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, hypotension, 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 1.87, 34.30). The 2 year risk with latanoprost reached 18% (51/277). Hyperaemia was also more often observed with latanoprost (relative risk =2.20, 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 effective 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.**

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Glaucoma is one of the most frequent causes of blindness in the industrialised world. The economic burden including direct and indirect costs of the disease in the UK was estimated to be £132 million in 1990.[1] The mainstay of drug treatment for glaucoma is timolol, a topical β blocker. However, β blockers are contraindicated in patients with cardiovascular or pulmonary disorders.[2–4] Pilocarpine, a cholinergic agonist, is sometimes used but it needs to be administered four times per day and causes miosis, myopia, and occasionally retinal detachment and progressive closure of the anterior chamber angle.[5 6] Given such problems, the search for new effective and safer antiglaucoma agents continues. Among the recently introduced agents, three are widely used as alternatives when β blockers are contraindicated or fail to control intraocular pressure—latanoprost (a prostaglandin $F_{2\alpha}$ analogue), dorzolamide (a topical carbonic anhydrase inhibitor), and brimonidine (a selective α_2 agonist). Latanoprost appears highly promising because of its comparable or better efficacy when compared with timolol. We therefore undertook a comparison of the effects of topical latanoprost and timolol on intraocular pressure (IOP) based on published randomised controlled trials conducted by both pharmaceutical companies and academics.

Materials and methods

RETRIEVAL OF PUBLISHED STUDIES

Reports of randomised controlled trials (RCTs) of latanoprost versus timolol were identified through a systematic search consisting of: (1) an electronic search of Medline, Embase, and Scientific Citation Index; (2) searches of reference lists of original reports and review articles, retrieved through the electronic searches; (3) searches for manufacturers' databases including Pharmacia Upjohn ophthalmology database and Merck glaucoma database. The computerised searches covered the period 1966 to end of July 2000.

The medical subject heading (MeSH) search used in Medline and Embase consisted of three stages, each contained any possible MeSH relevant to the target diseases, drugs, and study methods as shown in Table 1. All MeSHs were exploded. Three stages were then combined to produce citations associated with randomised controlled trials of latanoprost and timolol in the treatment of glaucoma.

Table 1 MeSH search strategy

Stage 1 Diseases		*Stage 2 Drugs*		*Stage 3 Study methods*	
1	exp glaucoma* or exp glaucoma, open angle*	4	exp prostaglandins F, synthetic*	7	exp clinical trials* or exp randomised controlled trials*
2	exp ocular hypertension*	5	exp adrenergic β antagonists*	8	exp double blind method*
3	1 or 2	6	4 and 5	9	exp single blind method*
				10	exp random allocation*
				11	7 or 8 or 9 or 10
Finally, we combined three stages together using: 3 and 6 and 11					

exp = explode.
*MeSH search including all subject headings under the title

A keyword search was undertaken in the Scientific Citation Index using the words glaucoma/ocular hypertension, latanoprost/prostaglandin*, timolol/beta-blocker*/beta blocker*/β-blocker*/β 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.[7] 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.

