Meta-Analysis of Randomized Controlled Trials Comparing Latanoprost with Timolol in the Treatment of Asian Populations with Chronic Angle-Closure Glaucoma

Shi-Ming Li¹,²*, Ru Chen²,³, Yuan Li³, Zhi-Rong Yang², Qiu-Ju Deng⁴, Zheng Zhong³, Moh-Lim Ong⁵, Si-Yan Zhan²*

¹Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China, ²Department of Epidemiology and Health Statistics, Peking University School of Public Health, Beijing, China, ³Pfizer China, Beijing, China, ⁴Department of Genetics, Peking University School of Oncology, Beijing Cancer Hospital & Institute, Haidian District, Beijing, China, ⁵Pfizer Global Pharmaceuticals, New York, New York, United States of America

Abstract

Background: To evaluate the efficacy and safety of latanoprost compared with timolol in the treatment of Asian patients with chronic angle-closure glaucoma (CACG).

Methods: Relevant trials were identified through systematic searches of Medline, EMBASE, PubMed, Cochrane Library, Google Scholar and several Chinese databases. The main outcome measures included absolute and relative reduction of intraocular pressure (IOP) at mean, peak and trough from baseline, ocular adverse effects and systemic adverse events.

Results: Seven randomized controlled trials with 685 patients were included. In comparison with timolol, latanoprost reduced absolute IOP in CACG patients by more than 2.3 mmHg (95%CI, 1.8–2.9, P<0.01) and 2.5 mmHg (95%CI, 1.6–3.3, P<0.01) at mean, peak and trough, respectively. For relative IOP, there is 9.0% (95%CI, 6.6–11.4, P<0.01), 9.7% (95%CI, 7.6–11.8, P<0.01), and 10.8% (95%CI, 7.4–14.3, P<0.01) greater reduction among latanoprost users than among timolol users. The differences were statistically significant at all time points (1, 2, 4, 8, 12, and 24 weeks). More ocular adverse effects (OR = 1.49, 95% CI, 1.05–2.10, P = 0.02) and less systemic adverse events (OR = 0.46, 95% CI, 0.25–0.84, P = 0.01) were observed in latanoprost group in comparison with timolol group.

Conclusion: Compared with timolol, latanoprost was significantly more effective in lowering IOP of Asian patients with CACG, with higher risk of ocular adverse effects but lower risk of systemic adverse events, and might be a good substitute for CACG patients.

Introduction

Chronic angle-closure glaucoma (CAG), a disease characterized by elevated intraocular pressure (IOP) resulting from gradual angle closure and a decrease in aqueous humor outflow, is considered as a major form of glaucoma in Asia [1–6]. First-line therapy for CAG is peripheral iridotomy (PI) which is an invasive procedure [7,8]. However, for many CAG patients, PI alone is insufficient to control IOP. Topical β-blockers such as timolol which reduces the aqueous humor generation is usually added to these patients to further lower their IOP.

Latanoprost, a representative of prostaglandin analogs which can significantly reduce IOP by increasing uveoscleral outflow, has been proved to be more effective in lowering IOP in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OH) than timolol [9,10]. As for CAG patients, however, the differences between these two eye drops in efficacy and safety have not been systematically evaluated. Previous studies [11,12] were designed differently, and were mainly performed in Asia-Pacific population. Whether there is difference in lowering IOP among different populations remains unclear. In addition, how long latanoprost can keep a stable level in lowering IOP than timolol is also of concern.

The purposes of this meta-analysis was to systematically evaluate the efficacy and safety of latanoprost compared with timolol in treating Asian patients with CAG, to compare the efficacy and safety difference among these two drugs in Chinese Mainland population and other Asia-Pacific population, and to...
evaluate how long could this difference last and the robustness of the available evidence.

