

# Long-term assessment of prostaglandin analogs and timolol fixed combinations vs prostaglandin analogs monotherapy

*Ai-Wei Liu<sup>1</sup>, Lin-Yang Gan<sup>2</sup>, Xiang Yao<sup>2</sup>, Jian Zhou<sup>1</sup>*

<sup>1</sup>Department of Ophthalmology, Dongfang Hospital, the Second Clinical Medical College of Beijing University of Chinese Medicine, Beijing 100078, China

<sup>2</sup>Department of Ophthalmology, Peking Union Medical College, Beijing 100730, China

**Correspondence to:** Jian Zhou. Department of Ophthalmology, Dongfang Hospital, the Second Clinical Medical College of Beijing University of Chinese Medicine, Fengtai District, Beijing 100078, China. zhj9667@126.com

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## Abstract

• **AIM:** To draw a Meta-analysis over the comparison of the intraocular pressure (IOP) -lowering efficacy and safety between the commonly used fixed-combinations of prostaglandin analogs and 0.5% timolol with prostaglandin analogs (PGAs) monotherapy.

• **METHODS:** After searching the published reports from MEDLINE, EMBASE, the Cochrane Library, all randomized controlled clinical trials (RCTs) comparing the fixed combination of PGAs/timolol therapy (FCs) and PGAs monotherapy with treatment duration at least 6mo were included. The efficacy outcomes were mean diurnal IOP, percentage of participants whose IOP were lower than 18 mm Hg, incidence of visual field change, while the safety outcomes included corneal side effects, hyperemia and eye irritation. The analysis was carried out in RevMan version 5.3 software.

• **RESULTS:** After six-month medical intervention, the mean diurnal IOP of FCs was lower than PGAs (MD -1.14, 95% CI -1.82 to -0.46,  $P=0.001$ ); the percentage of target IOP achieving between FCs and PGAs showed no significant difference (RR 1.18, 95% CI 0.97 to 1.43,  $P=0.10$ ). No statistically significant differences of the incidence of hyperemia (RR 0.67, 95% CI 0.45 to 1.01,  $P=0.06$ ) and eye irritation (RR 1.20, 95% CI 0.95 to 1.51,  $P=0.12$ ) between the FCs and PGAs monotherapy were detected. Only one research involved in corneal events, result of this trial revealed no difference between two intervention groups regarding corneal effects (central endothelial cell density, MD -0.20, 95% CI -0.72 to 0.32,  $P=0.45$ ; central corneal thickness, MD -0.01, 95% CI -0.02 to 0.00,  $P=0.23$ ). The evaluation of visual field change was not performed

due to the limited duration of the trials included in this Meta-analysis.

• **CONCLUSION:** The long-term efficacy of the FCs outweighed the PGAs monotherapy in lowering IOP, but in the incidence of hyperemia and eye irritation syndromes, the differences are not statically significant. More RCTs with detailed and authentic data over the assessments of visual functions and morphology of optic nerve heads are hoped to be conducted.

• **KEYWORDS:** fixed combination of prostaglandin analogs and timolol; latanoprost; bimatoprost; tafluprost; timolol; open angle glaucoma; ocular hypertension

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## INTRODUCTION

Eyedrops are the topical medical intervention in treating intraocular pressure (IOP) related conditions. All the eyedrops for the treatment of glaucoma and ocular hypertension (OHT) focus on lowering IOP. A single ocular hypotensive agent is the first line choice, but according to the Ocular Hypertension Treatment Study, over 40% of the patients enrolled in this study needed more than one medication to achieve the relatively modest target IOP<sup>[1]</sup>. In Collaborative Initial Glaucoma Treatment Study, almost three-fourths of the patients randomized to the medication arm required two or more agents to achieve a lower target IOP<sup>[2]</sup>. Benzalkonium chloride (BAK) is a commonly used preservative in eyedrops, which has been proved to cause dose-dependent toxic effects to the ocular surface, even to the corneal endothelia and trabecular meshwork cells<sup>[3-5]</sup>. More application of eyedrops means more exposures to BAK, which might increase the incidence of other eye disorders. The fixed combination might be able to solve the former problem. The main fixed combinations utilized currently are the fixed combination of 0.005% latanoprost and 0.5% timolol (FCLT), 0.04% bimatoprost and 0.5% timolol (FCMT), 0.004% travoprost and 0.5% timolol, 0.0015% tafluprost and 0.5% timolol (FCTT). Latanoprost,