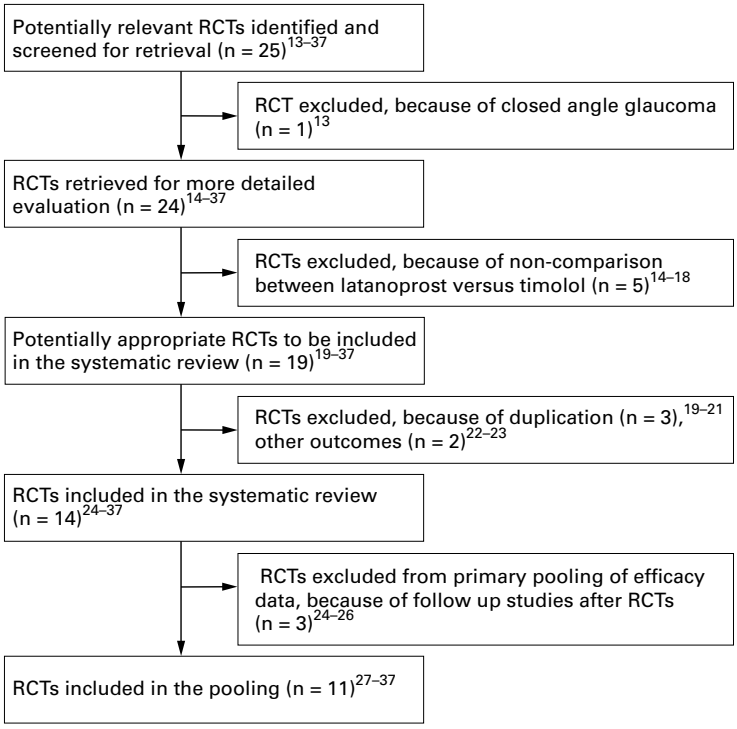

Figure 1 Flow of the RCTs included in our systematic review.

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 (SE_{IOPR}) using

$$IOPR = IOP_{baseline} - IOP_{endpoint}$$

$$SE_{IOPR} = \sqrt{SE^2_{baseline} + SE^2_{endpoint}}$$

The percentage IOP reduction (*IOPR%*) and its standard error ($SE_{IOPR\%}$) was then estimated by $IOPR\% = IOPR / IOP_{baseline}$ and $SE_{IOPR\%} = SE_{IOPR} / IOP_{baseline}$.

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 us was used.[8]

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.[9] In the pooling of relative risk and risk difference, the method described by DerSimonian and Laird[10] was used. The number needed to harm and its 95% confidence intervals (95% CI) were estimated as described by Cook.[11]

Table 2 Characteristics of randomised controlled trials comparing latanoprost and timolol

Trial (ref)	Design	Latanoprost (%)	Timolol (%)	Location	Length	No	Withdrawals (%)	Sex (M/F)	Mean age (range, years)	Types of glaucoma			Baseline IOP (mean (SE))		End point IOP (mean (SE))	
										POAG	OH	Others	Latanoprost	Timolol	Latanoprost	Timolol
Alm *et al* 1995 (27)	DB-P, DB-C	0.005 eve/mor	0.5 bid	Scand	6 months	267	15 (6)	116/151	67 (40–85)	91	123	53	25.3 (0.5)	24.6 (0.3)	17.0 (0.4)	17.9 (0.3)
Aquino *et al* 1999 (28)	DB-P	0.005 eve	0.5 bid	Philippines	3 months	60	/	/	/	/	/	/	29.9	29	18.8	19.6
Camras *et al* 1996 (29)	DB-P	0.005 eve	0.5 bid	USA	6 months	268	20 (7)	114/154	62 (30–90)	84	170	14	25.3	25.3	/	/
Drance *et al* 1998 (30)	DB-C	0.005 eve	0.5 bid	Canada	3 weeks	36	3 (8)	24/12	67	36	0	0	15.4 (0.4)	15.3 (0.4)	11.8 (0.3)	12.2 (0.3)
Diestelhorst *et al* 1997 (31)	DB-P, DB-C	0.0015/0.005 bid/eve	0.5 bid	Germany	6 weeks	30	20 (7)	9/21	62 (40–79)	25	0	5	28.1 (2.6)	27.2 (1.4)	19.8 (2.5)	22.6 (0.9)
Diestelhorst *et al* 1998 (32)	DB-P	0.005 eve	0.5 bid	Germany	1 month	46	2 (7)	20/26	60 (20–77)	42	0	4	25.2 (1.2)	24.8 (0.9)	20.3 (0.8)	22.7 (1.1)
Mastropasqua *et al* 1999 (33)	DB-P	0.005 eve	0.5 bid	Italy	12 months	36	2 (6)	21/15	46 (35–58)	0	0	36	24.5	24.0	/	/
Mishima *et al* 1996 (34)	DB-P	0.005 mor	0.5 bid	Japan	3 months	184	21 (11)	87/91	57 (22–81)	/	/	/	23.1 (0.2)	23.1 (0.2)	16.8 (0.3)	18.8 (0.3)
Nicolela *et al* 1996 (35)	DB-C	0.005 mor	0.5 bid	Canada	1 week	15	0 (0)	7/8	63 (47–80)	9	6	0	26.7 (1.3)	26.7 (1.3)	19.9 (0.9)	21.4 (0.6)
Rulo *et al* 1994 (36)	SB-P	0.006 bid	0.5 bid	Holland	1 week	20	1 (5)	8/12	63 (40–84)	2	18	0	28.5 (1.8)	24.2 (0.9)	/	/
Watson *et al* 1996 (37)	DB-P	0.005 eve	0.5 bid	UK	6 months	294	26 (9)	191/103	65 (39–88)	121	148	25	26.2 (0.3)	26.5 (0.3)	17.1 (0.2)	17.7 (0.2)
Total						1256	110 (9)	597	593	410	465	137				

