Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension

W Y Zhang, A Li Wan Po, H S Dua, A Azuara-Blanco

Abstract

Aim—To evaluate the comparative efficacy and tolerance of latanoprost versus timolol through a meta-analysis of randomised controlled trials (RCTs).

Methods—Systematic retrieval of RCTs of latanoprost versus timolol to allow pooling of results from head to head comparison studies. Quality of trials was assessed based on randomisation, masking, and withdrawal. Sensitivity analyses were used to estimate the effects of quality of study on outcomes. The data sources were Medline, Embase, Scientific Citation Index, Merck Glaucoma, and Pharmacia and Upjohn ophthalmology databases. There were 1256 patients with open angle glaucoma or ocular hypertension reported in 11 trials of latanoprost versus timolol. The main outcome measures were (i) percentage intraocular pressure (IOP) reduction for efficacy; (ii) relative risk, risk difference, and number needed to harm for side effects such as hyperaemia, conjunctivitis, increased pigmentation, hypothension, and bradycardia expressed as dichotomous outcomes; and (iii) reduction in systemic blood pressure and heart rate as side effects.

Results—Both 0.005% latanoprost once daily and 0.5% timolol twice daily reduced IOP. The percentage reductions in IOP from baseline (mean (SE)) produced by latanoprost and timolol were 30.2 (2.3) and 26.9 (3.4) at 3 months. The difference in IOP reduction between the two treatments were 5.0 (95% confidence intervals 2.8, 7.3). However, latanoprost caused iris pigmentation in more patients than timolol (relative risk = 8.01, 95% confidence intervals 1.33, 3.64). Timolol caused a significant reduction in heart rate of 4 beats/minute (95% confidence interval 2, 6).

Conclusion—This meta-analysis suggests that latanoprost is more efficacious than timolol in lowering IOP. However, it often causes iris pigmentation. While current evidence suggests that this pigmentation is benign, careful lifetime evaluation of patients is still justified.
A keyword search was undertaken in the Scientific Citation Index using the words glaucoma/ocular hypertension, latanoprost/ prostaglandin*, timolol/beta-blocker*/beta blocker*/beta-blocker*/beta blocker*. We then read the titles and abstracts of retrieved citations to identify possible RCTs. We also wrote to the manufacturers with our final lists to identify other possible RCTs which our searches failed to identify.

INCLUSION AND EXCLUSION CRITERIA

Only randomised controlled trials directly comparing latanoprost with timolol were included. To facilitate interpretation only studies undertaken in open angle glaucoma (including primary and secondary open angle glaucoma) or ocular hypertension were included.

QUALITY ASSESSMENT

Quality of studies was assessed based on randomisation, masking, and withdrawal as proposed by Jadad. However, we did not allocate any additional score to an RCT according to whether it described the method of randomisation. In our view, this is a feature of the reporting of the trials and allocation of additional points may be arbitrary. A randomised study was defined as one in which the investigators reported it as being randomised without necessarily defining the randomisation method explicitly since in the past this was not a requirement in the reporting of RCTs. Masking was differentiated as double blind, single blind and open label. Parallel and crossover designs were also categorised. The percentage of withdrawals was calculated. The impact of all these quality components on our meta-analysis was assessed using sensitivity analysis.

DATA EXTRACTION

Two of us (WYZ, ALWP) undertook data extraction independently. Any disagreement was resolved by discussion. A customised form was used to record the authors of the study, the year of publication, design of trial (double blind or single blind, parallel or crossover), location of trial, length of study, number of subjects, patient age, sex, type of glaucoma, baseline IOP, and end point IOP. In addition, we recorded the proportion of withdrawals, number of patients reporting local side effects (such as hyperaemia, conjunctivitis, and increased iris pigmentation) and systemic side effects (such as bradycardia, hypotension, and headache).

