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Original Article

Travoprost compared with other prostaglandin analogues or timolol in patients with open-angle glaucoma or ocular hypertension: meta-analysis of randomized controlled trials

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Abstract

Background: It is still uncertain whether travoprost has comparable or better efficacy compared with other prostaglandin analogues or timolol in patients with open-angle glaucoma or ocular hypertension. The authors performed a meta-analysis of randomized controlled trials to evaluate the incidence of reported side-effects and intraocular pressure (IOP)-lowering effect of travoprost versus other prostaglandin analogues (latanaprost, bimatoprost, unoprostone) or timolol.

Methods: Systematic literature retrieval was conducted in Pubmed, EMBASE, Chinese Bio-medicine Database and Cochrane Controlled Trials Register to identify the potentially relevant randomized controlled trials. The statistical analysis was performed by RevMan 4.1 software that was provided by the Cochrane Collaboration. The outcome measures were the incidence of reported side-effects (hyperaemia, iris pigmentation, eyelash changes) and mean IOP pooled over treatment visits.

Results: In total, 12 articles involving 3048 patients with open-angle glaucoma or ocular hypertension were included in this meta-analysis. The combined results showed that travoprost 0.004% was more effective than timolol or travoprost 0.0015% in lowering IOP, but not more effective than bimatoprost or latanoprost. Travoprost 0.004% caused a higher percentage of hyperaemia than timolol, latanoprost, or travoprost 0.0015%. There was an increased incidence of pigmentation with travoprost than timolol. Travoprost 0.004% caused a higher percentage of eyelash changes than timolol, latanoprost, or travoprost 0.0015%.

Conclusion: According to data available, travoprost is more effective than timolol in lowering IOP in patients with open-angle glaucoma or ocular hypertension. Compared with other prostaglandin analogues, travoprost appears to be equivalent to bimatoprost and latanoprost. Although a limited number of local side-effects were reported, no serious treatment-related side-effects were reported.

Key words: glaucoma, ocular hypertension, open-angle, prostaglandin analogue, timolol, travoprost.

Introduction

Glaucoma is the leading cause of irreversible blindness in the world. Elevated intraocular pressure (IOP) is a major risk factor for glaucoma, and reducing IOP to the normal level is the primary goal of treatments for glaucoma and ocular hypertension (OH).[1,2] A newly published meta-analysis suggests that lowering IOP in patients with OH or manifest glaucoma is beneficial in reducing the risk of visual field loss in the long term.[3]

Treatment of open-angle glaucoma (OAG) or OH is usually begun with a topical drug. Drugs used for the long-term management of glaucoma fall into five classes: β-adrenergic antagonists, prostaglandin analogues, adrenergic agonists, carbonic anhydrase inhibitors and cholinergic agonists. Topical β-adrenergic blocking agents, such as timolol, have been the most commonly prescribed initial therapy for glaucoma and OH. In recent years, a new family of drugs, the prostaglandin analogues, has become increasingly popular. Latanoprost, travoprost and bimatoprost were developed and became widely used in the treatment of primary open-angle glaucoma (POAG) and OH. Although these drugs have structural differences, they share

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similar characteristics and are often referred to as prostaglandin analogues.[4–7]

Travoprost 0.004% (the commercially available concentration) is a new medication that has been released in the commercial market since March 2001. Travoprost is a synthetic ester prodrug of a prostaglandin F2α analogue used in the treatment of OAG and OH. A meta-analysis suggests that bimatoprost, travoprost, latanoprost and timolol are the most effective IOP-reducing agents in POAG and OH patients.[8] It is still uncertain whether travoprost has comparable or better efficacy compared with other prostaglandin analogues or timolol in patients with OAG or OH. Therefore, we undertook this meta-analysis to assess the incidence of reported side-effects and IOP-lowering effect of travoprost compared with other prostaglandin analogues or the first-line agents, timolol.

METHODS

Search strategy

Reports of randomized controlled trials (RCTs) comparing travoprost with other prostaglandin analogues or timolol were identified through a systematic search. A computerized literature search was conducted in the PubMed (1966–1 August 2005), EMBASE (1980–1 August 2005), Chinese Biomedicine Database (1979–1 August 2005) and Cochrane Controlled Trials Register (1 August 2005) for relevant articles published in English or Chinese. The search term was travatan or travoprost. Literature reference proceedings were hand-searched at the same time. The title and abstract of all potentially relevant articles were screened to determine their relevance. Then full articles were scrutinized if the title and abstract were ambiguous. Two reviewers (Ni Li, Yong Zhou) conducted searches independently, and the results were combined.

Inclusion and exclusion criteria

The following selection criteria were used to identify published studies for inclusion in this analysis: (i) study design – randomized clinical trial; (ii) population – patients with OAG (including primary and secondary OAG) or OH; (iii) intervention – travoprost versus other prostaglandin analogues or timolol, initiated at the same time and with the same other treatment; (iv) outcome variables – at least one of the following primary outcome variables: IOP, side-effects. These articles were written in English or Chinese. Abstracts of conference without raw data available for retrieval and duplicate publications were excluded.

Data extraction

Two reviewers (Ni Li, Yong Zhou) performed the data extraction and methodological quality assessment of trials that were included independently. Any differences were resolved by discussion to reach consensus among the investigators. A customized form was used to record the authors of the study, the year of publication, information on study design (double-blind or single-blind, parallel or cross-over), 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 number of patients with reported side-effects, such as hyperaemia, iris pigmentation, eyelash changes (increased length, thickness, pigmentation and number of lashes). IOP and proportion of side-effects were used as the primary outcomes for all of the studies included in the meta-analysis.

Assessment of study quality

We assessed the sources of systematic bias in trials according to the methods described in Section 6 of the Cochrane Reviewers' Handbook.[9] Quality assessment followed Cochrane Eyes and Vision Protocol Development Guidelines. The following parameters were considered: adequate allocation concealment, randomization, masking, withdrawals/dropouts and intention-to-treat analysis. Masking was differentiated as double-blind, single-blind and open label. Parallel and cross-over designs were also categorized.

