

Efficacy and safety of 0.0015% tafluprost versus 0.005% latanoprost in primary open angle glaucoma, ocular hypertension: a Meta-analysis

Xi-Ting Yang, Lin Zhao, Li-Jun Wang, Yi Zhang, Ding-Ying Liao, Jian-Ming Wang

Department of Ophthalmology, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China

Co-first authors: Xi-Ting Yang and Lin Zhao

Correspondence to: Jian-Ming Wang. Department of Ophthalmology, the Second Affiliated Hospital of Xi'an Jiaotong University, 157 Xiwu Road, Xi'an 710004, Shaanxi Province, China. xajdwjm@163.com

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Abstract

• **AIM:** To evaluate the intraocular pressure (IOP)-lowering efficacy and safety of tafluprost 0.0015% eye drops [benzalkonium chloride (BAK) 0.1 mg/mL] compared with that of latanoprost 0.005% eye drops (BAK 0.2 mg/mL) for primary open angle glaucoma (POAG) and ocular hypertension (OHT).

• **METHODS:** All the randomized controlled trials (RCTs) about treating POAG and OHT comparing tafluprost and latanoprost were collected by searching PubMed, Embase, Cochrane Library, CNKI and VIP. The outcomes of interest to evaluate the clinical efficacy and adverse effects included IOP and patient-related drop discomfort.

• **RESULTS:** Five RCTs involving 888 glaucoma patients were included. The results showed that, 1) at the end of the study, no statistically significant differences were observed in IOP reduction [standard mean difference (SMD) = 0.48, 95%CI 0.07 to 0.88, $P=0.085$] between tafluprost and latanoprost; 2) No statistically significant differences were observed in adverse events of foreign-body sensation [relative risk (RR) = 0.62, 95%CI 0.26 to 1.46, $P=0.269$], eye irritation (RR=1.16, 95%CI 0.49 to 2.75, $P=0.744$), eye pain (RR=2.000, 95%CI 0.949 to 4.216, $P=0.07$), iris hyperpigmentation (RR=0.741, 95%CI 0.235 to 2.334, $P=0.61$), dry eye (RR=1.154, 95%CI 0.409 to 3.256, $P=0.79$) and eye pruritus (RR=1.600, 95%CI 0.536 to 4.774, $P=0.4$) between tafluprost and latanoprost. However, tafluprost showed more reported incidence of conjunctival hyperaemia than latanoprost (RR=2.11, 95%CI 1.24 to 3.59, $P=0.006$).

• **CONCLUSION:** Tafluprost 0.0015% eye drops (BAK 0.1 mg/mL) and latanoprost 0.005% eye drops (BAK 0.2 mg/mL) are comparable in lowering IOP for open angle glaucoma (OAG) and OHT. It does not differ in the incidence of foreign-body sensation, eye irritation, eye pain, iris hyper-pigmentation, dry eye and eye pruritus, but tafluprost shows less ocular tolerability because of more incidence of conjunctival hyperaemia.

• **KEYWORDS:** tafluprost; latanoprost; open angle glaucoma; ocular hypertension; efficacy; safety; Benzalkonium chloride; Meta-analysis

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INTRODUCTION

Currently lowering intraocular pressure (IOP) is the only evidence-based method in decreasing the risk of visual field progression for treating glaucoma^[1]. Among the many hypotensive medications, prostaglandin analogues (PGAs) have been recommended as the first-line therapy in glaucoma and ocular hypertension (OHT) by the Europe Glaucoma Society guidelines, in terms of their efficacy to reduce IOP, low risk of systemic adverse effects and convenient once-daily dosing^[2]. They lower the IOP mainly by increasing the uveoscleral outflow of aqueous humour^[3]. Among them, latanoprost was the first of the currently available topical prostaglandin F2 (PGF2 α) analogs to be launched for glaucoma or OHT and which still accounts for the majority of prescriptions^[4]. At the same time, however, due to the affinity for prostaglandin E1 (PGE1) receptor, long-term use of latanoprost and other prostaglandin analog is associated with increased iris and skin pigment. In order to reduce adverse events, tafluprost, a new prostanoid fluoro-prostaglandin (FP) receptor agonist have been developed with two fluorine atoms in the position 15 in the β -chain of the prostaglandin structure^[5-6]. Tafluprost has been reported to have a 12-fold higher affinity than latanoprost