Methods

Search strategy

Articles were identified through a computerized search up to March 2013 in the following data sources: MEDLINE, EMBASE, PubMed and Cochrane Library, Google Scholar and several Chinese databases including CBM (Chinese Biomedical Literature Database), CNKI (China National Knowledge Infrastructure), WANFANG DATA and VIP Database. The keywords were angle-closure glaucoma, latanoprost, xalatan, timolol and timotol. Mesh terms were used if available. Otherwise the keywords were searched in full text. See Table S1 for search strategy in PubMed. References within the retrieved articles from the above search were used to search for additional trials. We also searched in Chinese Clinical Trial Registry, WHO International Clinical Trials Registry Platform and ClinicalTrials.gov for ongoing trials.

Inclusion criteria

Relevant clinical trials (RCT) were selected based on the protocol-determined selection criteria. (i) Study type: RCTs. (ii) Population: Patients with chronic angle-closure glaucoma, including primary chronic angle-closure glaucoma and residual chronic angle-closure glaucoma after laser or surgical treatment. (iii) Intervention: Latanoprost versus timolol in each group without combination of any other drugs. (iv) Primary outcome measures: Absolute and relative IOP reduction from baseline at mean, peak and trough were used for efficacy analysis; Occurrences of ocular and systemic adverse effects were used for safety analysis.

For latanoprost 0.005% once daily, the time points were as close to 12 hours for peak and 24 hours for trough after administration as possible. For timolol 0.5% twice daily, the time points were as close to 2 hours for peak and 12 hours for trough after administration as possible [13]. Mean IOP was defined as the mean value of measurements at all time points throughout the 24-h cycle.

A broad focus on adverse effects was chosen to detect a variety of adverse effects, whether known or previously unrecognized. All cases reported in the studies with information falling under any of the terms ‘adverse effect’, ‘adverse drug reaction’, ‘side effect’, ‘toxic effect’, ‘adverse event’ and ‘complication’ were considered as adverse effects. Ocular adverse effects were defined as adverse effects related with eyes and the remaining was classified as systemic adverse effects in accordance with the term used in the trials.

Screening and data extraction

Trial eligibility was determined by two authors independently (C.R., D.Q.J.). Title, abstract, and medical subject heading words of the obtained publications were initially used for a rough judgment on eligibility of an article. Of the remaining identified publications, the full texts were downloaded for further judgment. Data extraction was performed according to a customized form by two authors (C.R., D.Q.J.) independently. The form covered information on article characteristics [authors, year of publication, location, language, center and funding], study design (type of study, control and intervention, length of wash-out period and study), participants (number, age, gender, race and surgical treatment), and outcomes (IOP, ocular and systemic adverse effects). Any disagreements in article selection and data extraction were resolved by discussion or a third authors (Y.Z.R).

Quality assessment

Methodological quality was evaluated (in duplicate by C.R. and D.Q.J.) using the Cochrane Collaboration tool for assessing risk of bias of clinical trials and figures were generated using RevMan (5.2) [14]. The tool included six individual domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome report and other sources of bias. Each domain had one entry with the judgment of ‘Low risk’, ‘High risk’, or ‘Unclear risk’ of bias and a description of the design, conduct or observations that underlie the judgment. We contacted with the authors by email and waited for a response for at least 4 weeks when information reported in the trials was insufficient to make a judgment.

Statistical analysis

Outcome measures were assessed on an intention-to-treat (ITT) analysis. The ITT population was comprised of all randomized patients who received a minimum of 1 dose of active treatment and provided a valid baseline measurement. Otherwise, available case analysis was used.