Outcome measure

The outcome measures were the incidence of reported side-effects and mean IOP pooled over treatment visits. In case the pooled data were not present, the data measured at last visit were accepted. If a study appeared in more than one publication, the most recent results with complementary data from previous articles were used for statistical analysis.

Statistical methods and assessment of heterogeneity

The statistical analysis was performed by RevMan 4.1 software, which was provided by the Cochrane Collaboration. For dichotomous outcomes we calculated a pooled odds ratio (OR). Weighted mean difference (WMD) or standard mean difference was calculated for continuous outcomes. We checked for heterogeneity by P-value.[10] If no heterogeneity detected within the trials ($P > 0.1$), we combined the results in a meta-analysis using the fixed effects model, otherwise, we used random effects model for pooling the data. A P-value of <0.05 was considered statistically significant.

When authors reported standard deviation, we used them directly. When standard deviations were not available, we computed them from the observed mean differences (either differences in changes or absolute readings) and the test statistics. When the test statistics were not available, given a P-value, we computed the corresponding test statistic from tables for the normal distribution. Potential publication bias was examined by funnel plot.[11]

RESULTS

Characteristics of trials

There were 254 articles relevant to the search term. A total of 19 potential RCTs of travoprost versus other prostaglandin analogues or timolol were identified through the literature search.[12–30] In total, 12 articles involving 3048 patients with OAG or OH were included in this meta-analysis.[19–30] The flow of the RCTs included in our analysis is shown in Figure 1. In one article,[12] data of IOP derived from the earlier study.[19] However, in this publication both the mean IOP and standard deviation were presented. Therefore, these values were extracted from it. Characteristics of studies included in the meta-analysis were presented in Table 1. RCTs included were undertaken in countries including the USA, Italy, Brazil and Australia. Length of studies varied from 3 to 12 months,[19–30] except one article whose follow-up duration was 2 weeks.[28] The range of mean age was 51.9–67.7 years. Of the data available on sex, 1463 of the patients were men and 1585 were women. According to data available on types of glaucoma, 2060 subjects had POAG, 840 had OH and 114 had other types of chronic OAG (others). IOP was used as the primary outcome for efficacy in all of the studies included in the meta-analysis.

Quality of trials

The methodological quality of trials that were included was summarized in Table 2. There were eight double-blind parallel studies[19–23,26,28,29] and four single-blind parallel studies.[24,25,27,30] Eight trials were multicentre RCTs.[19–22,24,25,29] Eight trials conducted intention-to-treat analysis.[19–22,25,27–29] Of these studies, five trials reported sample size calculation and all reported withdraws or dropouts.[19–22,25] Potential publication bias was not assessed by funnel plot because there were no sufficient studies.

Efficacy – mean IOP over treatment visits

The combined results showed that travoprost 0.004% was more effective than timolol 0.5% in lowering IOP (WMD = –0.81, 95% confidence interval [CI] [–1.16, –0.45], $P = 0.00001$) (Fig. 2). However, travoprost 0.004% did not show a better IOP-lowering effect, compared with bimatoprost 0.03% (WMD = 0.08, 95% CI [–0.62, 0.79], $P = 0.8$) (Fig. 3) or latanoprost 0.005% (WMD = –0.57, 95% CI [–1.18, 0.04], $P = 0.07$) (Fig. 4). Only one trial involving 33 patients showed that travoprost 0.004% was more effec-

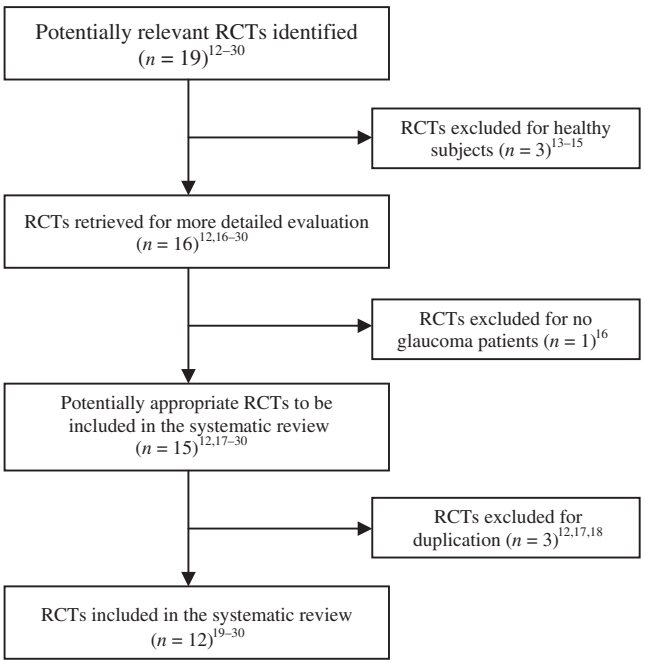

Figure 1. Flow of the randomized controlled trials (RCTs) included in the systematic review.

Table 1. Characteristics of included studies

Trial	Location	Duration	Mean age (years)	Sex (M/F)	Types of glaucoma			No.
					POAG	OH	Others	
Netland *et al.* 2001[19]	USA	12 months	64.2	392/395	530	247	10	787
Orengo-Nania *et al.* 2001[20]	USA	6 months	63.9	124/152	244	22	10	276
Goldberg *et al.* 2001[21]	Australia	9 months	63.3	284/288	313	221	38	572
Fellman *et al.* 2002[22]	USA	6 months	63.7	293/301	382	196	16	594
Cardascia *et al.* 2003[23]	Italy	6 months	51.9	11/7	18	0	0	18
Noecker *et al.* 2003[24]	USA	3 months	65.0	11/20	28	3	0	31
Parrish *et al.* 2003[25]	USA	3 months	65.0	172/238	309	95	6	410
Cellini *et al.* 2004[26]	Italy	6 months	64.0	32/28	60	0	0	60
Cantor *et al.* 2004[27]	USA	6 months	60.5	10/16	17	9	0	26
Dubiner *et al.* 2004[28]	USA	2 weeks	59.4	11/23	NA	NA	NA	34
Barnebey *et al.* 2005[29]	USA	3 months	63.0	89/87	125	47	4	176
Arcieri *et al.* 2005[30]	Brazil	6 months	67.7	34/30	34	0	30	64

M/F, male/female; NA, data not available; POAG, primary open-angle glaucoma; OH, ocular hypertension; others, other types of chronic open-angle glaucoma.