to the FP receptor^[6]. A few earlier reviews and studies have reported conflicting results on their relative OHT efficacy and tolerability^[5,7-13]. A former Meta-analysis of only two independent clinical Phase IIIb studies, performed by Uusitalo *et al*^[11], demonstrated an equal IOP-lowering efficacy after replacing 0.0015% latanoprost [with benzalkonium chloride (BAK), 0.2 mg/mL] with preservative-free tafluprost, and tafluprost group significantly decreased the symptoms and signs of ocular surface disease and outrated latanoprost group in drop comfort^[14]. BAK is the most common ophthalmic preservative^[15] and has been proved toxic to various tissues of the ocular face^[16-18]. However, the most widely used tafluprost worldwide are usually preservative with 0.1 mg/mL BAK^[7-11]. The present Meta-analysis was conducted to evaluate the safety and efficacy of tafluprost 0.0015% eye drops containing 0.1 mg/mL BAK and latanoprost 0.005% eye drops containing 0.2 mg/mL BAK, and to guide the selection of the optimal PGA agent for individual patients with primary open angle glaucoma (POAG) and OHT.

MATERIALS AND METHODS

Materials and Search Strategy We conducted a comprehensive search for the references published on the PubMed, Embase, Cochrane Library, CNKI and VIP of Controlled Trials databases. The database was searched in December 2017 and updated the search on February 2018. We did not impose any restrictions of the publication status, year, language, or methodology. The search strategy combined terms related to disease (POAG and OHT) with terms related to therapies (tafluprost and latanoprost). Search strategy was supplied as follows: “open angle glaucoma” OR “ocular hypertension” AND “tafluprost” OR “AFP-168” AND “latanoprost” OR “Xalatan” OR “PhXA34” OR “PHXA41”. In addition, we manually reviewed the reference lists from relevant original research. If a study was considered relevant, the full text was reviewed.

Inclusion Criteria 1) Study type: randomized controlled trials (RCTs); 2) Population: patients with OAG and OHT; 3) Intervention: tafluprost 0.0015% with 0.1 mg/mL BAK versus latanoprost 0.005% with 0.2 mg/mL; 4) Outcomes: a study had to report at least one of following outcome measures: efficacy outcomes and safety outcomes, and participants had to be followed for at least 28d.

Exclusion Criteria 1) Non-clinical experiments, animal studies, case reports or review articles; 2) Duplicate publications; 3) Studies lack of accessibility to original articles; 4) Studies enrolling fewer than 10 participants in each group; 5) The experimental drugs utilized in the studies contained other drugs for lowering IOP or combined operation or other drug therapies.

Outcomes Measures Efficacy outcomes were classified as the mean IOP-lowering effects or the mean IOP of beginning

and end of studies. Safety outcomes were defined as any of the following events: conjunctival hyperaemia, hyperpigmentation, dry eye, eye pain, eye pruritus, foreign-body sensation or eye irritation. When multiple publications of the same study were available, only the latest one was included. Missing data were obtained by consulting authors via e-mails.

Data Extraction and Quality Assessment Two independent reviewers who were blind to each other (Yang XT and Zhao L) extracted data. Any disagreements were discussed by the two reviewers or resolved by adjudicating senior authors (Wang JM). The data included are as follows (using a standardized form data abstraction instrument): the first author, year of publication, sample size, length of follow-up period, average age, gender ratio, type of glaucoma number of cases, study type and countries/regions. The details of characteristics on each study were listed in Table 1.

The Methodological Quality Assessment (Modified Jadad Score) are used to assess the quality of the included studies. The quality assessment involved four items (random sequence generation, concealment of allocation, double blind, withdrawals and dropouts). For each item, it can be given a score from 0 to 2. The total score below 3 was defined as inferior quality, and 4 to 7 was defined as high quality study. Two independent reviewers who were blind to each other (Yang XT and Zhao L) assessed the quality scales and resolved any disagreements through discussion with a senior author (Wang JM). The information of quality assessment was listed in Table 2.