Original data were obtained from the articles as much as possible; data that could not be obtained were calculated when necessary. When mean and standard deviation (SD) of IOP reduction (IOPR) were not available directly, they were calculated by the formulas as the following [15–17]:

\[
IOP = IOP_{baseline} - IOP_{endpoint}
\]

\[
SD_{IOPR} = \sqrt{SD_{baseline}^2 + SD_{endpoint}^2 - 2 \times \text{Corr} \times SD_{baseline} \times SD_{endpoint}}
\]

\[
\text{Corr} = \frac{SD_{baseline}^2 + SD_{endpoint}^2 - SD_{change}^2}{2 \times SD_{baseline} \times SD_{endpoint}}
\]

The correlation coefficient indicates correlation between baseline SD and endpoint SD of the measurement, and was calculated from trials with known SD_{change}. For studies that only reported standard errors (SEs), SD was calculated by the formula SD = SE \times \sqrt{n}. The mean and SD of relative IOPR (IOPR\%) were then estimated by the formulas [13,18,19]:

\[
IOPR\% = \frac{IOPR}{IOP_{baseline}}
\]

\[
SD_{IOPR\%} = SD_{IOPR} / IOP_{baseline}
\]

A random-effects model was used if trials were heterogeneous on the basis of the Q statistic for heterogeneity and the reasons for the heterogeneity could not be identified [20,21]. Otherwise a fixed-effect model was used to estimate the pooled effects.

The mean difference (MD) was used to measure the absolute difference between the mean values of two groups in a clinical trial. The MD here referred to the subtraction of mean value in latanoprost group from the mean value in timolol group. The odds ratio (OR) were estimated for the adverse effects using ITT analysis. In the pooling of odds ratio, the Mantel-Haenszel method was used for the fixed-effect model. The method described by
DerSimonian and Laird [22] was used for the random-effects model.

Subgroup analyses between Chinese Mainland population and other Asia-Pacific population were used to investigate heterogeneity of efficacy in different populations. Sensitivity analyses were undertaken to evaluate the effect of quality of randomized controlled trials in terms of the study design, withdrawal rate and pharmaceutical industry support. To detect publication biases, we explored asymmetry in funnel plots. Egger’s measure of publication bias was calculated if more than 10 studies were included [23].

Results

Study eligibility

The selection flow of studies was summarized in Figure 1. In case more than one reason for exclusion was present, only the first reason encountered was listed. The initial search identified 125 studies in English and 140 studies in Chinese. Finally, 7 RCTs [24–30] were included in this meta-analysis.

Trials characteristics

Characteristics of 7 RCTs were summarized in Table 1. These RCTs were conducted in various countries including China [26,28–30], Indonesia [25], Malaysia [25], Philippines [25], Singapore [24,25], Thailand [25], and India [27]. A total of 685 patients were included with 343 in latanoprost group and 342 in timolol group. Three trials [24,27,30] claimed that the authors had no relevant financial interest. Baseline and endpoint IOP were summarized in Table 2. Four trials [24,25,27,28] reported the severity of the adverse effects and no treatment related serious adverse events were observed.

Trials quality

Five authors [24,25,27,28,30] replied our emails with detailed information. Figure 2 presented all judgments (‘Low risk’, ‘High risk’ and ‘Unclear risk’) in a cross-tabulation of study by entry. We were confident of blinding of participants and personnel in three trials [24,25,27], blinding of outcome assessment in four trials [24,25,27,28], random sequence generation in four trials [24,25,27,30], and allocation concealment in five trials [24,25,27,28,30]. There was no clear evidence of publication bias on the funnel plot, although the number of publications included was small (Figure 3).

Efficacy

(1) Absolute IOP reduction. Pooled absolute IOP reductions from baseline for latanoprost and timolol were shown in Figure 4. Mean differences in absolute IOP reduction between two groups were 2.3 mmHg (P<0.01) at mean, 2.4 mmHg (P<0.01) at peak and 2.5 mmHg (P<0.01) at trough, respectively.

(2) Relative IOP reduction. Relative IOP reductions from baseline of two drugs were shown in Figure 5. Mean differences in relative IOP reduction between latanoprost and timolol were 9.0% (P<0.01) at mean, 9.7% (P<0.01) at peak, and 10.8% (P<0.01) at trough, respectively.

(3) Effects at different time points. Absolute reductions in mean and peak IOP between latanoprost and timolol at various time points were shown in Table 3. The differences were all statistically significant with greater reduction in IOP of latanoprost.