Table 2. Methodological quality of included studies

Trial	Design	Allocation concealment	Withdraws or dropouts	ITT	Study centre	Sample size calculation
Netland *et al.* 2001[19]	DB-P	Adequate	Yes	Yes	Multicentre	Yes
Orengo-Nania *et al.* 2001[20]	DB-P	Adequate	Yes	Yes	Multicentre	Yes
Goldberg *et al.* 2001[21]	DB-P	Unclear	Yes	Yes	Multicentre	Yes
Fellman *et al.* 2002[22]	DB-P	Adequate	Yes	Yes	Multicentre	Yes
Cardascia *et al.* 2003[23]	DB-P	Unclear	Yes	No	Single centre	Unclear
Noecker *et al.* 2003[24]	SB-P	Adequate	Yes	No	Multicentre	Unclear
Parrish *et al.* 2003[25]	SB-P	Adequate	Yes	Yes	Multicentre	Yes
Cellini *et al.* 2004[26]	DB-P	Unclear	Yes	No	Single centre	Unclear
Cantor *et al.* 2004[27]	SB-P	Adequate	Yes	Yes	Single centre	Unclear
Dubiner *et al.* 2004[28]	DB-P	Unclear	Yes	Yes	Single centre	Unclear
Barnebey *et al.* 2005[29]	DB-P	Unclear	Yes	Yes	Multicentre	Unclear
Arcieri *et al.* 2005[30]	SB-P	Adequate	Yes	No	Single centre	Unclear

DB-P, double-blind parallel group; ITT, intention-to-treat analysis; SB-P, single-blind parallel group.

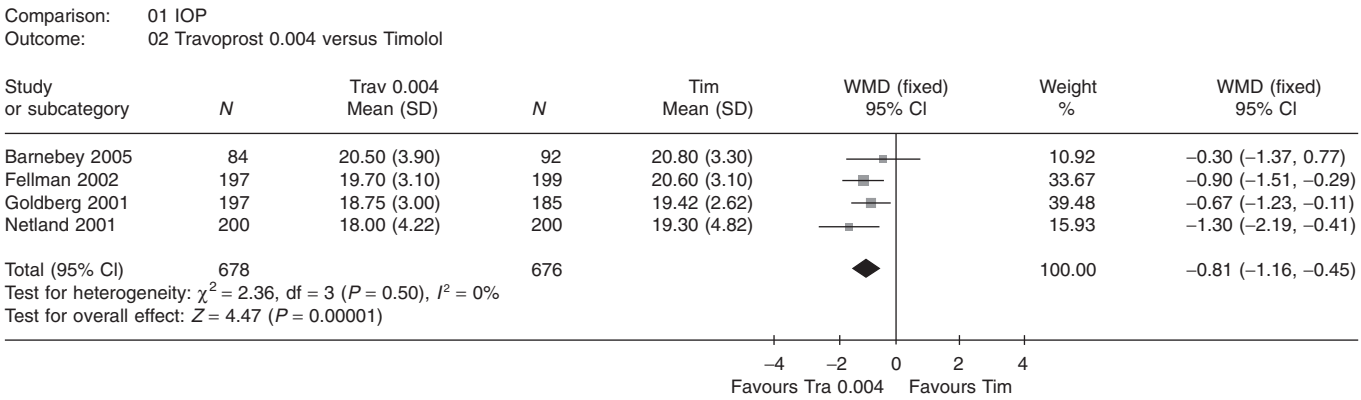

Figure 2. Travoprost 0.004% versus timolol in IOP. CI, confidence interval; IOP, intraocular pressure; SD, standard deviation; WMD, weighted mean difference.

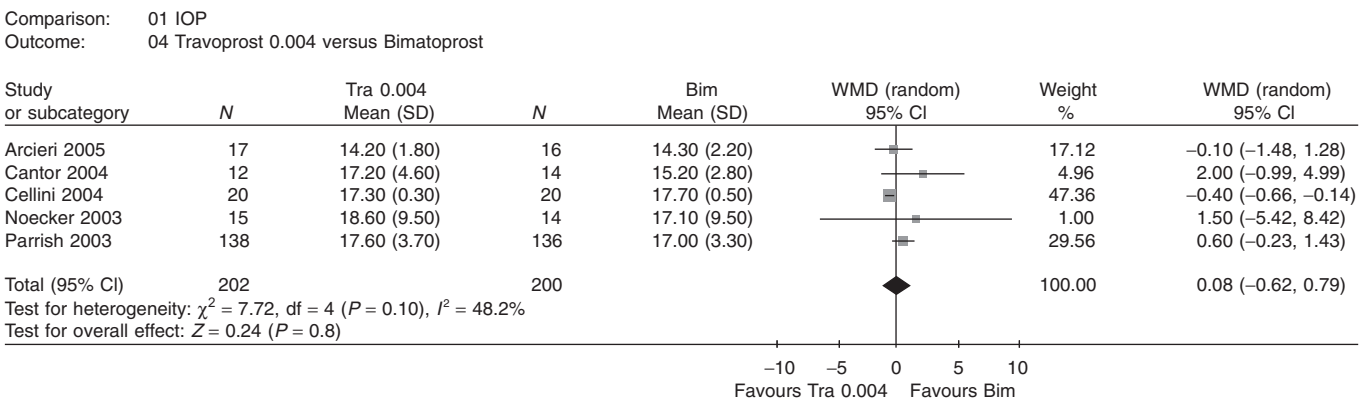

Figure 3. Travoprost 0.004% versus bimatoprost in IOP. CI, confidence interval; IOP, intraocular pressure; SD, standard deviation; WMD, weighted mean difference.