No = number of patients; IOP = intraocular pressure (mm Hg); SE = standard error.
DB-P = double blind parallel, SB-P = single blind parallel, DB-C = double blind crossover, DB-P, DB-C = parallel design between latanoprost and timolol, but crossover design between different regimens of latanoprost. For example, in Alm's study,[27] patients receiving latanoprost were divided into two groups, one received latanoprost in the morning and placebo in the evening for 3 month and then latanoprost in the evening and placebo in the morning, another started with evening application and then switched after 3 months. In Diestelhorst's report,[31] 20 patients were treated with latanoprost 0.0015% twice daily or 0.005% once daily for 3 weeks in a crossover design. Ten patients received timolol 0.5% twice daily as control.
/ = not reported.
POAG = primary open angle glaucoma, OH = ocular hypertension, Others = including other types of open angle glaucoma, eg, exfoliation syndrome and pigment dispersion syndrome.
Scand = Scandinavia.
mor = morning regimen, eve = evening regimen, bid = twice per day.

A random effects model was used if trials were heterogeneous on the basis of the Q statistic for heterogeneity[12] 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.[13–37] Eleven of them met our inclusion criteria.[27–37] 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 one single blind parallel studies. Five are multicentre RCTs.[28 30 32 34 37] 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

(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

Trial	Percentage IOP reduction (mean (SE))		Difference of the reduction (95% CI)	p Value
	Latanoprost	Timolol		
1 week				
Diestelhorst *et al* 1998[32]	19.8 (6.2)	11.3 (5.4)	8.5 (−7.6, 24.7)	0.30
Nicolela *et al* 1996[35]	25.5 (5.8)	19.8 (5.3)	5.62 (−9.9, 21.1)	0.48
Rulo *et al* 1994[36]	31.2 (2.8)	24.4 (2.9)	6.85 (−1.0, 14.7)	0.09
Pooled	28.7 (2.3)	21.2 (2.3)	6.9 (0.4, 13.4)	0.04
χ^2_{heter}	3.16	4.59	0.07	
1 month				
Diestelhorst *et al* 1998[32]	19.4 (5.6)	8.5 (2.4)	11.0 (−0.9, 22.8)	0.07
Mishima *et al* 1996[34]	24.1 (1.3)	19.9 (1.1)	5.2 (1.9, 8.4)	0.00
Watson *et al* 1996[37]	34.3 (1.5)	34.0 (1.5)	0.4 (−3.9, 4.6)	0.86
Pooled	27.3 (4.0)	20.9 (6.3)	3.8 (1.2, 6.3)	0.00
χ^2_{heter}	24.64**	94.22**	4.57	
3 months				
Alm *et al* 1995[27]	33.7 (2.6)	29.7 (1.7)	4.0 (−2.1, 10.1)	0.20
Aquino *et al* 1999[28]	37.1 (4.0)	31.7 (3.8)	5.41 (−5.5, 16.3)	0.16
Mastropasqua *et al* 1999[33]	24.9 (2.9)	21.7 (2.8)	3.2 (−4.7, 11.1)	0.42
Mishima *et al* 1996[34]	26.8 (1.3)	19.0 (1.1)	7.8 (−4.4, 11.2)	0.00
Watson *et al* 1996[37]	34.7 (1.4)	32.8 (1.5)	1.9 (−2.2, 6.1)	0.37
Pooled	31.2 (2.3)	26.9 (3.4)	5.0 (2.8, 7.3)	0.00
χ^2_{heter}	24.01**	65.50**	4.97	
6 months				
Alm *et al* 1995[27]	32.1 (2.6)	27.2 (1.7)	4.8 (−1.3, 11.0)	0.12
Camras *et al* 1996[29]	26.5 (1.2)	19.4 (1.0)	7.1 (4.0, 10.2)	0.00
Mastropasqua *et al* 1999[33]	24.5 (4.3)	20.0 (3.0)	4.5 (−5.7, 14.8)	0.39
Watson *et al* 1996[37]	34.7 (1.4)	33.2 (1.5)	1.5 (−2.8, 5.6)	0.47
Pooled	29.9 (2.6)	25.0 (3.7)	5.0 (2.8, 7.3)	0.00
χ^2_{heter}	21.14**	64.61**	4.57	
12 months				
Mastropasqua *et al* 1999[33]	24.1 (4.6)	19.2 (3.1)	4.9 (−5.9, 15.8)	0.37