(4) Sensitivity analysis. All trials were divided into subgroups by method of blinding and withdrawal, respectively. There

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Figure 1. Flow diagram of the results of the search strategy.
doi:10.1371/journal.pone.0096852.g001
### Table 1. Baseline Characteristics of Eligible Randomized Clinical Trial.

| Studies Design | Latanoprost (%) | Timolol (%) | Center | Location | Funding | Total No. | Withdrawals (%) | Age (Mean ± SD) | Sex (M/F) | Population | Types of glaucoma | Operations | Washout period | Length |
|----------------|-----------------|-------------|--------|----------|---------|-----------|----------------|----------------|------------|------------|-----------------|------------|---------------|--------|
| Aung 2000      | 0.005 eve       | 0.5 bid     | Multi  | Singapore | Singapore Eye Research Institute (partly) | 32         | 9.4             | T:64±7 C:64±8 | 16/16      | Chinese, Malay, Indian | Primary chronic angle-closure glaucoma | After peripheral iridotomy | Yes    | 2 w       |
| Chew 2004      | 0.005 eve       | 0.5 bid     | Multi  | Hong Kong, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand | Pharmacia Corporation | 275        | 6.2             | T:63.3±9.4 C:63.1±9.5 | 70/205    | Asian or Pacific Islander | Chronic angle-closure glaucoma | After peripheral iridotomy | Yes    | 12 w      |
| Kong 2005      | 0.005 eve       | 0.5 bid     | Single | China    | NR       | 49        | 16.3            | T:61.6±8.8 C:60.4±7.9 | 14/35     | Chinese | Residual angle-closure glaucoma | After out-filtrating surgery or iridotomy | NR     | Yes         | 8 w    |
| Liu 2006       | 0.005 eve       | 0.5 bid     | Single | China    | NR       | 60        | 0               | -                | 35/25     | Chinese | Chronic angle-closure glaucoma | NR         | Yes | 2 w         |
| Sihota 2004    | 0.005 eve       | 0.5 bid     | Single | India    | NR       | 30        | 0               | T:57.7±7.4 C:61/24 | 18/12     | Indian | Primary chronic angle-closure glaucoma | After laser iridotomy | Yes | 3 m         |
| Wang 2002      | 0.005 eve       | 0.5 bid     | Single | China    | NR       | 68        | 17.6            | -               | -         | Chinese | Residual angle-closure glaucoma | After peripheral iridotomy | Yes | 6 m         |
| Zhao 2012      | 0.005 eve       | 0.5 bid     | Multi  | China    | Pharmacia Upjohn, China (acquired by Pfizer Inc) | 142        | 0.7             | T:63±7.3 C:61.3±8.9 | 47/94     | Chinese | Chronic angle-closure glaucoma | After laser or surgical peripheral iridotomy | Yes | 8 w         |

CR indicates crossover; DB, double blind; NR, not reported; OL, open label; PG, parallel group; SB, single blind.
eve = evening regimen, bid = twice per day, w = week, m = month.
doi:10.1371/journal.pone.0096852.t001
Table 2. Outcome Measurements of Eligible Randomized Clinical Trial.