travoprost, tafluprost belong to prostaglandin analogs (PGAs). The classification of bimatoprost has been controversial as some scholars classified it as prostaglandin analogs, while some others sorted it as prostamide for its chemical structure [6]. Latanoprost, travoprost and tafluprost lower the IOP mainly by increasing uveoscleral outflow [7-8], while the physiological mechanisms of bimatoprost still remain to be clarified, but reports showed that increasing uveoscleral outflow might be one of its significant methods in lowering IOP [6,9]. Nevertheless, these four agents showed similar efficacy in reducing IOP [10]. In this analysis, bimatoprost is classified as PGAs. Timolol, belonging to beta-blockers, reduces IOP through many complicated mechanisms, but it has been proved that it mainly functions by decreasing the production of aqueous humor [11]. The recommended dose of timolol varies from once to twice daily. The fixed combinations are recommended to use once daily.

Two recent Meta-analyses demonstrated that the fixed combinations of timolol and PGAs (FCs) were more efficacious than the individual components monotherapy, and brought a lower risk of conjunctival hyperemia [12-13]. However, the treatment duration of most studies included in these two analyses was relatively not long enough, which was inconsistent with the fact that as a chronic condition, glaucoma requires long-term intervention. To evaluate the long-term safety and efficacy of the fixed combinations compared with PGAs, this Meta-analysis was conducted.

## MATERIALS AND METHODS

**Criteria for Considering Studies for Review** We included all randomized controlled trials (RCTs) which compared the FCs administrated daily in the morning or in the evening with the PGAs monotherapy twice daily. Only those studies with a follow-up of at least 6mo were included in our study for adequate assessment of the long-term efficacy and safety. The majority participants of the included studies had to be diagnosed as open angle glaucoma (OAG) or OHT, with a mean untreated IOP above 21 mm Hg. OAG patients should have typical optic disc damage with glaucomatous cupping and loss of the neuroretinal rim, or visual field defects compatible with glaucomatous optic neuropathy. There were no age or gender limitations for the patients. We excluded studies without ethical approval or informed consent.

As patients with chronic angle-closure glaucoma (CACG) and patent peripheral iridotomy were treated in the same way as those with OAG, studies including such patients were also considered to be eligible.

The efficacy outcomes of this review were: 1) the mean diurnal IOP; 2) the proportion of patients who met the target IOP (18 mm Hg) set by the study investigators; 3) the incidence of visual field defect (if the treatment duration was

longer than 5y). The safety outcomes of this review were: 1) the incidence of conjunctival hyperemia; 2) the incidence of eye irritation, including but not limited to foreign body sensation, pain, *etc*; 3) corneal side effects.

**Search Strategy** We searched MEDLINE (from 1946), EMBASE (from 1980), and the Cochrane Library (from 1898) for published reports. The limit for the research was RCT. We did not make any date or language restrictions in searches. Search terms used in our study included "glaucoma", "ocular hypertension", "timolol", "prostaglandin analog", "latanoprost", "travoprost", "bimatoprost" and "tafluprost". The last search was conducted in March, 2015. References of eligible articles and review articles were also hand searched for relevant citations.

**Study Selection and Data Extraction** Two authors independently screened the titles and abstracts of reports and excluded obviously irrelevant reports. The full texts of potentially eligible trials were obtained and assessed in detail. The study design, patient characteristics, interventions, and outcomes were recorded by two reviewers independently, and were cross-checked for accuracy. Any disagreements were resolved by consensus.

**Risk of Bias Assessment** Eligible studies were assessed for risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions v5.1.0. The components assessed were "random sequence generation", "allocation concealment", "blinding of participants and personnel", "blinding of outcome assessment", "incomplete outcome data", "selective reporting", and "other biases". Each component was judged as "low risk", "unclear risk", or "high risk of bias" as outlined in the Cochrane Handbook.