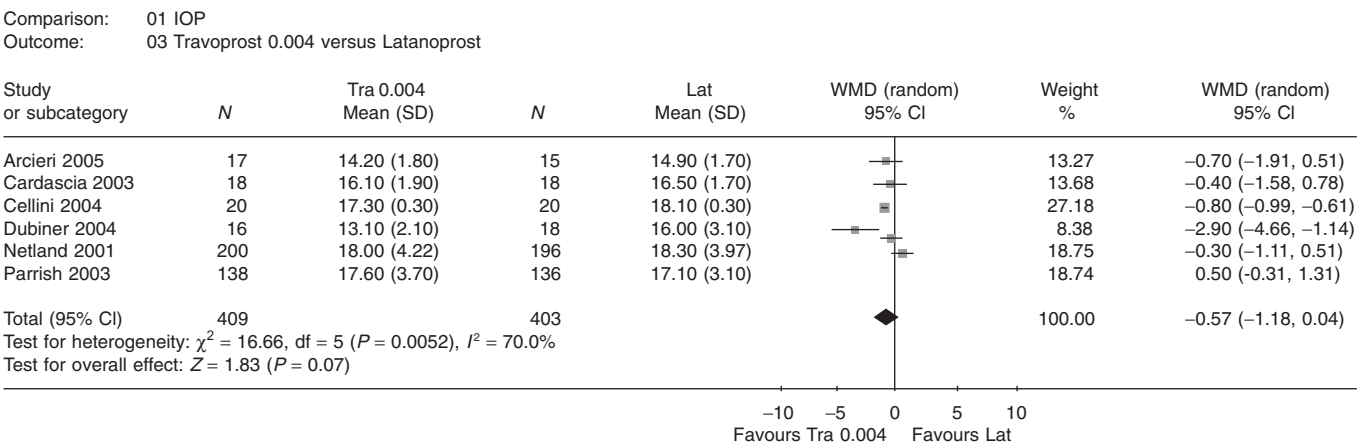

Figure 4. Travoprost 0.004% versus latanoprost in IOP. CI, confidence interval; IOP, intraocular pressure; SD, standard deviation; WMD, weighted mean difference.

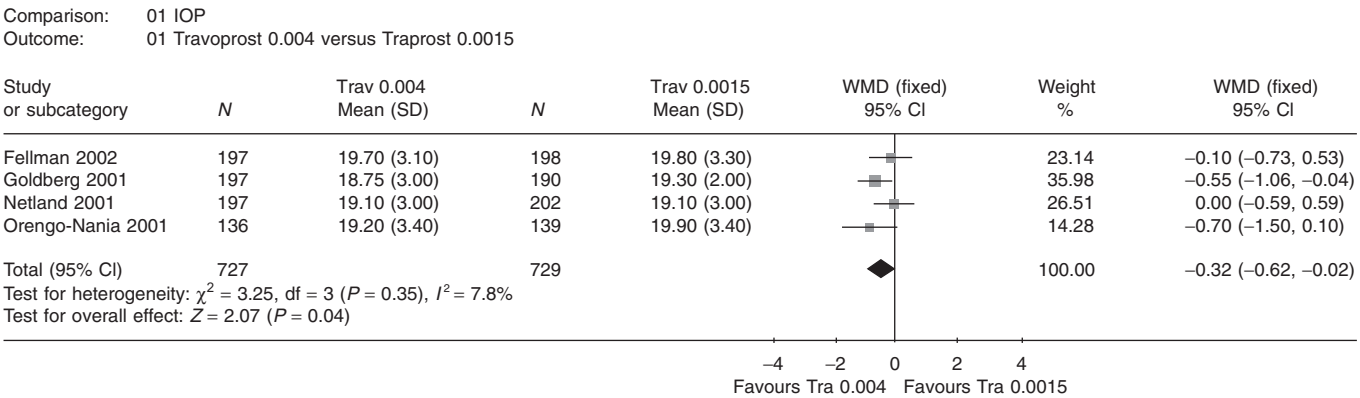

Figure 5. Travoprost 0.004% versus travoprost 0.0015% in IOP. CI, confidence interval; IOP, intraocular pressure; SD, standard deviation; WMD, weighted mean difference.

tive than unoprostone 0.12% in lowering IOP.[30] When the two concentrations of travoprost were compared, 0.004% travoprost appears to have better IOP-lowering effect than 0.0015% travoprost (WMD = – 0.32, 95% CI [–0.62, –0.02], P = 0.04) (Fig. 5).

Side-effects

Ocular hyperaemia was the most common side-effect of prostaglandin analogues. The combined results suggested that travoprost 0.004% caused a higher percentage of ocular hyperaemia than timolol 0.5% (OR = 6.76, 95% CI [4.93, 9.25], P < 0.00001) (Fig. 6), or latanoprost 0.005% (OR = 2.03, 95% CI [1.49, 2.75], P = 0.00001) (Fig. 7), travoprost 0.0015% (OR = 1.64, 95% CI [1.32, 2.04], P = 0.00001) (Fig. 8). However, there was no statistically significant difference between travoprost 0.004% and bimatoprost 0.03% (OR = 0.65, 95% CI [0.42, 1.00], P = 0.05) (Fig. 9) in hyperaemia.