| Studies   | Time Points       | Baseline IOP (mmHg) (Mean(SD)) | Endpoint IOP (mmHg) (Mean(SD)) | Ocular adverse effects (Times) | Systemic adverse effects (Times) |
|-----------|-------------------|--------------------------------|--------------------------------|-------------------------------|---------------------------------|
|           |                   | Latanoprost | Peak | Trough | Latanoprost | Peak | Trough | Latanoprost | Peak | Trough | Latanoprost | Peak | Trough | Latanoprost | Peak | Trough | Latanoprost | Peak | Trough | Latanoprost | Peak | Trough | Latanoprost | Peak | Trough | Latanoprost | Peak | Trough |
| Aung2000  | Mean, peak(9AM), | 25.7(3.6)  | 25.2(4.1)  | 26.8(3.8)  | 24.2(3.8)  | 23.5(4.3)  | 16.9(5.2)  | 19.4(2.4)  | 17.0(4.7)  | 20.0(2.6)  | 16.8(5.8)  | 18.9(2.8)  | 14  | 12  | 0  | 1 |
|           | trough (5PM)      |             |           |           |           |           |           |           |           |           |           |           |     |     |   |   |
| Chew2004  | Mean, peak(9AM), | 25.0(5.5)  | 25.9(6.3)  | 25.2(5.5)  | 25.9(6.5)  | 24.8(6.0)  | 25.9(7.1)  | 17.5(5.0)  | 20.7(6.9)  | NR       | NR       | NR       | NR       | 61  | 57  | 17 | 28|
|           | trough (5 PM)     |             |           |           |           |           |           |           |           |           |           |           |     |     |   |   |
| Kong2005  | Mean, peak(9AM), | 24.8(3.3)* | 25.8(3.9)* | 24.7(3.9)  | 26.0(4.4)  | 24.8(3.3)  | 25.5(4.2)  | 15.7(3.2)* | 18.1(3.6)* | 16.1(3.9)  | 17.5(4.0)  | 15.3(3.2)  | 18.8(4.1) | 0  | 3   | 0  | 2 |
|           | trough(4PM)       |             |           |           |           |           |           |           |           |           |           |           |     |     |   |   |
| Liu2006   | Peak(9AM)         | NR          | NR        | 25.3(4.1)  | 24.2(3.5)  | NR        | NR        | 25.3(3.5)  | 25.3(3.5)  | NR       | NR       | 19.1(3.4)  | 20.3(2.5)  | NR  | 2   | 0  | 0 |
| Sihota2004| Mean, peak(10AM),| 23.4(2.1)  | 23.4(2.1)  | 24.6(3.9)  | 22.4(3.1)  | 22.4(3.1)  | 15.3(1.8)  | 17.4(1.7)  | 14.6(2.8)  | 17.9(3.6)  | 15.6(3.1)  | 16.9(3.8)  | 6  | 2   | 0  | 0 |
|           | trough(7PM)       |             |           |           |           |           |           |           |           |           |           |           |     |     |   |   |
| Wang2002  | Peak(9AM)         | NR          | NR        | 24.1(1.0)  | 24.1(1.1)  | NR        | NR        | 24.1(1.0)  | 24.1(1.1)  | NR       | NR       | 17.0(1.0)  | 19.1(1.3)  | NR  | 4   | 5  | 0 |
| Zhao2012  | Mean, peak(9AM),  | 24.3(3.0)  | 24.2(3.0)  | 24.2(3.0)  | 24.2(3.0)  | 24.2(3.0)  | 24.2(3.0)  | 24.2(3.0)  | 24.2(3.0)  | 24.2(3.0)  | 24.2(3.0)  | 24.2(3.0)  | 42 | 24  | 1  | 5 |
|           | trough(4PM)       |             |           |           |           |           |           |           |           |           |           |           |     |     |   |   |

*Pooled value of IOP measured at 10 AM and 4 PM; NR, not reported.

doi:10.1371/journal.pone.0096852.t002
were no statistically significant differences in absolute and relative IOP reduction between double blind/single blind group and open label/not reported group (P = 0.26, 0.36), and between groups with withdrawal rate less than 10% or 10% or more (P = 0.10, 0.22). (See Table S2)

(5) **Subgroup analysis.** Mean differences in absolute IOP reductions at average, peak and trough between latanoprost and timolol were 1.7 mmHg, 2.1 mmHg and 2.7 mmHg in Chinese Mainland population, and 2.5 mmHg, 3.2 mmHg and 2.4 mmHg in other Asia-Pacific population, respectively. For relative IOP reduction at mean, peak and trough, the mean differences between latanoprost and timolol were 7.3%, 8.7% and 11.7% in Chinese mainland population, and 9.6%, 12.2% and 10.7% in other Asia-Pacific population, respectively. The differences between subgroups were neither statistically significant in absolute nor relative mean IOP reduction (P > 0.05). There were no significant differences in absolute IOP reduction between studies with pharmaceutical industry funding and studies without funding (P = 0.38), though greater mean difference of IOP reduction was observed in funded studies (2.6 mmHg, 95%CI, 1.7–3.4) than the studies that did not report any funding (2.1 mmHg, 95%CI, 1.3–3.0). (See Table S3 and Figure S1)