**Data Analysis** For a multi-arm study, we chose intervention groups that were relevant to the review and met the criteria of inclusion. We collected all efficacy and safety outcomes from the eligible studies. We expressed dichotomous outcomes as risk ratios (RR) with their 95% confidence intervals (CI). For continuous outcomes, we obtained the mean and standard deviations, summarized the results as mean differences with 95% CI. The  $I^2$  statistic was used to measure heterogeneity among the trials in each analysis, with  $I^2$  values over 50% as suggestive of substantial heterogeneity [14]. We calculated the overall effects using a random-effects model regardless of the level of heterogeneity. To detect publication bias, a funnel plot would be applied to identify publication bias if ten or more studies were included. All of the statistical analyses were made using the Review Manager software (RevMan 5.3).

## RESULTS

The electronic searches revealed 746 records of articles, but 732 did not meet the eligibility criteria. We obtained full text copies of 14 potentially relevant records and examined in detail for inclusion, no additional studies were identified

Table 1 Characteristics of included studies

Studies	Washout	Treatment duration (mo)	Center	Observation unit	Disease	Medication/ time	Total patients	Mean age (a)	Sex (M/F)	Races
Lass 2001 <sup>[19]</sup>	No	12	Multi	Mean	OAG+OHT	FCLT/morning	116	61±13	56/60	85W24B7O
						L/morning	127	61±12	68/59	103W19B5O
Higginbotham 2002 <sup>[18]</sup>	No	6	Multi	Mean	OAG+OHT	FCLT/morning	138	61±12	67/71	90W38B7H3O
						L/morning	140	63±12	68/72	96W37B6H1O
Pfeiffer 2002 <sup>[17]</sup>	No	6	Multi	Mean	OAG+OHT	FCLT/morning	140	64±13	67/73	Unknown
						L/morning	147	63±12	77/70	Unknown
Lewis 2010 <sup>[16]</sup>	Yes	12	Multi	Mean	OAG+OHT+CACG	FCBT/morning	533	62±12	286/247	397W84B46H5A1O
						B/evening	265	59±12	132/133	181W47B29H5A3O
Pfeiffer 2014 <sup>[20]</sup>	Yes	6	Multi	Right	OAG+OHT	FCTT/morning	188	65.4±10	70/118	Unknown
						T/morning	187	65.4±10	61/126	Unknown

Multi: Multicenter; Mean: Mean of the 2 eyes; Right: Right eye; OAG: Open-angle glaucoma; OHT: Ocular hypertension; CACG: Chronic angle closure glaucoma; FCLT: Fixed combination of latanoprost and timolol; L: Latanoprost; FCBT: Fixed combination of bimatoprost and timolol; B: Bimatoprost; FCTT: Fixed combination of tafluprost and timolol; T: Tafluprost; W: White; B: Black; H: Hispanic; A: Asian; O: Other.

from their references. A further 9 articles were excluded for these reasons: one was a post hoc analysis of two already included studies<sup>[15]</sup>; 8 were less than 6mo; the remaining 5 articles<sup>[16-20]</sup> met the inclusion criteria for this review. The relevant article selection process is demonstrated in Figure 1.

**Study Characteristics** Table 1 shows the characteristics of the included 5 studies. All of the studies were randomized controlled double-masked multicenter clinical trials with a washout or run-in period. Four trials recruited patients with OHT or OAG; one trial enrolled patients with OAG, OHT, or CACG. The intervention of treatment groups was FCs (three latanoprost, one bimatoprost and one tafluprost), which was used once daily in the morning. The intervention of control group included in this review was the same PGAs monotherapy once daily in the morning or evening. All the trials measured the IOP using Goldmann applanation tonometer. Two studies reported mean diurnal IOP measured at 8:00, 10:00, and 16:00<sup>[17-18]</sup>. Three trial did not report extractable data of mean IOP. As for the safety outcomes, only one study measured the change of corneal endothelial cell density and corneal thickness<sup>[19]</sup>, four trials reported the incidence of conjunctival hyperemia and eye irritation<sup>[16-18,20]</sup>.