There was an increased incidence of pigmentation with travoprost 0.004% than timolol 0.5% (OR = 11.06, 95% CI [2.07, 59.08], P = 0.005) (Fig. 10). There was no statistically significant difference between travoprost 0.004% and travoprost 0.0015% (OR = 0.74, 95% CI [0.38, 1.46], P = 0.4) (Fig. 11) in iris pigmentation. Only one trial involving 396 patients compared travoprost 0.004% with latanoprost 0.005% in incidence of pigmentation, and there was no statistically significant difference between the two groups.[19]

Travoprost 0.004% caused a higher percentage of eyelash changes than timolol 0.5% (OR = 38.81, 95% CI [20.65, 72.93], P < 0.00001) (Fig. 12). There was also an increased incidence of eyelash changes with travoprost 0.004% than latanoptost 0.005% (OR = 3.82, 95% CI [2.50, 5.84], P < 0.00001) (Fig. 13), or travoprost 0.0015% (OR = 1.79, 95% CI [1.40, 2.27], P < 0.00001) (Fig. 14). Only one trial involving 275 patients compared travoprost 0.004% with bimatoprost 0.03% in incidence of eyelash changes, and

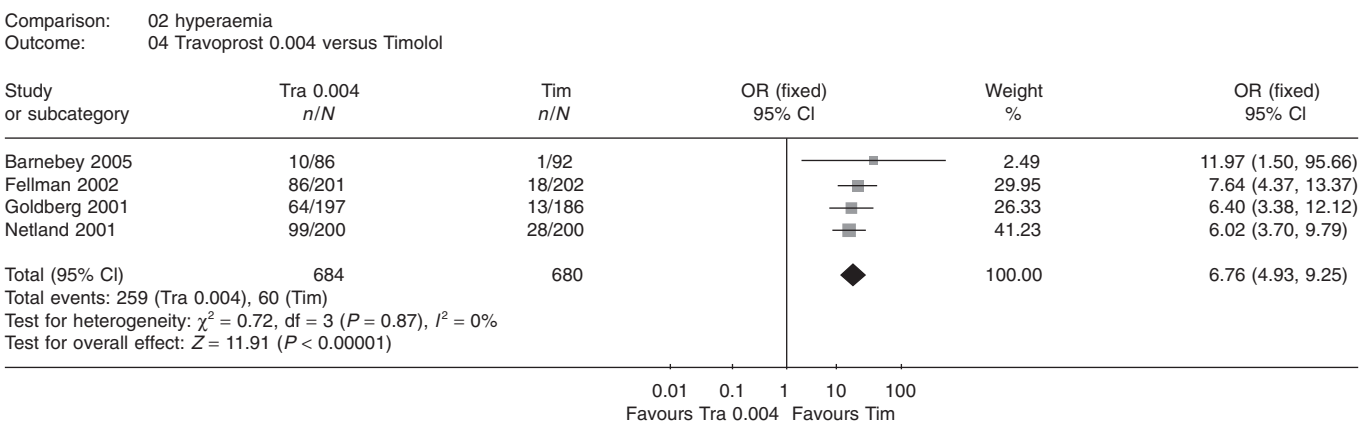

Figure 6. Travoprost 0.004% versus timolol in hyperemia. CI, confidence interval; OR, odds ratio.

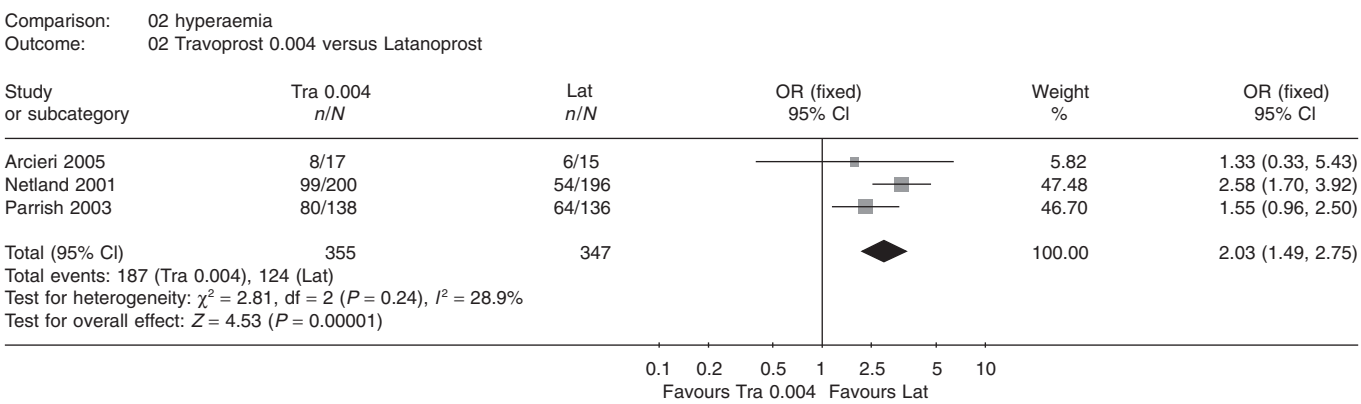

Figure 7. Travoprost 0.004% versus latanoprost in hyperemia. CI, confidence interval; OR, odds ratio.

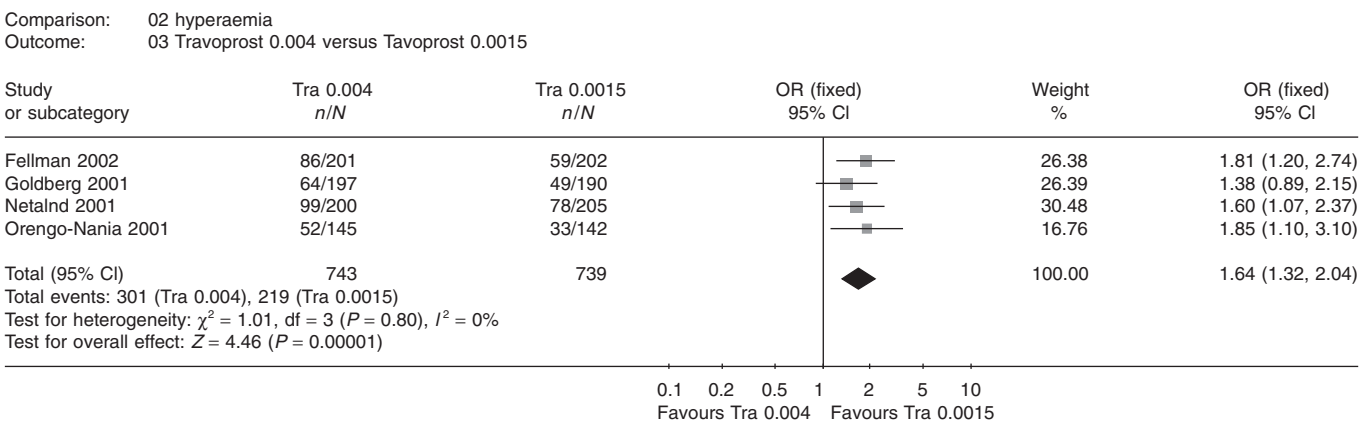

Figure 8. Travoprost 0.004% versus travoprost 0.0015% in hyperemia. CI, confidence interval; OR, odds ratio.