Statistical Analysis We used mean fluctuating intervals of IOP as the effectiveness index, and define acceptable time range as 1 to 3mo. IOP were not reported at the same time of each studies. So, we utilized standard mean difference (SMD) to achieve the effectiveness Meta-analysis. For one study that lack of variance of the mean standard deviation, we utilized a formulas that applied to the baseline and endpoint IOP, the variation mean of the IOP, the basis and the final IOP deviation, as provided: intraocular pressure reduction (IOPR) = $IOPR_{\text{baseline}} - IOPR_{\text{end point}}$, $SD_{IOPR} = (SD_{\text{baseline}}^2 + SD_{\text{end point}}^2 - SD_{\text{baseline}} \times SD_{\text{end point}})^{1/2}$ ^[19]. The incidence of all adverse reactions was less than ten percent. We used relative risk (RR) as adverse reaction assessment indicator. Heterogeneity between studies was analyzed by I^2 statistics. A *P* value of I^2 statistics <0.05 was defined as an indicator of heterogeneity. The grade of heterogeneity was described as low, substantial and high heterogeneity based on I^2 values of 25%, 50% and 75%, respectively. If heterogeneity existed, a random-effect model was used to assess the overall estimate. Otherwise, a fixed-effect model was chosen. Sensitivity analysis was carried out to eliminate the heterogeneity source and determine the reliability of the results. A funnel plot would be applied to

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Table 1 Characteristics of studies included in the Meta-analysis

First author	Year	Countries/regions	Type of study	No. of eyes (taf/lat)	Male (%)	Mean age (y)	Diagnosis (n)			Follow-up (mo)	Loss to follow-up
							OAG	OHT	NTG		
Uusitalo	2010	Multi countries & centers	RCT	269/264	221 (41.5)	62.5	533	0	24	131/533	
Traverso	2010	Italy & Finland	RCT	19/19	12 (31.6)	NA	26	12	0	1.5	2/38
Park	2015	Korea	RCT	20/21	18 (43.9)	55.1	14	0	27	3	0/41
Ge	2015	China	RCT	122/124	125 (63.8)	44.1	144	52	0	1	21/246
Ikeda	2016	Japan	RCT	15/15	15 (50)	66.3	0	0	30	3	0/30

taf: Tafluprost; lat: Latanoprost; OAG: Open angle glaucoma; OHT: Ocular hypertension; NTG: Normal tension glaucoma; RCT: Randomized controlled trial; NA: Not available.

Table 2 Quality assessment

First author	Random sequence generation	Concealment of allocation	Double blind	Withdrawals and dropouts	Total score
Uusitalo	1	1	2	1	5
Traverso	2	1	2	1	6
Park	2	2	2	1	7
Ge	2	1	2	1	6
Ikeda	1	1	0	1	3

detect publication bias if ten or more studies were included. All of the statistical analysis was conducted with StataMP 14.0 software.

RESULTS

Study Selection and Characteristic We retrieved a total of 59 related RCTs, of which 49 were excluded from the Meta-analysis based on the exclusion criteria. We obtained full text copies of 10 potentially relevant records and examined detail for inclusion, no additional studies were identified from their references. A further 3 articles were excluded for utilizing preservative-free tafluprost, and 2 utilized tafluprost of different concentration. Totally 5 RCTs^[7-11] met the inclusion criteria for this Meta-analysis. Detailed search strategy is outlined in Figure 1. A total of 888 patients were included with the follow-up period ranged from 1 to 24mo. The mean age of patients was 57.0y, and 44.0% were male.

Evaluation of Risk of Bias According to the revised Jadad scale, the average score of each research is 5.4 points, in line with the general analysis standard. Detailed baseline data is outlined in Table 1^[7-11]. Since only 5 trials were included in this analysis, we did not perform funnel plot to assess published bias.