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

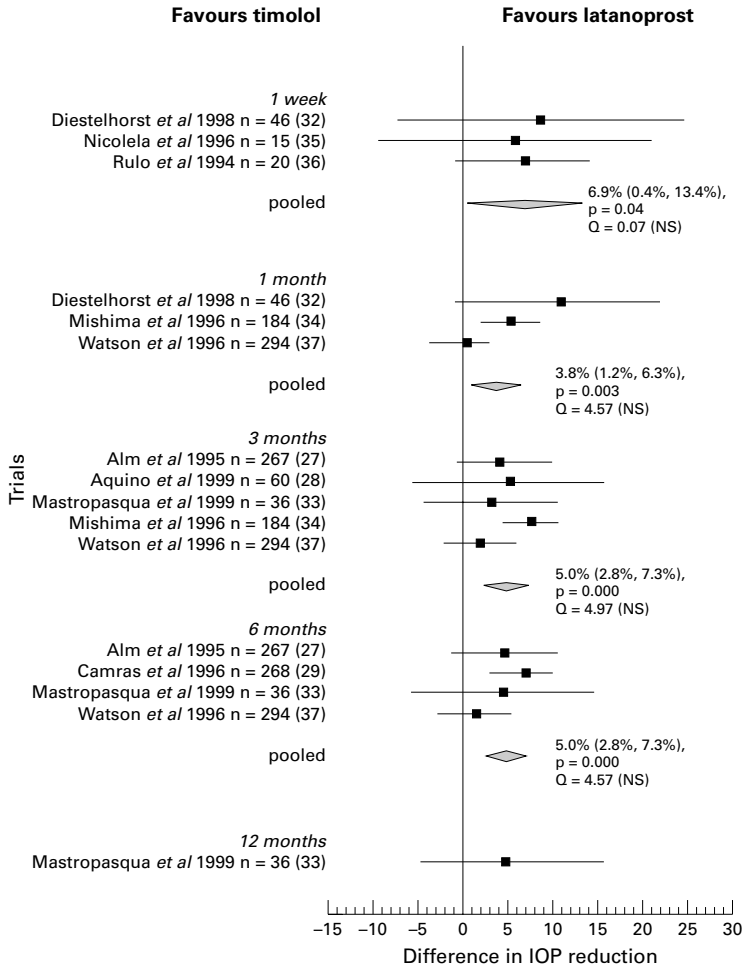

Figure 2 Difference in percentage IOP reduction from baseline between latanoprost and timolol. Mean difference and associated 95% confidence interval (—■—). IOP = intraocular pressure; Q = statistic of χ^2 test for heterogeneity; NS = no statistical heterogeneity. Numbers in parentheses are references.

with latanoprost, 21 (4.39%) developed iris pigmentation. In contrast, none of the patients treated with timolol showed this effect (0/387).