there was no statistically significant difference between the two groups.[25]

Discussion

The hypotensive prostaglandin analogues are a novel class of intraocular-lowering medications used primarily for the treatment of glaucoma. Prostaglandins are a large family of naturally occurring fatty acids. They are found throughout the body and produce a multitude of physiological and pharmacological effects by acting on a diverse number of prostanoid receptors in the body.[31] Travoprost is an ester prodrug of a PGF2α analogue and is hydrolysed to the active acid. When it is absorbed into the eye following topical ocular

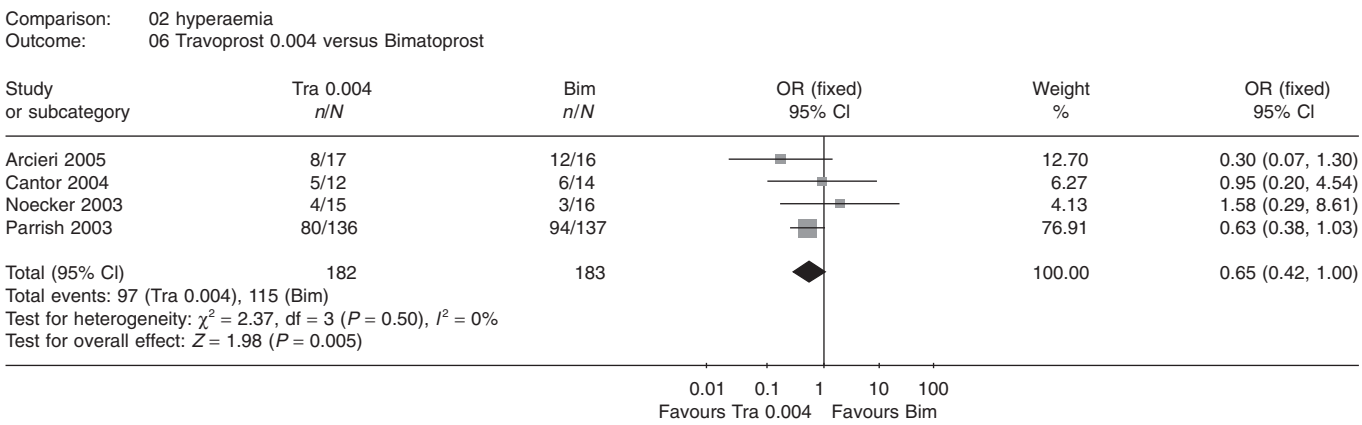

Figure 9. Travoprost 0.004% versus bimatoprost in hyperemia. CI, confidence interval; OR, odds ratio.

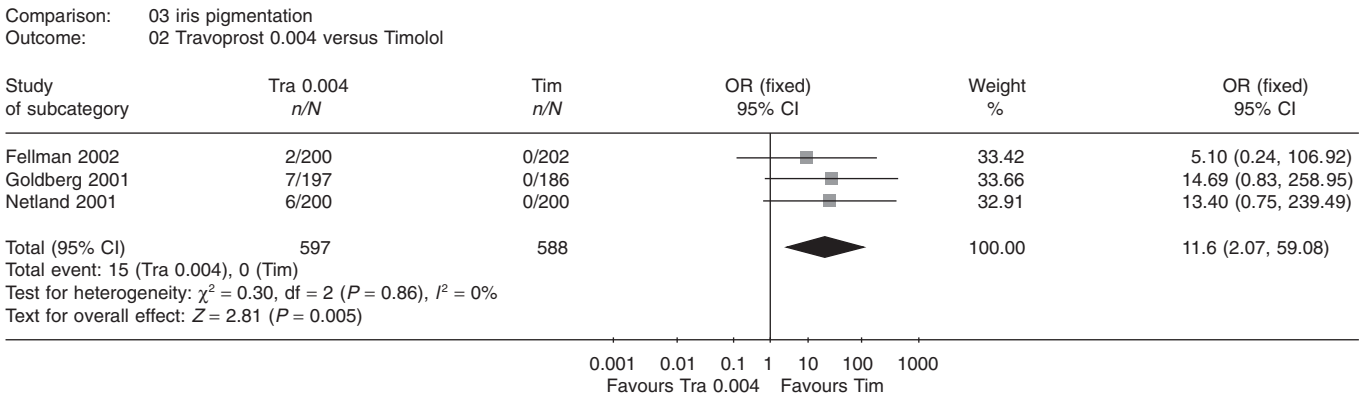

Figure 10. Travoprost 0.004% versus timolol in iris pigmentation. CI, confidence interval; OR, odds ratio.