Efficacy Outcomes Four studies evaluated IOP-lowering effect as an efficacy outcome measure^[7-10]. Heterogeneity test result across two groups was $P=54.7\%$, $P=0.085$, Chi-square=6.62. We used randomized effect model and got SMD of mean IOP-lowering effect across two groups was 0.48 (95%CI 0.07 to 0.88, $Z=2.33$, $P=0.085$; Figure 2) for IOP-lowering effect Meta-analysis tafluprost vs latanoprost. Efficacy outcomes showed no differences between two groups.

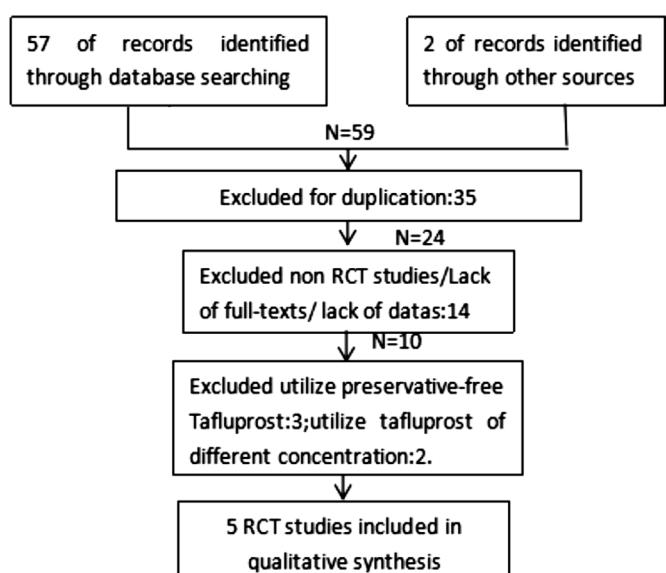


Figure 1 Flow chart of the literature search process.

Safety Outcomes Three trials reported conjunctival hyperemia outcomes^[7,10-11]. Heterogeneity test got Chi-square=0.84, $P=0.659$, $I^2=0$. Pooled conjunctival hyperemia outcomes by fixed-effect model, tafluprost was associated with more incidence of conjunctival hypermia significantly than latanoprost ($RR=2.11$, 95%CI 1.24 to 3.59, $P=0.006$, $Z=2.76$; Figure 3). Three studies reporting eye irritation outcomes were pooled^[6,9-10]. Heterogeneity test got Chi-square=2.99, $P=0.224$, $I^2=33.2\%$ ($RR=1.16$, 95%CI 0.49 to 2.75, $P=0.744$, $Z=2.76$; Figure 4). There is no statistically difference between two groups. Three trials reported foreign-body sensation outcomes^[7,10-11]. Heterogeneity test got Chi-square=0.55, $P=0.761$, $I^2=0$. There is no statistically difference between two groups ($RR=0.62$, 95%CI 0.26 to 1.46, $P=0.269$, $Z=1.10$;

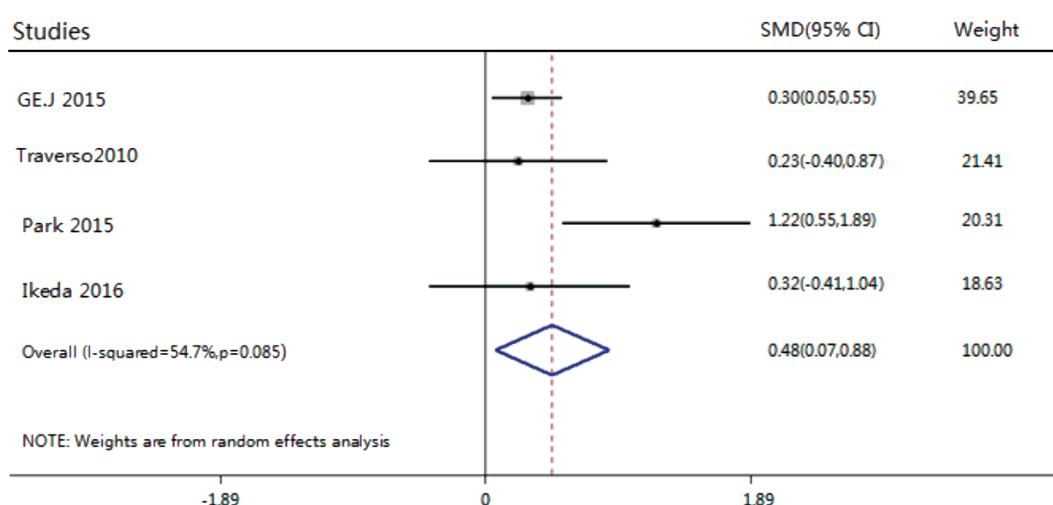


Figure 2 Forest plots (random-effect model) for IOP-lowering effect Meta-analysis tafluprost vs latanoprost.