**Risk of Bias** The methodological quality of the studies was generally good (Figure 2). Three studies described the methods of sequence generation, two trial only mentioned "randomly assigned" without sufficient information for judgment<sup>[17,20]</sup>. Two studies described the methods of allocation concealment, so were judged as "low risk of bias"<sup>[18-19]</sup>. All five trials were double-masked of the participants and study personnel. Only two studies described a part of methods of blinding outcome assessment<sup>[18-19]</sup>, the remaining three did not report mask in details. But outcome measurement is not likely to be influenced by lacking of blinding, so we still judged them as "low risk of detection

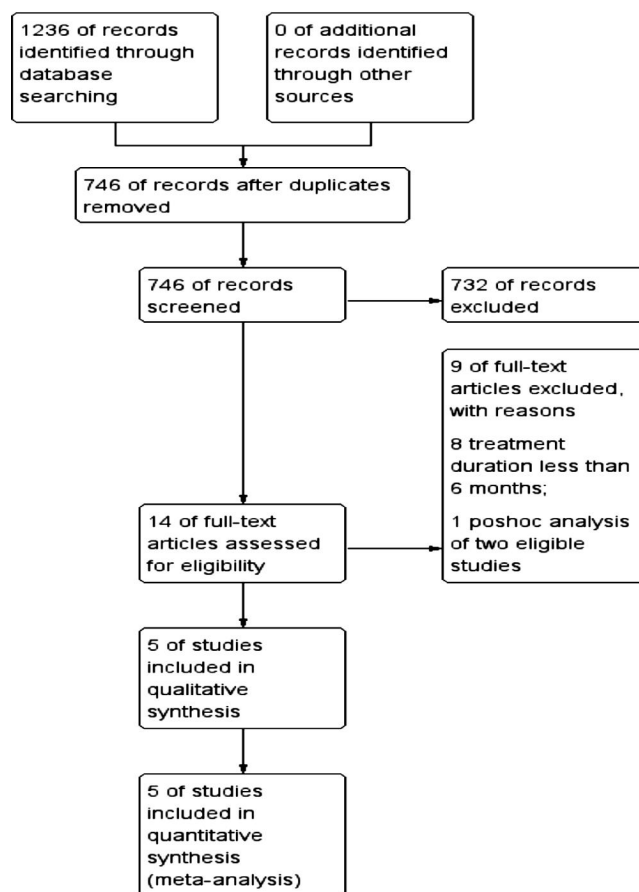


Figure 1 Flow chart of the literature search process.

bias". Withdrawal were not evenly distributed between groups in three studies<sup>[16,18-19]</sup>, more adverse event or uncontrolled iIOP were found in PGAs monotherapy group. One study<sup>[20]</sup> did not report the outcome of corneal thickness in the result, which was measured during the follow-up, so we judged it as "high risk of reporting bias". The protocols of other four trials were not available, so we had insufficient information for judgment. Only in two trials the patients