(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 37] 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.[25]

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

Table 4 Risk of side effects with latanoprost and timolol

Side effects	No of trials	Crude event rate		RR (95% CI)	RD (95% CI)	NNH (95% CI)
		Latanoprost	Timolol			
Withdrawals due to adverse effects	2	9/277	14/285	0.70 (0.30, 1.66)	−0.02 (−0.05, 0.16)	NA
Hyperaemia	6	51/586	20/503	2.20 (1.33, 3.65)**	0.05 (0.02, 0.07)**	21 (14, 42)**
Conjunctivitis	3	7/419	5/320	0.80 (0.25, 2.53)	0.006 (−0.001, 0.02)	NA
Increased pigmentation	4	21/478	0/387†	8.01 (1.87, 34.30)*	0.03 (0.01, 0.04)**	36 (22, 91)**
Hypotension	1	0/149†	2/145	0.19 (0.01, 4.02)	−0.01 (−0.04, 0.01)	NA
Bradycardia	1	0/87†	2/91	0.21 (0.01, 4.29)	−0.02 (−0.06, 0.02)	NA

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 × 2 table to calculate RR, RD, or NNH.
*p≤0.05, **p≤0.01.

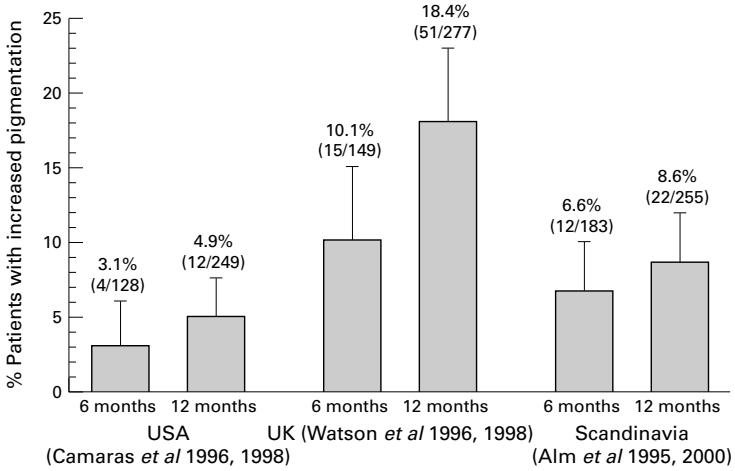

Figure 3 Percentage of patients with increased iris pigmentation after use of latanoprost. Error bar shows 95% confidence intervals.

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.[38]

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[39–41] 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.[42]

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

Table 5 Number of patients with increased pigmentation with long term treatment of latanoprost

Iris colour	USA, 1 year experience[25]		UK, 2 year experience[26]		Scandinavia, 2 year experience[24]	
	No	Increased pigmentation (%)	No	Increased pigmentation (%)	No	Increased pigmentation (%)
Blue/grey	21	0 (0)	27	0 (0)	89	0
Blue/grey with slightly brown	36	0 (0)	76	1 (1)	89	1 (1)
Blue/grey-brown	34	3 (9)	79	12 (15)	33	5 (15)
Green with slightly brown	4	0 (0)	2	0 (0)	3	0 (0)
Green-brown	46	6 (12)	70	34 (49)	31	14 (45)
Yellow-brown	23	3 (13)	3	2 (67)	2	2 (100)
Brown	80	0 (0)	20	2 (10)	7	0 (0)
Total	247	12 (5)	277	51 (18)	255	22 (9)

Table 6 Mean reduction of systemic blood pressure and heart rate and their 95% confidence intervals after using timolol or latanoprost