STATISTICAL ANALYSIS

We abstracted the mean and standard error of the IOP at baseline and end point from individual studies to calculate the mean IOP reduction (IOPR) and within group standard error (SEIOPR) using

\[
IOPR = \frac{IOP_{\text{baseline}} - IOP_{\text{endpoint}}}{IOP_{\text{baseline}}} 
\]

\[
SE_{IOPR} = \sqrt{SE_{IOP_{\text{baseline}}}^2 + SE_{IOP_{\text{endpoint}}}^2} 
\]

The percentage IOP reduction (IOPR%) and its standard error (SEIOPR%) was then estimated by

\[
IOPR\% = \frac{IOP_{\text{baseline}} - IOP_{\text{endpoint}}}{IOP_{\text{baseline}}} \times 100 
\]

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

The difference of the IOP reduction and its standard error between treatment groups was then calculated for each individual study. For estimating the weighted pooled difference in effect, the method previously described by was used. The relative risk (RR), risk difference (RD), and number needed to harm (NNH) were estimated for the adverse effects using intention to treat analysis. Interval estimation of relative risk and risk difference were as described by Rothman. In the pooling of relative risk and risk difference, the method described by DerSimonian and Laird was used. The number needed to harm and its 95% confidence intervals (95% CI) were estimated as described by Cook.

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**Table 1 MeSH search strategy**

<table>
<thead>
<tr>
<th>Stage 1 Diseases</th>
<th>Stage 2 Drugs</th>
<th>Stage 3 Study methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>exp glaucoma* or exp glaucoma, open angle*</td>
<td>exp prostaglandins I, synthetic*</td>
<td>exp clinical trials* or exp randomised controlled trials*</td>
</tr>
<tr>
<td>exp ocular hypertension*</td>
<td>exp adrenergic β antagonists*</td>
<td>exp double blind method*</td>
</tr>
<tr>
<td>1 or 2</td>
<td>4 and 5</td>
<td>8 exp single blind method*</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>9 exp single blind method*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 exp random allocation*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 7 or 8 or 9 or 10</td>
</tr>
</tbody>
</table>

Finally, we combined three stages together using: 3 and 6 and 11

exp = explode.

*M MeSH search including all subject headings under the title
Meta-analysis of RCTs comparing latanoprost with timolol in the treatment of open angle glaucoma or ocular hypertension

A random effects model was used if trials were heterogeneous on the basis of the $Q$ statistic for heterogeneity and the reason for the heterogeneity could not be identified. In addition, to compare latanoprost and timolol, the study also investigated the effects of the evening regimen, morning regimen, and twice daily regimen of latanoprost in reducing IOP.

### Results

**Characteristics of trials**

Twenty-five potential RCTs associated with latanoprost and timolol in the treatment of glaucoma were identified through the literature search. Eleven of them met our inclusion criteria. The flow of the RCTs included in our analysis is shown in Figure 1.

Randomised controlled trials included were undertaken in various countries including the USA, Canada, Japan, the UK, other European nations, and Scandinavia (Table 2). There were eight double blind parallel studies, two double blind crossover studies, and five multicentre RCTs. Length of studies varied from 1 week to 1 year. Latanoprost 0.005 % or 0.006% eye drops were directly compared with timolol 0.5% eye drops in all of the studies. Patients received two identical dropper bottles labelled morning or evening. For patients treated with timolol, both bottles contained timolol, whereas for those treated with latanoprost, one contained the vehicle. A total of 1256 patients were included in the analysis. Withdrawals varied from 0% to 11%. The range of mean ages was from 46 to 67 years. Of the data available on sex, 597 of the patients were male and 593 were female. Of the data available on types of glaucoma, 410 subjects had primary open angle glaucoma (POAG), 465 ocular hypertension (OH), and 137 other types of chronic open angle glaucoma (others). IOP was used as the primary outcome for efficacy in all of the studies included in the meta-analysis. Baseline and end point IOP were summarised in Table 2.

### Efficacy—IOP reduction

The percentage reductions in IOP with latanoprost and timolol at various time points are shown in Table 3. Both drugs significantly decreased IOP. Latanoprost showed better IOP lowering effects than timolol with an additional 4–7% reduction. The differences were all statistically significant except for the result from a single 12 month study (Fig 2).