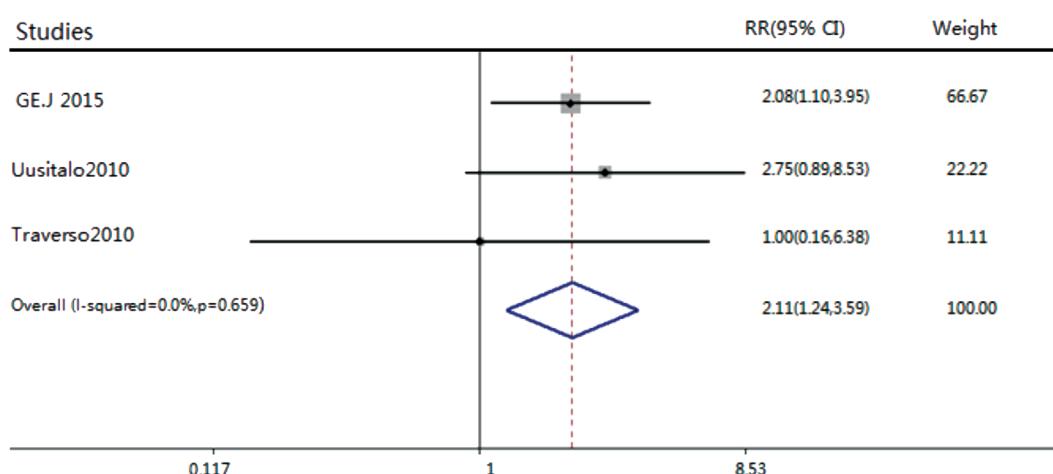


Figure 3 Forest plots (fixed-effect model) for conjunctival hyperemia rate across tafluprost and latanoprost group.

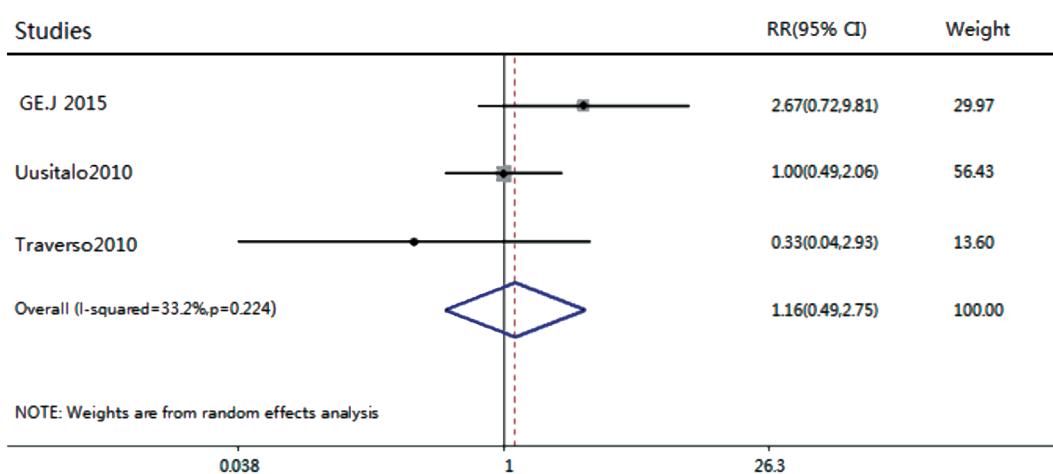


Figure 4 Forest plots (random-effect model) for eye irritation rate across tafluprost and latanoprost.