Trial	Timolol			Latanoprost		
	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Heart rate (beats/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Heart rate (beats/min)
Camras *et al* 1996[29]						
2 weeks	2.0 (−2.3, 6.3)	0.0 (−2.3, 2.3)	2 (0, 4)	1.0 (−3.2, 5.2)	0.0 (−2.6, 2.6)	1 (−2, 4)
3 months	3.0 (−1.4, 7.4)	0.0 (−2.3, 2.3)	4 (2, 6)**	0.0 (−4.3, 4.3)	0.0 (−2.4, 2.4)	2 (−1, 5)
6 months	3.0 (−1.4, 7.4)	0.0 (−2.6, 2.6)	4 (2, 6)**	0.0 (−4.4, 4.4)	0.0 (−2.6, 2.6)	1 (−2, 4)
Drance *et al* 1998[30]						
3 weeks	5.0 (1.5, 8.5)	2.0 (0.2, 4.2)	/	−0.6 (−4.1, 2.9)	−0.4 (−2.4, 1.6)	/
Nicolela *et al* 1996[35]						
1 week	1.3 (−12.6, 15.2)	0.2 (−7.7, 8.1)	0 (−8, 8)	1.8 (−11.3, 14.9)	0.3 (−7.3, 7.9)	5 (−8, 18)
Watson et al 1996[37]						
6 months	/	/	2 (−1, 5)	/	/	/

BP = blood pressure.
**p<0.01.

Table 7 Percentage IOP reduction from baseline with evening regimen and morning regimen of latanoprost (3 month treatment)

Trial	Percentage IOP reduction (mean (SE))		Difference of IOP reduction	p Value
	Evening	Morning		
Alm *et al* 1995[27]	35.7 (1.6)	31.0 (2.0)	4.6 (2.6)	0.08
Alm *et al* 1995[45]	36.7 (3.6)	/	/	/
Mastropasqua *et al* 1999[33]	24.9 (2.9)	/	/	/
Mishima *et al* 1996[34]	/	26.8 (1.3)	/	/
Watson *et al* 1996[37]	34.7 (1.4)	/	/	/
Pooled	33.2 (1.4)	28.1 (1.1)	5.1 (1.8)	0.006
χ^2_{heter}	12.00**	3.02	/	/

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

Table 8 Percentage IOP reduction from baseline with evening regimen and twice daily (bid) regimen of latanoprost (3 month treatment)

Trial	Percent IOP reduction (mean (SE))		Difference of IOP reduction	p Value
	Evening	Twice daily		
Alm *et al* 1995[27]	35.7 (1.7)	/	/	/
Alm *et al* 1995[45]	36.7 (3.6)	27.7 (3.7)	9.0 (5.2)	0.08
Mastropasqua *et al* 1999[33]	24.9 (2.9)	/	/	/
Watson *et al* 1996[37]	34.7 (1.4)	/	/	/
Pooled	33.2 (1.4)	27.7 (3.7)	5.5 (4.0)	0.17
χ^2_{heter}	12.00**	/	/	/

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

Table 9 Sensitivity analysis to evaluate the effect of quality of randomised controlled trials on IOP reduction between latanoprost and timolol

	Difference in percentage IOP reduction	95% Confidence intervals
Design of trial		
All trials	6.0	4.3, 7.8
Double blind, parallel	6.0	4.2, 7.8
Double blind, crossover	5.6	−9.9, 21.1
Single blind, parallel	6.8	−1.0, 14.7
Withdrawals		
All trials	6.0	4.3, 7.8
Withdrawals ⩽10%	5.4	3.3, 7.5
Withdrawals >10%	7.8	4.4, 11.2

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

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 with timolol.[43]

It has been suggested that the time of IOP measurement is important when comparing latanoprost with timolol.[37] 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.[37] 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*[27] 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*[44] 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.[45] Others have reported the superiority of the higher concentration of latanoprost (0.005%) once daily over the lower concentration of latanoprost (0.0015%).[31 46] 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 α_2 agonists, latanoprost acts on outflow rather than formation of aqueous humour.[47 48] Because latanoprost increases uveoscleral outflow,[48] it can theoretically reduce IOP below episcleral venous pressure. This may be advantageous in patients with normal tension glaucoma. In fact, one trial[30] suggested that 0.005% latanoprost produced better lowering 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[49–51] and bronchospasm[52–54] 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,[29 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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