**Safety**

Overall, 129 ocular adverse events (AEs) and 18 systemic AEs were recorded in latanoprost group and 103 ocular AEs and 36 systemic AEs were recorded in timolol group by the 7 clinical studies in our analysis. The frequencies of the most common ocular and systemic AEs in both groups are shown in Table 4.

(1) **Ocular Adverse Effects.** Latanoprost caused more ocular adverse effects (OR = 1.49, 95% CI, 1.05–2.10, P = 0.02) than timolol. The risks for discomfort and conjunctival hyperemia were significantly higher in latanoprost than timolol (P = 0.03 and P < 0.01) (Table 4).
Systemic Adverse Events. More systemic adverse effects were observed in patients treated with timolol than latanoprost (OR = 0.46, 95% CI, 0.25–0.84, P = 0.01). The risk for cardiac disorder was higher in timolol with a borderline statistical value (P = 0.06) (Table 4).

Discussion

In this meta-analysis, the findings from 7 RCTs showed that latanoprost once daily could achieve lower IOP in Asian patients with CACG than timolol twice daily, with differences in absolute IOP reduction for mean, peak and trough of 2.3 mmHg, 2.4 mmHg and 2.5 mmHg, and differences in relative IOP reductions of 9.0%, 9.7% and 10.8%, respectively. These differences could last from 1 week up to 6 months with magnitudes of 2.0 mmHg, 2.0 mmHg, 1.9 mmHg, 1.9 mmHg, 2.3 mmHg, and 2.2 mmHg at 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks and 24 weeks, respectively. Sensitivity analysis based on study design and withdrawal rate didn’t change the results. There were no statistically significant differences in lowering IOP between Chinese Mainland population and Asia-Pacific population (non-Chinese Mainland). As for safety, latanoprost caused more ocular adverse effects and less systemic adverse events than timolol. Our findings confirmed the results of previous trials that latanoprost might be a substitute for timolol in the treatment of patients with CACG.

The difference of mean IOP reduction between these two drugs (2.3 mmHg and 9.0%) in patients with CACG was similar to that in patients with POAG or OH [11,12], for whom the mechanism of latanoprost in reducing IOP was mainly due to increase uveoscleral outflow. One important inclusion criteria for the 7 trials was that there should be at least one quadrant without peripheral anterior synechiae. This criterion was a consideration of the traditional mechanism of latanoprost which was thought to be dependent on the area of visible ciliary body face. However, Ritch et al. [31] found that the efficacy of latanoprost in lowering IOP was independent of the height of ciliary body face. The trial by Kook et al. [32] demonstrated that latanoprost could still significantly reduce the IOP of CACG patients with no visible ciliary body face by percentages of 25.5%, 36.1%. Therefore, latanoprost might produce IOP-lowering effect via passage other than ciliary body face, for example, trabecular meshwork. If so, latanoprost might be a treatment choice for CACG patients at different stages, which deserved further study.