Figure 5). We conducted Meta-analysis of eye pain hyperpigmentation, dry eye, and eye pruritus separately in 4 groups of two related studies. RR values are respectively: RR=2.000, 95%CI 0.949 to 4.216, $P=0.07$; RR=0.741, 95%CI 0.235 to 2.334, $P=0.61$; RR=1.154, 95%CI 0.409 to 3.256, $P=0.79$; RR=1.600, 95%CI 0.536 to 4.774, $P=0.4$. The detailed results

of Meta-analysis and heterogeneity of four adverse reactions were showed in Table 3.

DISCUSSION

By selectively combining with the FP receptor in the eye tissue, prostaglandins induce a dose-dependant increase in metallo-proteinases in human ciliary smooth muscle cells that

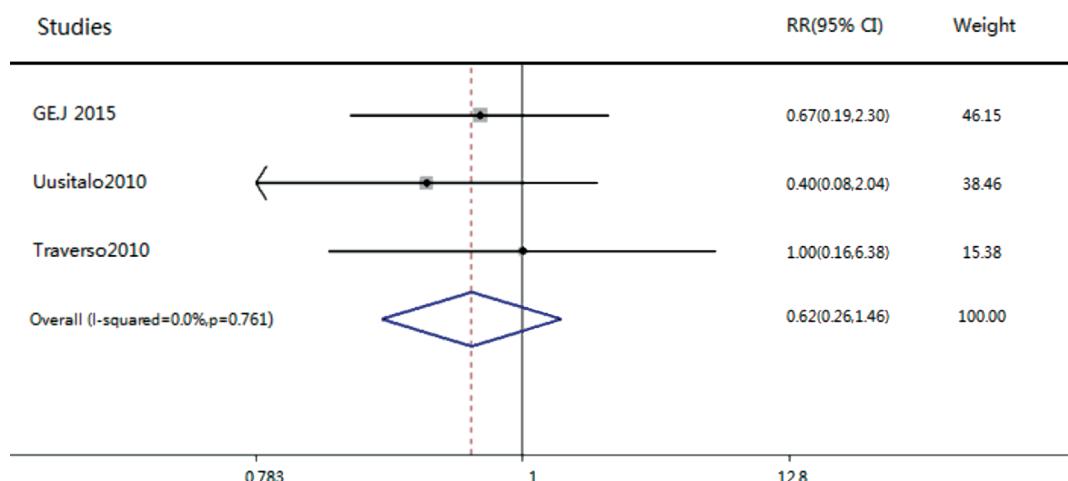


Figure 5 Forest plots (random-effect model) for foreign-body sensation rate across tafluprost and latanoprost.

Table 3 Meta-analysis and heterogeneity results of four adverse reactions

Adverse reaction	Studies	RR	95%CI	I^2 (%)	P	Z
Hyper-pigmentation	Uusitalo 2010 & Ikeda 2016	0.741	(0.235, 2.334)	0	0.61	0.51
Dry eye	Taverso 2010 & Uusitalo 2010	1.154	(0.409, 3.256)	0	0.79	0.27
Eye pain	Ge 2015 & Uusitalo 2010	2.000	(0.949, 4.216)	0	0.07	1.82
Eye pruritus	Taverso 2010 & Uusitalo 2010	1.600	(0.536, 4.774)	0	0.40	0.84

results in remodeling of the extracellular matrix and increases the space between the bundles of smooth muscle cells, allowing an enhanced uveoscleral outflow for IOP reduction^[20]. However, despite having excellent pharmacokinetic properties, it still causes various unacceptable ocular surface disorders, which can include eye pain, conjunctival hyperaemia and foreign-body sensation^[21-22]. These side effects may lead to reduced treatment compliance. This Meta-analysis was conducted to evaluate the safety and efficacy of tafluprost 0.0015% eye drops containing 0.1 mg/mL BAK and latanoprost 0.005% eye drops containing 0.2 mg/mL BAK and guide the selection of the optimal PGA agent for individual patients with POAG and OHT.