### Side effects

**Pigmentation**

(1) Short term

Latanoprost caused hyperaemia and iris pigmentation in more patients than timolol (Table 4). The risk for hyperaemia was over twice that seen with timolol ($RR = 2.20$, 95% CI 1.33, 3.65). The number needed to harm was 21 (14, 42) relative to timolol. Treating 21 patients with latanoprost will on average lead to one more patient developing hyperaemia. Moreover, of 478 patients who were treated...
Table 3 Percentage IOP reduction from baseline with latanoprost and timolol

<table>
<thead>
<tr>
<th>Trial</th>
<th>Percentage IOP reduction (mean (SE))</th>
<th>Percentage IOP reduction (mean (SE))</th>
<th>Difference of the reduction (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latanoprost</td>
<td>Timolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week</td>
<td>19.8 (6.2)</td>
<td>11.3 (5.4)</td>
<td>8.5 (−7.6, 24.7)</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>25.8 (5.8)</td>
<td>19.8 (5.3)</td>
<td>6.0 (−5.9, 21.3)</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>31.2 (2.8)</td>
<td>24.4 (2.9)</td>
<td>6.8 (−1.0, 14.7)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>28.7 (2.3)</td>
<td>21.2 (2.5)</td>
<td>7.5 (1.0, 14.0)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>3.16</td>
<td>4.59</td>
<td>-0.43 (−1.8, 0.9)</td>
<td>0.48</td>
</tr>
<tr>
<td>1 month</td>
<td>19.4 (5.6)</td>
<td>8.5 (2.4)</td>
<td>11.0 (−9.0, 22.8)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>24.1 (1.3)</td>
<td>19.9 (1.1)</td>
<td>5.2 (−0.8, 8.2)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>34.3 (1.5)</td>
<td>34.0 (1.5)</td>
<td>0.3 (−3.9, 4.6)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>27.3 (4.0)</td>
<td>20.9 (6.3)</td>
<td>3.8 (1.2, 6.3)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>24.0 (4.4)**</td>
<td>94.22**</td>
<td>4.57</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>33.7 (2.6)</td>
<td>29.7 (1.7)</td>
<td>4.0 (−2.1, 10.1)</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>37.1 (4.0)</td>
<td>31.7 (3.8)</td>
<td>5.4 (−5.5, 16.3)</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>24.9 (2.9)</td>
<td>21.7 (2.8)</td>
<td>3.2 (−4.7, 11.1)</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>26.8 (1.3)</td>
<td>19.0 (1.1)</td>
<td>7.8 (−4.4, 11.2)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>34.7 (1.4)</td>
<td>32.8 (1.5)</td>
<td>1.9 (−2.6, 6.1)</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>31.2 (2.3)</td>
<td>26.9 (3.4)</td>
<td>5.0 (2.8, 7.3)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>24.01**</td>
<td>65.50**</td>
<td>4.97</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>32.1 (2.6)</td>
<td>27.2 (1.7)</td>
<td>4.8 (−1.3, 11.0)</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>26.5 (1.2)</td>
<td>19.4 (1.0)</td>
<td>7.1 (4.0, 10.0)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>24.3 (4.3)</td>
<td>20.0 (3.0)</td>
<td>4.5 (−5.7, 14.6)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>34.7 (1.4)</td>
<td>33.2 (1.3)</td>
<td>1.5 (−2.8, 5.6)</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>29.9 (2.6)</td>
<td>25.0 (3.7)</td>
<td>5.0 (2.8, 7.3)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>21.14**</td>
<td>64.61**</td>
<td>4.57</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>24.1 (4.6)</td>
<td>19.2 (3.1)</td>
<td>4.9 (−5.9, 15.8)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure. Percentage IOP reduction = (baseline IOP − end point IOP)/baseline IOP × 100%. SE = standard error. \( \chi^2 \) = \( \chi^2 \) test statistic for heterogeneity. **p < 0.001, random effects model were used for pooling.

(2) Long term

Three studies\(^{24-26}\) explored the long term iris darkening effects of latanoprost for up to 2 years after the randomised controlled blinded phases.\(^{27-29}\) The risks of iris pigmentation are shown in Figure 3.

There was an increased incidence of pigmentation with time although in none of the studies did the difference reach statistical significance at the usual 5% level. The iris pigmentation appears more likely to be with brownish mixed iris colour eyes and this may explain the apparently different incidence rates in the different countries (Table 5).

Four studies compared systemic adverse reactions to timolol versus latanoprost, such as their effects on systolic blood pressure and heart rate. Timolol caused slowing of heart rate after 3 or 6 months of treatment (Table 6), and this returned to the baseline level after switching to latanoprost.\(^{27}\)

EFFECTS OF DIFFERENT REGIMENS OF LATANOPROST

The evening regimen was compared with the morning regimen of latanoprost (Table 7). The pooled percentage IOP reductions (mean (SE)) were 33.2 (1.4) and 28.1 (1.1) for the evening regimen and the morning regimen respectively. The pooled difference was 5.1% (p = 0.006) (Table 7).

