour cycle. The study was undertaken because of concern that topical β -blockers may be less efficacious during the night and may also decrease ocular perfusion due to alterations in systemic circulatory parameters.^{9-11, 16-19} Hayreh et al have found that patients with normal tension glaucoma treated with timolol have lower nocturnal BP and heart rate,⁹ and Netland et al have reported that nocturnal heart rate dipping (<60 beats/minute) is more frequent in timolol-treated patients.¹⁰ Liu et al have found that patients on β -blockers do not experience any nocturnal reduction in supine IOP.¹⁶

Our findings show that the 2 timolol formulations are equally effective in reducing the IOP of POAG patients throughout the 24-hour cycle. It is worth noting that the nocturnal IOP measurements were made using a Perkins tonometer with the patients lying supine, and so our results differ from those of Liu et al, who did not detect any ocular hypotensive effect in POAG patients receiving 0.5% gel-forming timolol once daily in the morning.¹⁶ It is also worth noting that our patients showed an average difference of 1.3 mm Hg between sitting diurnal and supine nocturnal IOP at baseline, whereas the difference in the patients studied by Liu et al was 2.7 mm Hg.¹⁶ Although we used Goldmann tonometry for the diurnal measurements and Perkins tonometry for the nocturnal measurements, and Liu et al used a pneumatometer for all of the measurements, differences in the study samples might account for these discrepancies.¹⁶

Our efficacy data are in line with those of others^{11,18,20} and with those of a recently published meta-analysis by Lee et al.²¹ In particular, they found that topical timolol treatment is effective throughout the 24 hours, and we found that both timolol formulations were equally efficacious in lowering mean 24-hour, diurnal, nocturnal, and individual time point IOP.²¹

The potential effects of topical β -blockers on BP described in other studies^{9,11,17-19} were not observed during our study. These findings are in line with those of other studies and the recent meta-analysis by Lee et al.^{21,22}

Table II Intraocular Pressure (IOP), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Diastolic Ocular Perfusion Pressure (DOPP) Results

| Endpoints | Baseline | Timolol Mean (SD) | T-Gel 0.1% | Mean Difference (95% Confidence Interval) | Paired <i>t</i> Test (27 df) |
|------------------------|-------------|-------------------|-------------|---|------------------------------|
| Nocturnal IOP | 24.0 (1.3) | 21.1 (0.6) | 21.0 (1.0) | | |
| Difference vs baseline | | -3.0 (1.6) | -3.0 (1.6) | 0.1 (-0.4 to 0.6) | <i>P</i> = .775 |
| 24-hour IOP | 23.1 (0.6) | 18.9 (0.6) | 18.9 (0.8) | | |
| Difference vs baseline | | -4.2 (0.7) | -4.2 (0.9) | 0.0 (-0.39 to 0.37) | <i>P</i> = .975 |
| IOP 10 AM | 17.1 (1.0) | 21.4 (1.4) | 21.1 (1.4) | | |
| Difference vs baseline | | -5.7 (1.6) | -6.0 (1.8) | 0.3 (-0.6 to 1.1) | <i>P</i> = .496 |
| IOP 2 PM | 23.6 (1.7) | 21.1 (1.0) | 21.0 (1.4) | | |
| Difference vs baseline | | -5.3 (2.9) | -5.2 (2.8) | 0.0 (-1.3 to 1.2) | <i>P</i> = .954 |
| IOP 6 PM | 24.5 (1.6) | 21.0 (1.2) | 21.0 (1.4) | | |
| Difference vs baseline | | -4.4 (2.5) | -4.3 (2.7) | 0.1 (-1.0 to 0.7) | <i>P</i> = .731 |
| IOP 10 PM | 20.4 (1.6) | 16.5 (1.3) | 16.8 (1.8) | | |
| Difference vs baseline | | -3.9 (1.8) | -3.6 (1.8) | -0.3 (-1.0 to 0.4) | <i>P</i> = .434 |
| IOP 2 AM | 23.6 (1.7) | 21.1 (1.0) | 21.0 (1.4) | | |
| Difference vs baseline | | -2.5 (2.0) | -2.6 (1.7) | 0.1 (-0.5 to 0.8) | <i>P</i> = .736 |
| IOP 6 AM | 24.5 (1.6) | 21.0 (1.2) | 21.0 (1.4) | | |
| Difference vs baseline | | -3.5 (2.1) | -3.5 (2.2) | 0.0 (-0.6 to 0.7) | <i>P</i> = .914 |
| 24-hour SBP | 126.7 (7.9) | 125.4 (7.1) | 124.8 (9.0) | | |
| Difference vs baseline | | -1.7 (5.5) | -1.5 (4.6) | 0.6 (-2.7 to 4.0) | <i>P</i> = .708 |
| 24-hour DBP | 75.8 (5.9) | 74.1 (6.2) | 74.3 (6.4) | | |
| Difference vs baseline | | -1.3 (7.2) | -1.9 (9.1) | -0.2 (-2.2 to 1.8) | <i>P</i> = .826 |
| 24-hour DOPP | 52.3 (6.9) | 54.9 (6.1) | 54.7 (6.9) | | |
| Difference vs baseline | | 2.61 (5.2) | 2.39 (5.1) | 0.2 (-2.2 to 2.6) | <i>P</i> = .854 |

Epidemiological studies have shown that low calculated DOPP is associated with an increased prevalence and incidence of POAG.²³⁻²⁶ We found that both timolol formulations tended to improve diurnal calculated DOPP, although the improvement did not reach statistical significance.

As we did not examine the long-term prognosis of patients treated with the 2 formulations, no conclusion can be drawn concerning their usefulness in a clinical setting. Similarly, the real advantage of once-daily T-Gel 0.1% instillation over the twice-daily administration of the conventional timolol 0.5% solution remains to be determined. Some other limitations of our study also need to be borne in mind. Specifically, we did not assess patient compliance, and our study sample may have been inadequate to detect differences in adverse events. Additionally, although both Goldmann and Perkins tonometry have been studied in detail and are widely used for similar investigations,^{11,27,28} our findings may not be perfectly comparable with those of investigators who have used different tonometers.¹⁶

In conclusion, the T-Gel 0.1% formulation administered once daily is as well tolerated and has at least the same 24-hour efficacy as the 0.5% timolol solution administered twice daily. Furthermore, both formulations have minimal effects on BP and calculated DOPP throughout the 24-hour cycle.

Financial disclosure: None declared.

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