In this meta-analysis, it was found that both latanoprost and timolol were well tolerated by CACG patients. However, latanoprost produced more cases of ocular discomfort (P = 0.03) and conjunctival hyperemia (P<0.01) than timolol, but less systemic advents especially cardiac disorder (P = 0.06). As a whole,

![Figure 4. Comparison of Absolute IOP reductions between latanoprost and timolol.](doi:10.1371/journal.pone.0096852.g004)
Table 3. Absolute IOP reduction from baseline at different time points.

| Time Points | No. of trials | No. of patients | Mean difference (mmHg)(95%CI) | $\chi^2_{sub}$ (p value) | Zoverall (p value) |
|-------------|---------------|----------------|-------------------------------|------------------------|-------------------|
| IOP reduction at mean | | | | | |
| 1 week | 1 | 71 | 70 | 1.8[0.4,3.2] | - | 2.54(0.01) |
| 2 weeks | 2 | 87 | 84 | 2.1[0.9,3.3] | 0.58(0.45) | 3.48(<0.01) |
| 4 weeks | 1 | 71 | 70 | 1.6[0.3,3.0] | - | 2.32(0.02) |
| 8 weeks | 2 | 95 | 87 | 1.7[0.5,2.9] | 0.04(0.83) | 2.81(<0.01) |
| 12 weeks | 2 | 167 | 168 | 2.5[1.8,3.2] | 1.56(0.21) | 6.99(<0.01) |
| IOP reduction at peak | | | | | |
| 1 week | 3 | 69 | 58 | 2.0[1.3,2.6] | 0.99(0.61) | 6.15(<0.01) |
| 2 weeks | 4 | 99 | 88 | 2.0[1.4,2.6] | 1.79(0.62) | 6.42(<0.01) |
| 4 weeks | 2 | 53 | 44 | 1.9[1.3,2.6] | 1.00(0.32) | 5.90(<0.01) |
| 8 weeks | 2 | 53 | 44 | 1.9[1.4,2.5] | 1.54(0.21) | 6.64(<0.01) |
| 12 weeks | 2 | 196 | 195 | 2.3[1.8,2.9] | 3.45(0.18) | 8.25(<0.01) |
| 24 weeks | 1 | 29 | 27 | 2.2[1.5,2.9] | - | 6.29(<0.01) |

$\chi^2_{sub}$ = $\chi^2$ test for subgroup differences.
All pooling was undertaken using fixed effect model as no heterogeneity was detected by Q test.
doi:10.1371/journal.pone.0096852.t003
Latanoprost produced higher risk of ocular adverse effects (P = 0.02) and lower risk of systemic adverse events than timolol (P = 0.01). More ocular adverse effects observed in patients treated by latanoprost might be related to its proinflammatory effect [33]. In addition, higher percentage of benzalkonium chloride, a known irritant of conjunctiva and cornea [34], was involved in latanoprost eyedrop (0.2 mg/ml) than that in timolol eyedrop (0.1 mg/ml), which might be another reason of ocular discomfort [25]. On the contrary, it should be noted that systemic adverse events were more serious than ocular adverse effects. One trial [30] included in the meta-analysis reported that some cases of the timolol group had to stop using timolol because of its systemic adverse events. In view of this, latanoprost may be more suitable for those CACG patients who had concurrently systemic diseases.

The seven trials included in the present study had relatively high quality (Figure 2). Most trials suffered no clear bias in randomization, allocation concealment and outcome reporting. Although only three of these seven trials were free of bias in terms of blindness, sensitivity analysis based on blinding found no significant difference. Considering that the effect of eyedrops is usually dependent on the compliance of patients, we also did sensitivity analysis based on withdrawal rate less than 10% or not. There was no significant difference between the two subgroups. Although only seven trials were included, we did funnel plots and found no publication bias. From the above, we believe that the results in this meta-analysis are robust.

Besides the discriminating among mean, peak, and trough moments, the analysis included both absolute and relative IOP reduction. The included studies did not vary in concentration of the drug, moment of applying, and frequency of dosing for the different medicines. Latanoprost 0.005% eye drops were directly compared with timolol 0.5% eye drops in all of the trials. We undertook subgroup analysis and sensitivity analyses to explore the heterogeneity between population, study design and withdrawals and the results were all robust. However, it should be noted that the differences between these two drugs might be only due to the different frequency of use daily. That is, latanoprost once daily might produce better compliance than timolol twice daily [35,36]. This issue needs to be addressed in future studies.