In addition, the once daily evening regimen of latanoprost was compared with the twice daily regimen (Table 8). Although the evening regimen was marginally better than the twice daily regimen (p = 0.08) in one of the trials, pooling with other trials produced numerically
but not statistically different IOP reductions (5.5%, \(p=0.17\)) (Table 8).

**SENSITIVITY ANALYSES**

Sensitivity analyses were undertaken to evaluate the effect of quality of randomised controlled trials in terms of the study design and withdrawal rate. Trials designed as double blind parallel, double blind crossover, and single blind parallel studies were stratified and the percentage IOP reduction between latanoprost and timolol were compared. There were no statistically significant differences between the groups. In addition, we divided the studies into two groups according to withdrawal rate (less than 10% and more than 10%). The results showed that the withdrawal rate was not a significant factor (Table 9).

**Discussion**

Glaucoma which causes optic nerve damage and visual field loss is the most important cause of irreversible blindness worldwide. About 66.8 millions people have glaucoma, 6.7 million of whom are bilaterally blind. Pharmacological treatments for glaucoma aim to lower IOP and thereby reduce the risk of optic nerve damage. Studies have shown that reduction of IOP prevents development of glaucoma or visual field loss and indeed if the IOP is substantially lowered through treatment, the rate of progression of glaucoma is reduced even among those patients with normal tension glaucoma.

Latanoprost is one of the first prostaglandins to be used on a chronic basis in glaucoma patients. Our meta-analysis based on 11

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**Table 4 Risk of side effects with latanoprost and timolol**

<table>
<thead>
<tr>
<th>Side effects</th>
<th>No of trials</th>
<th>Crude event rate</th>
<th>RR (95% CI)</th>
<th>RD (95% CI)</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals due to adverse effects</td>
<td>2</td>
<td>9/277</td>
<td>14/285</td>
<td>0.70 (0.30, 1.66)</td>
<td>−0.02 (−0.05, 0.16)</td>
</tr>
<tr>
<td>Hyperaemia</td>
<td>6</td>
<td>51/586</td>
<td>20/503</td>
<td>2.20 (1.33, 3.65)**</td>
<td>0.05 (0.02, 0.07)**</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3</td>
<td>7/419</td>
<td>5/320</td>
<td>0.80 (0.25, 2.53)</td>
<td>0.006 (−0.001, 0.002)</td>
</tr>
<tr>
<td>Increased pigmentation</td>
<td>4</td>
<td>21/478</td>
<td>0/387†</td>
<td>8.01 (1.87, 34.30)*</td>
<td>0.03 (0.01, 0.04)**</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>0/149†</td>
<td>2/145</td>
<td>0.19 (0.01, 4.29)</td>
<td>−0.01 (−0.04, 0.01)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1</td>
<td>0/87†</td>
<td>2/91</td>
<td>0.21 (0.01, 4.29)</td>
<td>−0.02 (−0.06, 0.02)</td>
</tr>
</tbody>
</table>

RR = relative risk; RD = risk difference or attribute risk; NNH = number needed to harm; CI = confidence interval.

†For trials with event rate of zero, 0.5 was added to each cell of the individual \(2 \times 2\) table to calculate RR, RD, or NNH.

*\(p<0.05\), **\(p<0.01\).
published clinical trials shows that 0.005% latanoprost applied topically once daily is superior to 0.5% timolol twice daily in reducing IOP. Latanoprost brings about an additional 5% decrease in IOP (95% CI 3%, 7%), or an average 1.6 mm Hg (p<0.001) further lowering in IOP when compared to timolol. The studies include both company sponsored and non-company sponsored RCTs and were undertaken in various countries including North America (USA and Canada), Asia (Japan and Philippines), and Europe (UK, Germany, Holland, Italy, and Scandinavia). The results are similar to those of a previous meta-analysis of eight company sponsored studies, which demonstrated that latanoprost produced an additional 1.7 mm Hg (p<0.001) reduction in IOP compared to timolol. It has been suggested that the timing of IOP measurement is important when comparing latanoprost with timolol. The peak IOP reducing effect of latanoprost is reached 8–12 hours after the drug has been administered, and at this time point timolol is at trough values. Therefore, a single time measurement of IOP in the morning—for example, at 9 am, would catch the peak value of latanoprost but not the trough value of timolol when both are administered the previous evening. In order to avoid such bias, we calculated the mean value of IOP measured in the morning, noon, and afternoon for our analysis except for the Japanese trial, which only measured IOP in the morning. In the Japanese trial, although the IOP was measured in the morning at 9 am, latanoprost was comparable with timolol because it was administered in the morning while the second dose of timolol was administered in the evening. The comparison therefore presented trough values for both drugs.