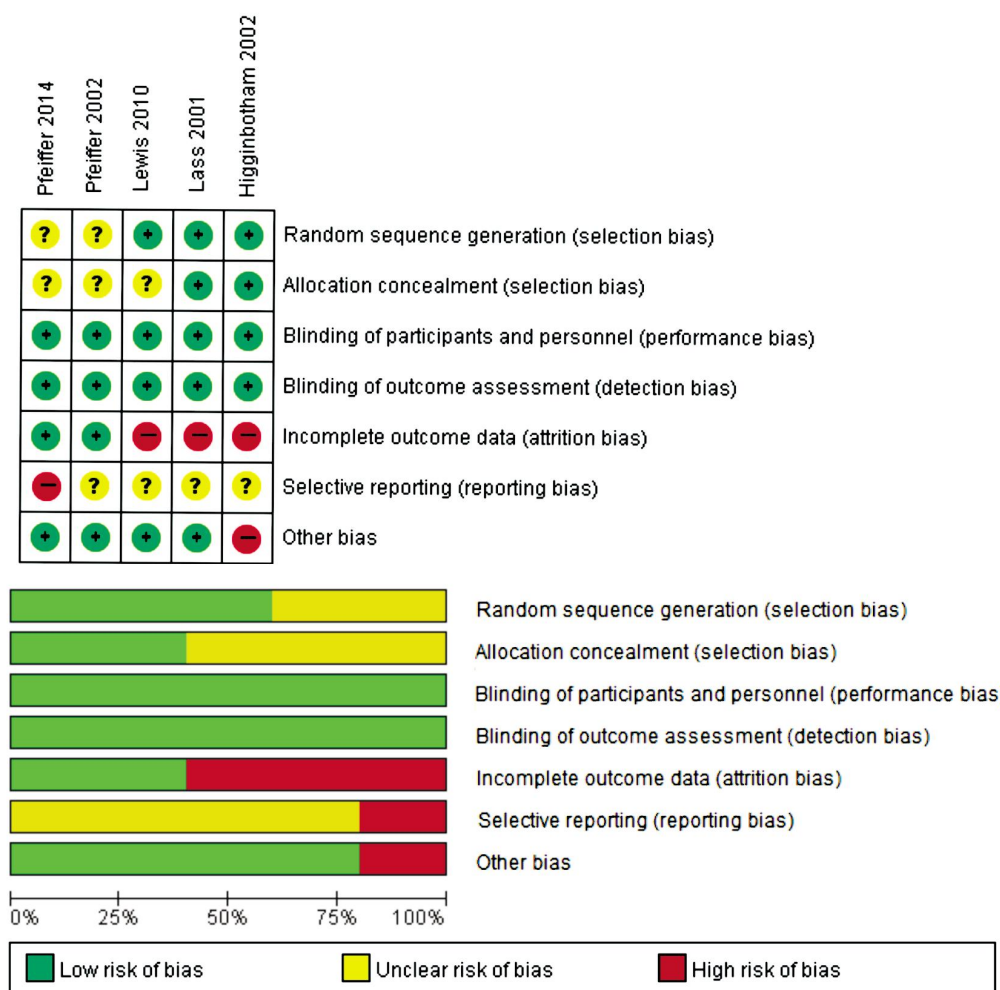


Figure 2 Risk of bias: review authors' judgments about each risk of bias item for each included study and presented as percentages across all included studies.

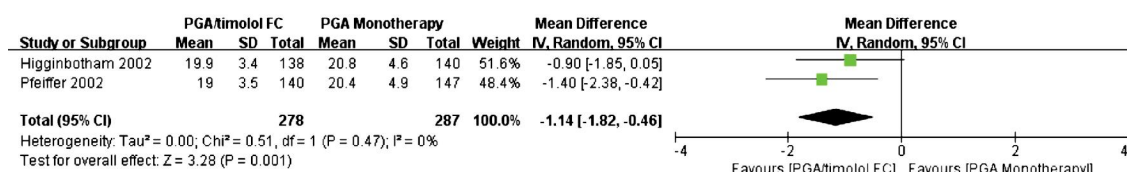


Figure 3 The mean IOP.

underwent a washout of ocular hypertensive medication<sup>[16,20]</sup>, other studies all used timolol during the 2-4wk run-in period, since this review was attempt to assess the long-term effect of fixed combination of PGAs and timolol, lacking washout was not likely to influence the outcome of interest at least 6mo later. One study was judged as "high risk of bias" because of baseline imbalance<sup>[18]</sup>. Since only five trials were included in this review, funnel plot was not performed to assess publication bias.

**Mean Diurnal Intraocular Pressure** Two trials<sup>[17-18]</sup> reported data on the mean diurnal IOP. These two studies both compared the fixed combination of latanoprost and timolol with latanoprost monotherapy. We input post intervention mean diurnal IOP to compare the difference of the effect between the two groups. The differences were statistically significant (MD -1.14, 95% CI -1.82 to -0.46,  $P=0.001$ ), and no heterogeneity was detected in the trials ( $I^2=0$ ) (Figure 3).