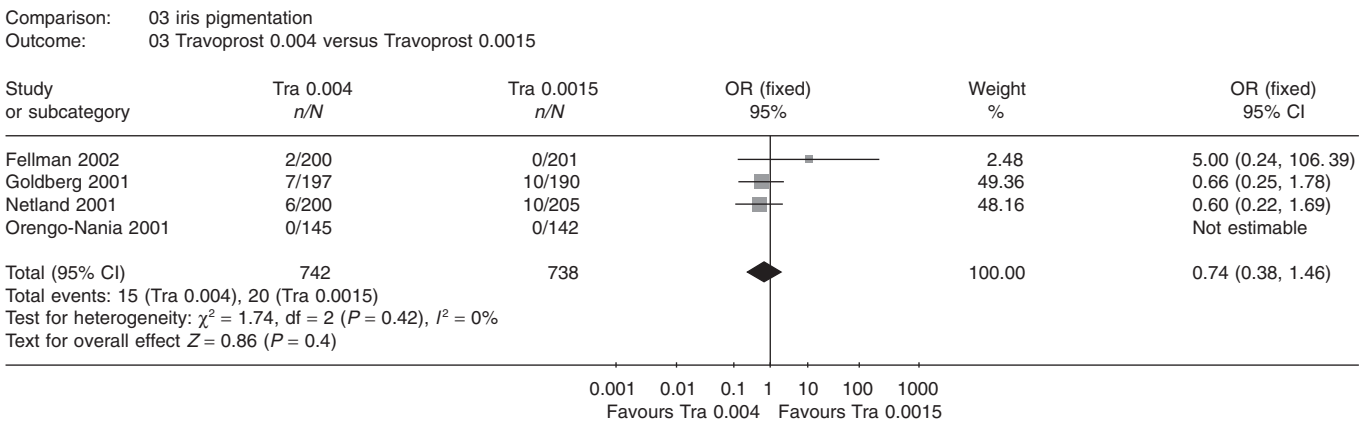

Figure 11. Travoprost 0.004% versus travoprost 0.0015% in iris pigmentation. CI, confidence interval; OR, odds ratio.

administration, it is hydrolysed to the active free acid. The free acid is a synthetic prostaglandin F2α-analogue that is highly selective for the FP prostaglandin receptor.[32–36] Like other compounds of this class, travoprost is thought to lower IOP primarily by facilitating the drainage of the aqueous humour through uveoscleral outflow pathway.[32,34,35]

The results from this meta-analysis indicated that, when used as monotherapy, the IOP-lowering effect of travoprost 0.004% was equivalent to that of latanoprost 0.005% or bimatoprost 0.03% and more effective than that of timolol 0.5% in patients with OAG or OH. The meta-analysis also showed statistically significant difference in

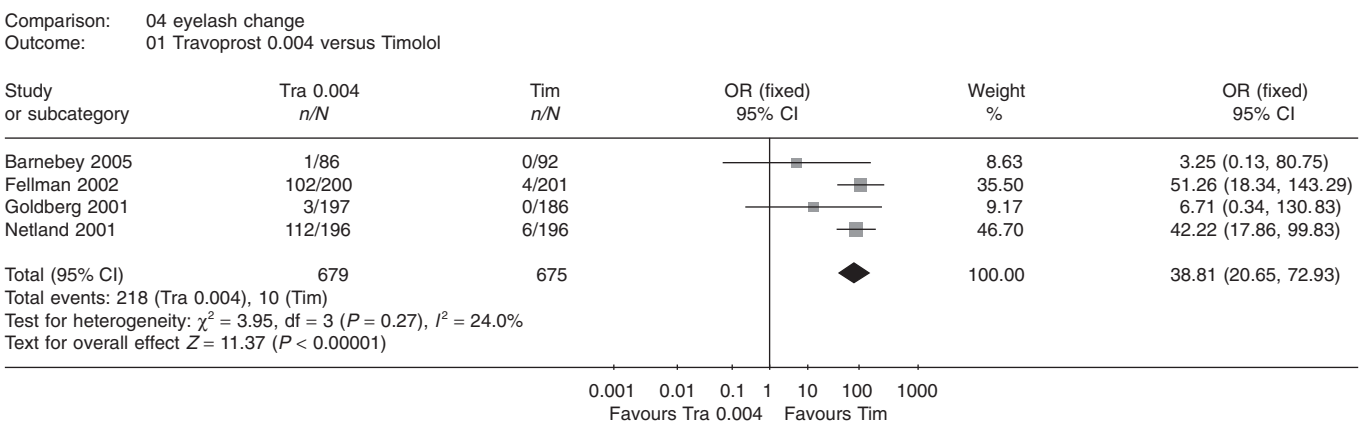

Figure 12. Travoprost 0.004% versus timolol in eyelash changes. CI, confidence interval; OR, odds ratio.

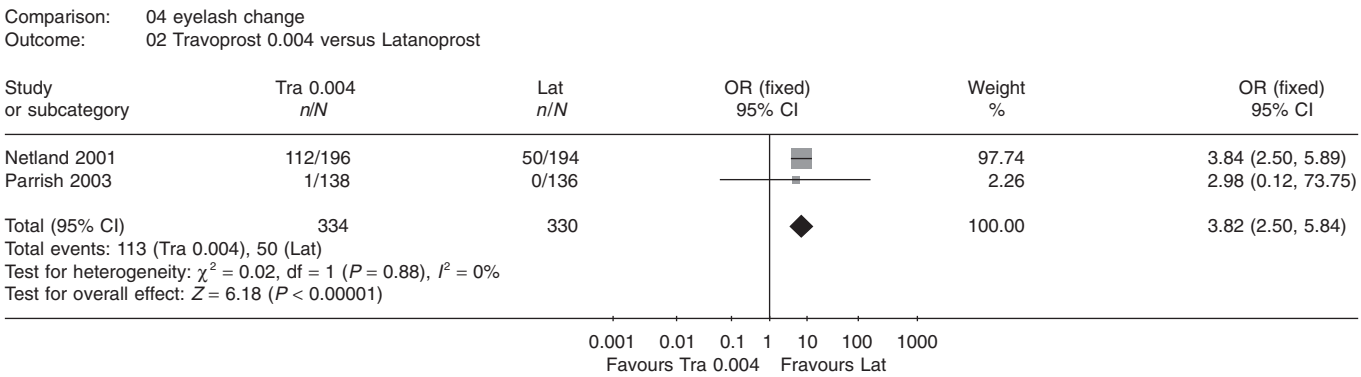

Figure 13. Travoprost 0.004% versus latanoprost in eyelash changes. CI, confidence interval; OR, odds ratio.