Alm et al compared evening and morning administrations of latanoprost and found that the evening application was more effective than the morning application at 3 months but not at 6 months. This may be caused by carryover effect from the crossover design. Konstas et al also failed to establish the superiority of an evening regimen over a morning regimen from his 2 month crossover study. To exclude carryover effect, only the results from the first period before crossover were used to compare the two treatment regimens (Table 7). The results confirm that the once daily evening regimen of 0.005% latanoprost is superior to the once daily morning regimen.

Poor compliance is a major problem with most topical agents in the treatment of open angle glaucoma because they usually require at least three times daily administrations. In contrast, latanoprost only needs a once daily administration. Some studies have compared the once daily regimen with the twice daily regimen of this agent and did not find any statistical difference with the same concentration. Others have reported the superiority of the lower concentration of latanoprost (0.005%) once daily over the lower concentration of latanoprost (0.0015%).

Our meta-analysis shows no statistically significant difference in IOP reductions between the two regimens of 0.005% latanoprost twice daily. Thus, once daily application appears adequate for this agent. This is obviously due to the longer action of latanoprost, which may be particularly useful for the elderly. Compliance should be good but comparative data with other treatments are necessary.

Unlike β blockers and some other currently used medications such as carbonic anhydrase inhibitors and α2 agonists, latanoprost acts on outflow rather than formation of aqueous humour. Because latanoprost increases uveoscleral outflow, it can theoretically reduce IOP below episcleral venous pressure. This may be advantageous in patients with normal tension glaucoma. In fact, one trial suggested that 0.005% latanoprost produced lower reducing of ocular perfusion pressure than 0.5% timolol in normal tension glaucoma. Latanoprost may reduce IOP without reducing systemic blood pressure. In contrast, timolol may reduce both of these.

Bradycardia and bronchospasm caused by ophthalmic timolol have been
reported in patients with cardiovascular or pulmonary disorders. Therefore, caution is necessary in the use of timolol in such patients. In contrast, latanoprost does not alter heart rate and blood pressure,
12 30 35 and does not affect respiratory function in asthmatic patients.
55 The major adverse reaction to latanoprost is an increase in iris pigmentation. This risk may be as high as 18% within a 2 year period and varies according to the types of iris colour (Table 5). The iris darkening associated with latanoprost may reflect induction of tyrosinase, the rate limiting enzyme in the formation of melanin.
56 Latanoprost does not induce iris melanocyte mitosis.
57 While recent evidence suggests that the problem is purely cosmetic, ongoing surveillance is necessary.

UK prices suggest that if we adopt a conservative approach and assume that latanoprost once daily and timolol twice daily are equivalent in effectiveness, latanoprost is three times more expensive than timolol. However, a rigorous economic evaluation considering differences in both efficacy and side effects of these two agents is required. Intercountry differences in prices will obviously also need to be considered.

In summary, latanoprost is superior to timolol for reducing intraocular pressure. Increase in iris pigmentation is still a concern. For patients in whom timolol is contraindicated, latanoprost is in our view a suitable alternative.

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23 Orzalesi N, Circhton A, Mills RP. Comparison of the effect of latanoprost 0.005% and timolol 0.5% on the calculated ocular perfusion pressure in patients with normal-tension glaucoma. Am J Ophthalmol 1998; 125:585–92.
24 Dietelhordt M, Reters S, Kriegstein GK. The effect of latanoprost 0.005% once daily versus 0.005% timolol once daily on intraocular pressure and aqueous humor protein concentration in glaucoma patients: A randomised, double-masked, comparative study with timolol 0.5%. Graefes Arch Clin Exp Ophthalmol 1997; 235:20–26.


Toris CB, Camras CB, Yablonski ME. Effects of PhX441, a new prostaglandin F₂, analog on aqueous humor dynamics in human eyes. *Ophthalmology* 1993;100:1312–17.