**Percentage of Participants Who Achieved the Target Intraocular Pressure** Three trials<sup>[16-18]</sup> reported data on percentage of participants whose IOP<18 mm Hg at the end of the trials. Two<sup>[17-18]</sup> of these trials assessed latanoprost and the other one<sup>[16]</sup> used bimatoprost. According to the result, the percentage of achieving 18 mm Hg between FCs and PGAs showed no significant difference (RR 1.18, 95% CI 0.97 to 1.43,  $P=0.10$ ) (Figure 4).

**Incidence of Visual Field Change** The treatment duration of included studies is relatively short, we did not perform Meta-analysis to evaluate the incidence of visual field change.

**Incidence of Hyperemia** Four trials<sup>[16-18,20]</sup> reported data on the incidence of conjunctival hyperemia. Meta-analysis failed to achieve clear statistical evidence between FCs and PGAs monotherapy (RR 0.67, 95% CI 0.45 to 1.01,  $P=0.06$ ) (Figure 5).

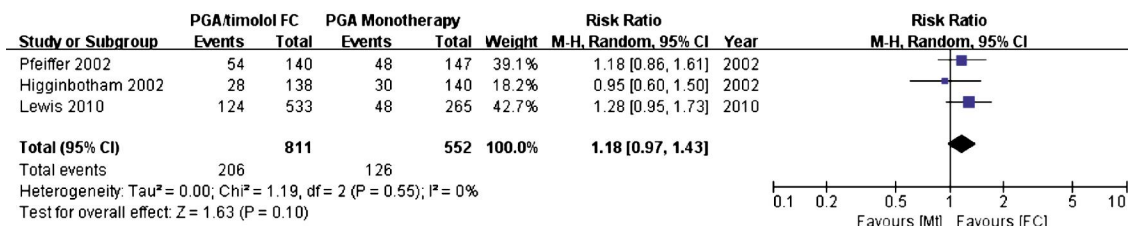


Figure 4 Percentage of patients who achieved the target IOP (<18 mm Hg).

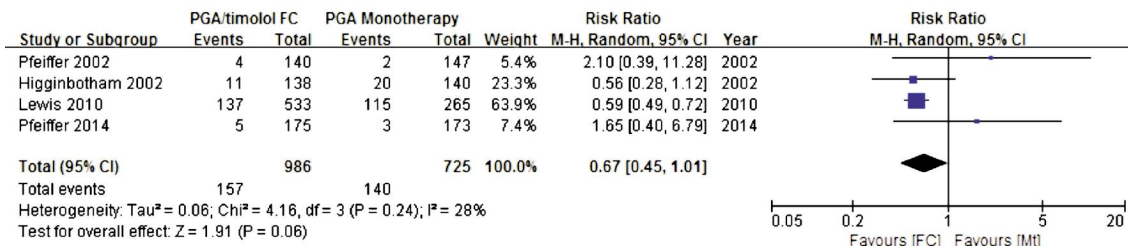


Figure 5 Incidence of Hyperemia.

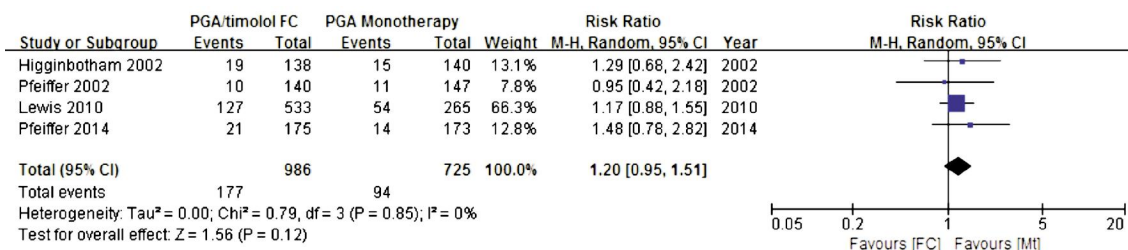


Figure 6 Incidence of eye irritation.