Some limitations remain in the present study. Firstly, only 7 studies met our inclusion criteria and were included in this meta-analysis, and the numbers of participants in the trials were also limited (range, 30–275). Secondly, several trials lacked adequate randomization, allocation concealment, masking, and complete outcome data, which may leave them vulnerable to bias. The imputation of missing values also introduces bias. However, the studies that contributed the most weight to this meta-analysis were the most methodologically stringent, and according to the result of sensitivity analysis, it is unlikely that poorer quality trials significantly biased the pooled estimates. Thirdly, timolol is commonly used in Europe as 0.25% slow release gel, once or twice daily, so the applicability of the present study may not be as relevant in other populations. Fourthly, not all included studies have all the data for all time points. This might cause bias to the results. Finally, publication bias is inevitable; our research was restricted to studies published in journals or in certain trial registers.

In summary, the present meta-analysis showed that latanoprost once daily could achieve better effect in lowering IOP of CACG patients than timolol twice daily, with higher risk of ocular adverse effects but lower risk of systemic adverse events. Thus, latanoprost may be a good substitute for timolol to lower IOP of CACG patients.

**Supporting Information**

Figure S1 Subgroup analysis of IOP reduction between latanoprost and timolol in studies with and without pharmaceutical industry funding.

![Table 4. Risk of adverse effects with latanoprost and timolol.](TIF)

| Adverse Effects | No. of trials | No. of events/No. of patients | Pooled OR (95%CI) | \( \chi^2 \) _het | P value |
|----------------|---------------|------------------------------|------------------|----------------|--------|
| **Ocular**     |               |                              |                  | \( \chi^2 \) _het | P value |
| Discomfort**   | 5             | 30/284                       | 16/284           | 1.97 (1.05,3.69) | 0.82   | 0.03   |
| Blurred vision | 3             | 29/224                       | 23/224           | 1.33 (0.72,2.46) | 3.70   | 0.37   |
| Conjunctival hyperemia | 4 | 29/254 | 12/254 | 2.72 (1.33,5.59) | 1.33 | <0.01 |
| Keratitis      | 1             | 9/137                        | 8/138            | 1.14 (0.43,3.05) | -      | 0.79   |
| Uncontrolled IOP | 2 | 4/59  | 8/58   | 0.48 (0.14,1.62) | 1.24 | 0.24   |
| Total          | 7             | 129/343                      | 103/342          | 1.49 (1.05,2.10) | 9.75   | 0.02   |
| **Systemic**   |               |                              |                  | \( \chi^2 \) _het | P value |
| Headache       | 2             | 2/153                        | 4/154            | 0.55 (0.11,2.63) | 0.16   | 0.45   |
| Cardiac disorder** | 2 | 0/96 | 6/94 | 0.13 (0.02,1.08) | 0.06 | 0.06   |
| Dizziness      | 1             | 1/137                        | 4/138            | 0.25 (0.03,2.23) | -      | 0.21   |
| Total          | 4             | 18/249                       | 36/248           | 0.46 (0.25,0.84) | 1.41   | 0.01   |

* Discomfort include: eye discomfort, foreign body sensation, eye irritation.
**Cardiac disorder include: palpitation, cardiac arrhythmia.

All pooling was undertaken using fixed effect model as no heterogeneity was detected by Q test.

doi:10.1371/journal.pone.0096852.t004
Table S1 | Search strategy and results.

Table S2 | Sensitivity analysis of absolute IOP reduction at peak between latanoprost and timolol.

Table S3 | Subgroup analysis of IOP reduction between latanoprost and timolol in Chinese Mainland population and Other Asia Pacific population.

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Author Contributions

Conceived and designed the experiments: SML RC YL ZZ SYZ. Performed the experiments: SML RC. Analyzed the data: SML RC. Contributed reagents/materials/analysis tools: SML RC YL ZZ QJD ZRY. Wrote the paper: SML RC SYZ MLO.