Sutton *et al*^[5] drew a conclusion that IOP reductions with tafluprost 0.005% were superior to those with latanoprost 0.005%. In our analysis, the concentration of tafluprost 0.0015% is 1/3 that of latanoprost 0.005%. We took the mean of IOP reduction to evaluate the effectiveness of treatment and analyze four articles. Due to time inconsistent when extracted data of IOP, we chose SMD as the evaluation index. The result (SMD=0.48, 95% CI 0.07 to 0.88, P=0.085) shows the non-inferiority of the IOP-lowering effect of tafluprost 0.0015%. Among these 5 articles, Uusitalo *et al*'s^[11] study failed to participate in the analysis of efficacy due to the absence of standard deviation, but it was consistent with the results of our Meta-analysis.

A poor drug tolerance and safety can lead to invalidity of treatment. Safety of tafluprost 0.0015% has obvious

advantages over that of latanoprost 0.005%, which has been demonstrated by several relevant studies. However, tafluprost utilized in these studies does not contain BAK. Our analysis showed that in the incidence of foreign-body sensation, eye irritation, eye pain, iris hyper-pigmentation, dry eye and eye pruritus, the differences were not statistically significant, but tafluprost showed less ocular tolerability with more incidence of conjunctival hyperaemia. There may be some reasons. First, while tafluprost has a stronger affinity with FP receptor and the IOP-reduction effect is more stable, it is possible that in the meanwhile, the combination ability with the side effect channel of the prostaglandins were increased^[23]. Second, latanoprost cannot be metabolized. It is stable after absorbed by the cornea and reaches the peak value in 2h. And tafluprost can be rapidly absorbed by eye tissue, whereas the radiation levels peak in the cornea will be at the first 15min of the eye^[18]. The absorption and metabolism rates of drugs may also be relevant factors for the occurrence of adverse reactions. BAK is typically used with concentrations ranging from 0.04 to 0.25 mg/mL, and the toxicity is in a dose-dependent manner to cause deleterious effects on cornea, conjunctiva and trabecular meshwork^[16-17]. In this study, the incidence of conjunctival hyperaemia was still higher in tafluprost group. It was an interesting finding that the higher tolerance of latanoprost with BAK 0.2 mg/mL when compared to tafluprost with BAK 0.1 mg/mL, which may indicate that BAK at low concentration contained in PGEs did not lead to a lower incidence of side effects. This suggests that it could be tafluprost itself, independently of

the preservative product, that has a higher pro-inflammatory activity than latanoprost and gives rise to local damage of the ocular surface.

This review has a few limitations. First, a small amount of included studies, among which there was a self-crossover study and only two large sample studies, may lead to a bias. The article by Traverso *et al*^[7] is the phase II study, while the article by Uusitalo *et al*^[11] is the phase III study of tafluprost 0.0015%. However, the participants in each group and the experimental drugs utilized in both studies are consistent with our inclusion and exclusion criteria. A sensitivity analysis was used to assess the robustness of the Meta-analysis results and to analyze the source of heterogeneity by sequentially omitting individual studies. The sensitivity analysis could not ascertain the source of heterogeneity, and the Meta-regression analysis could not be used because the number of included studies is too few. Thus, a random effects model was used to analyze the IOP-lowering effect. Second, for each study, the time difference between the mean of IOP reduction was not exactly the same. A total of 2 of the research on the evaluation of effectiveness evaluation were included in the study. Third, the classification of the side effects in 5 articles were different, so the data was biased. And individual articles have failed to describe the method of measurement of the IOP, and there was a possibility of measuring error. Besides, patients' individual differences in sensitivity and tolerability to prostaglandins can be a system error. Finally, in all the five RCTs included in this analysis, IOP was the only numeric data over the measurement of efficacy, which was not comprehensive for the assessment of glaucoma. Furthermore, the limited no more than 3-month duration of the RCTs for lowering IOP effect did not allow for investigation of the long-term effects, and more RCTs of high-quality with large sample are hoped to be conducted in order to evaluate more and long-term results.

A comparison of lowering IOP effect on glaucoma patients revealed no difference between tafluprost and latanoprost, and a lower concentration of BAK contained in tafluprost did not lead to less ocular side effects. It is still in need of further investigation to know how to reduce the ocular toxicity of prostaglandins in the treatment of POAG and OHT patients.

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