**Incidence of Eye Irritation** Four trials [16-18,20] reported data on eye irritation. Two trials [17-18] provided the incidence of eye irritation as a whole symptom, while the other two [16,20] displayed different symptoms including burning sensation, eye pruritus, foreign body sensation, *etc*. We summed up event numbers of these different symptoms and conducted the Meta-analysis. We did not detect any heterogeneity in these trials ( $I^2=0$ ). And there were no statistically significant differences between the FCs and PGAs monotherapy (RR 1.20, 95% CI 0.95 to 1.51,  $P=0.12$ ) (Figure 6).

**Corneal Adverse Events** Only one study [19] compared the mean percent change in central endothelial cell density and central corneal thickness between FCLT and latanoprost monotherapy groups at 12mo. The result of this trial showed no differences between two intervention groups regarding corneal effects (central endothelial cell density, MD -0.20, 95% CI -0.72 to 0.32,  $P=0.45$ ; central corneal thickness, MD -0.01, 95% CI -0.02 to 0.00,  $P=0.23$ ).

**DISCUSSION**

This systematic review was intended to evaluate and compare safety and efficacy of PGAs/timolol FCs and monotherapy of PGAs in relatively long-term therapies. In clinical practice, multidrug therapy is frequently applied in the management of glaucoma, and beta-blockers are common agents added to PGAs. A previous Meta-analysis demonstrated that the addition of a beta-blocker to a PGA is more efficacious than that of alpha-adrenergic or topical carbonic anhydrase inhibitor [21].

According to the result of the present analysis, the IOP in

participants from FCs group was lower ( $P=0.001$ ) than the PGAs group. This result is consistent with the findings of other investigators [12-13,22], although one of them showed that there were slight differentiations between the efficacy of three PGAs/timolol FCs [13]. As the times of peak effect of timolol and PGAs are different (timolol is 2h after dosing, PGAs is 12h), the lowered IOP observed during the day-time might be mainly affected by timolol. Thus, the real efficacies of FCs administered in the morning might be underestimated [23]. A post hoc analysis [15] also reported the fluctuation of IOP in FCs group was lower compared to latanoprost monotherapy ( $P=0.010$ ). A recent animal study [24] had found that fluctuations in IOP increased the trabecular meshwork extracellular matrix, which is probably a risk factor for glaucomatous progression. The effect of FCs on both lowering and stabilizing the IOP may make it a more reasonable choice for intervention.

The 18 mm Hg was recognized as a relatively safe quantitative value which was set by the investigators from these RCTs as a universally undifferentiated target IOP for those participants and it is also recommended as initial superior limit IOP for all glaucoma patients in clinical practice [25]. However, at the end of the 6mo, the difference of proportions of who attained the IOP within 18 mm Hg from two groups was not detected. As the safe IOP, or target IOP, varies in different patients according to different conditions, it seemed that the significance of this datum might not be so crucial for the reason and a recent report suggested that failure to use target IOP does not lead to bad outcomes [26].

Glaucoma is now recognized as a chronic and progressive neurodegenerative disease which is a leading cause of blindness worldwide [27]. The patients suffering from glaucoma need long term cares. It has been reported that the effect of lowering IOP on retinal ganglion cells (RGCs) apoptosis requires a longer follow-up (e.g. five years post intervention) to be detected [28]. Thus, treatment duration of 6mo to 1y is far from adequate to draw a conclusion over visual field change. As a result, we did not perform any Meta-analysis to evaluate the incidence of visual field change.