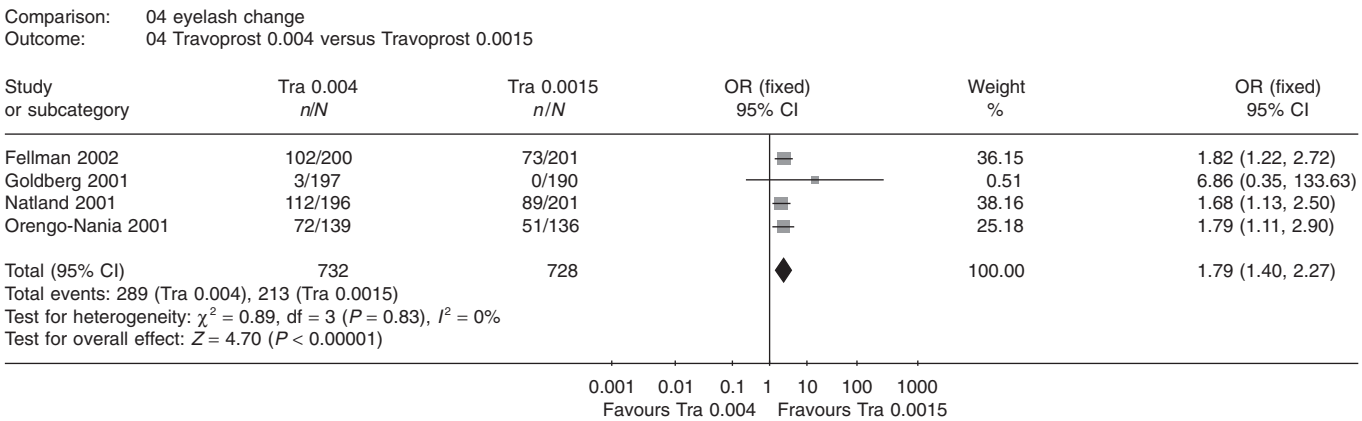

Figure 14. Travoprost 0.004% versus travoprost 0.0015% in eyelash changes. CI, confidence interval; OR, odds ratio.

IOP reductions between the two concentrations of travoprost 0.004% and 0.0015%. Travoprost 0.004% appeared more effective at lowering IOP. Because the baseline IOP values of including patients were from 24 to 36 mmHg, the overall beneficial effect can only be safely assumed in patients with IOP over 24 and no more than 36 mmHg. For patients whose IOP is not adequately controlled, ophthalmologists may consider concomitant administration of travoprost and other antiglaucoma agents. Recent studies have reported clinically effective IOP reduction of travoprost 0.004% + timolol 0.5% fixed combination.[29,37]

The meta-analysis showed that the incidence of reported side-effects of timolol 0.5% was lower than travoprost 0.004%. Travoprost 0.004% caused a higher percentage of ocular hyperaemia, iris pigmentation and eyelash changes than timolol 0.5%. In trials that were included, investigators monitored the objective signs of side-effects and patients spontaneously reported subjective symptoms. Ocular hyperaemia was the most common side-effect of prostaglandin analogues. Hyperaemia was observed at approximately the same rate in the travoprost and bimatoprost groups, but with statistically higher occurrences of hyperaemia for travoprost versus latanoprost. In addition, travoprost increased pigmentation of the iris and changed length, thickness, pigmentation, growth of lashes in some patients. Patients who received treatment in only one eye should be informed of the possibility of iris pigmentation and changes of eyelashes. These changes may be permanent or very slowly reversible and therefore cause heterochromia between the eyes in unilaterally treated patients.[38] Although recent evidence suggests that the problem is purely cosmetic, ongoing surveillance is necessary because of the limited follow-up time.

This meta-analysis may have some limitations. First, we cannot fully exclude publication bias, because there were no sufficient studies to detect asymmetry in a funnel plot. Second, RCTs included in this meta-analysis were mainly undertaken in countries including the USA, Brazil, Australia and Italy; we cannot eliminate location bias. For example, prostaglandin studies carried out on populations with predominantly brown irides may report a lower incidence of a change in ocular or periocular pigmentation compared with studies carried out on a predominantly Caucasian population. Therefore, more research is needed in the IOP-lowering effect of travoprost for different races. Third, several methodological aspects of our meta-analysis deserve further consideration. In general, in most reports on randomized trials too little or insufficient information was provided to be able to judge properly whether randomization and masking were adequate and whether allocation of treatments truly was concealed.

One study calculated daily patient cost of medical glaucoma therapy.[39] The prostaglandin analogues were comparably priced with bimatoprost (Lumigan; Allergan, Irvine, CA, USA) $0.95 per day, latanoprost (Xalatan; Pharmacia and Upjohn, Kalamazoo, MI, USA) $1.25 per day, travoprost (Travatan; Alcon Laboratories, Fort Worth, TX, USA) $1.01 per day and unoprostone (Rescula; Novartis, Duluth, GA, USA) $0.90 per day. The cost of timolol products per day ranged from a low of $0.38 per day to $0.46 per day. For patients in developing countries the prostaglandin analogues may be too expensive to afford. Therefore, in addition to efficacy and side-effect profile, cost should be considered when determining which agent to prescribe to glaucoma patients.

Travoprost can be stored at room light and temperature (2–25°C). It can be taken along conveniently, which may potentially improve patient compliance.[40] Patients may also comply better with travoprost's once-a-day dosing regimen than timolol's twice daily.

In summary, this meta-analysis suggested that travoprost 0.004% was more effective than timolol 0.5% for reducing IOP in patients with OAG or OH. Compared with other prostaglandin analogues, travoprost 0.004% appeared to be equivalent to bimatoprost 0.03% and latanoprost 0.005%. Although a limited number of local side-effects were reported, no serious treatment-related side-effects were reported. However, there may be studies that have been published in languages other than English and Chinese that may have influenced the results significantly had they been included. Because differences between prostaglandin analogues in IOP reduction are not significant, other aspects such as side-effects, compliance and costs may be taken into consideration to decide on the starting therapy for OAG or OH. Further clinical data published in article are required to better assess potential differences among these prostaglandin analogues.

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