In aspect of safety, it was deemed from this Meta-analysis that the FCs groups did not perform better than PGAs monotherapy. In this Meta-analysis, both the incidence of hyperemia ( $P=0.06$ ) and eye irritation syndromes ( $P=0.12$ ) showed no statistically significant differences. The rational explanations might be the varied concentrations of preservatives and PGAs in those medications might have differentiated side effects. An *in vitro* experiment showed different proportions of cell survival in different common-used anti-glaucoma eyedrops [3]. Hypothetically and theoretically speaking, it was thought that the less exposure to BAK might lead to a lower incidence of hyperemia and eye irritation syndromes as the toxicity of BAK is dose-dependent [3-5]. Although the FCTT was preservative free, it seemed that the side effects were increased with the combination of timolol [20]. Our Meta-analysis reached a different outcome with two recent Meta-analyses [12-13]. The detailed mechanisms are still waiting to be further explored. Regarding the corneal adverse effects, although no Meta-analysis was carried out, the only datum showed no differences between two intervention groups in central endothelial cell density ( $P=0.45$ ) and central corneal thickness ( $P=0.23$ ). The possible comprehension for this might be for the reason that the side effects of BAK to corneal endothelia is feeble *in vivo*, although the *in vitro* experiment showed BAK is easily to cause cultured corneal and conjunctival epithelia's death [3].

Some limitations of this Meta-analysis should be detailedly discussed. Firstly, the majority of the subjects in this analysis from the three articles which gave the data of the race ratios were white (72.2%). It was reported that, compared with latanoprost, travoprost was more effective in lowering IOP in black than nonblack statistically [29], although travoprost was not discussed in this analysis. Thus, the results might not be comprehensively applicable to all the ethnic groups. Secondly, the efficacy of timolol in a noticeable proportion who has applied timolol for a long term would decrease [30], which was called "long term drift". The phenomenon was not mentioned in these four articles, which remained to be further studied. Thirdly, the criterion of target IOP (18 mm Hg) in these researches was not objective enough. In fact, the definition of target IOP has been controversial ever since: the American Academy of Ophthalmology defined it as "a range

of IOP adequate to stop progressive pressure induced injury" [31]; the European Glaucoma Society guidelines gave a definition as "an estimate of the mean IOP obtained with treatment that is expected to prevent further glaucomatous damage" [32]; the definition from World Glaucoma Association is "an estimate of the mean IOP at which the risk of decreased vision-related quality of life due to glaucoma exceeds the risk of the treatment" [33]; while the National Collaborating Centre for Acute Care of UK gave the definition infra: "a dynamic, clinical judgement about what level of intraocular pressure is considered by the healthcare professional treating the patient to be sufficiently low to minimize or arrest disease progression or onset and avoid disability from vision loss within a person's expected lifetime" [34]. These varied definitions also described a fact that there was no generally acknowledged consensus in defining target IOP. Besides, the target IOP should be individualized in different situations [26].

In summary, the results of this systematic review suggested that, in over 6-month's therapy durations, the fixed combination drugs containing timolol can effectively lower IOP in patients with OAG or OHT, and latanoprost/timolol, bimatoprost/timolol were capable to achieve lower IOP compared to the PGAs monotherapy.

However, concerning the similarity incidence of conjunctival hyperemia and eye irritations, bare differences were detected. Considering both the FCs had better performances in efficacy and a similar safety in comparison with PGAs monotherapy, the recommendation of applying them other than latanoprost/bimatoprost/tafluprost monotherapy on OAG and OHT patients is justifiable after the exclusion of contraindications. But the therapy of glaucoma should be individualized and adjusted according to the patients' current situations of the affected eyes, differentiated levels of IOP, ages, genders, family histories, systemic histories and other risk factors.

This review demonstrates that FCs performed better than PGAs monotherapy in lowering IOP in the therapies durations over 6mo. However, in all the five RCTs included in this analysis, IOP was the only numeric datum over the measurement of OAG, which was not comprehensive for the assessment of glaucoma. As glaucoma is a chronic disease, it also need a long enough therapy to achieve a more comprehensive conclusion over the IOP and visual functions. More data related to the assessments of visual functions (changes in mean sensitivity of visual fields, mean defect of visual fields) and morphological measurements of retinal ganglion cells (retinal nerve fiber layer thickness, RNFLT) in long-term trials should also be introduced to enhance the reliability of effects of those medications towards IOP related ocular conditions. The tests of visual functions and the morphology of optic nerve should be conveyed in further RCTs. Plus, large sample studies among different ethnic groups are still required to be conducted in order to make more solid analyses.

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