

Efficacy and safety of different regimens for primary open-angle glaucoma or ocular hypertension: a systematic review and network meta-analysis

Fei Li, Wenbin Huang and Xiulan Zhang 

State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China

ABSTRACT.

Purpose: To assess the efficacy and safety of different regimens, including monotherapy and double therapy, for primary open-angle glaucoma (POAG) or ocular hypertension.

Methods: We searched PubMed, EMBASE and clinicaltrials.gov for studies that fit our inclusion criteria in this network meta-analysis. Randomized controlled trials that report data on efficacy and safety of medications for POAG or ocular hypertension are included. Data on intra-ocular pressure (IOP) lowering effect and incidence of adverse events including hyperaemia and ocular discomfort were extracted and used in mixed-comparison analysis.

Results: This study includes 72 randomized trials. Data were available on 12 medical treatments of POAG or ocular hypertension. Of 66 possible comparisons of outcome efficacy, 15 treatments were compared directly. Compared to prostaglandin analogues (PGA), beta-blockers (BB) showed relatively weaker ability to lower IOP, followed by α 2-adrenergic agonists (AA) and carbonic anhydrase inhibitors (CAI). For dual therapy, regimens composed of a combination of PGA with another treatment demonstrated more powerful IOP lowering efficacy, while the combination of two non-PGA drugs had lower efficacy in controlling IOP than PGA alone. There was no statistical significance in combinations that did not include PGA on efficacy of IOP control. In terms of tolerance, PGA alone leads to more severe hyperaemia than any other monotherapy regimen, while BBs have the lowest effect on the incidence of hyperaemia. Most dual therapy regimens containing PGA also lead to serious hyperaemia, with the exception of PGA + AA. Compared to regimens containing PGA, those with BB are less likely to cause hyperaemia.

Conclusion: Our network meta-analysis showed that PGAs provide best IOP lowering effect among all the monotherapy regimen. Combination of PGA and other category of drugs leads to better IOP decrease. Combination of BB and another non-PGA drug may have less ocular side-effects than PGA alone.

Key words: efficacy – medical therapy – network meta-analysis – primary open-angle glaucoma – safety

Introduction

Glaucoma is one of the leading causes of blindness in the world. It is estimated that by 2020 there will be 79.6 million glaucoma patients worldwide (Quigley & Broman 2006). Glaucoma can be classified based on the irido-corneal angle into open-angle, closed-angle and developmental glaucoma, which are further divided into primary and secondary types (Kwon et al. 2009). Primary open-angle glaucoma (POAG) is the predominant form of glaucoma in western countries and has the highest incidence rate in people of African descent and the lowest rate in people of Asian descent (Tielsch et al. 1991; Salmon et al. 1993; Dielemans et al. 1994; Mitchell et al. 1996; Wensor et al. 1998; Buhrmann et al. 2000; Quigley et al. 2001; Chan et al. 2016; Kapetanakis et al. 2016). Incidence of POAG increases with age and is higher in women than men (Quigley & Broman 2006).

Primary open-angle glaucoma (POAG) is associated with high IOP. Elevation of IOP often leads to degeneration of the optic nerve. The main clinical features of glaucomatous damage to the optic nerve include deepening of excavation of the optic disc, bleeding of the optic disc (often seen in normal tension glaucoma) and defects of the retinal nerve fibre layer. Visual field loss may follow optic nerve damage. Previous research has shown that the extent of damage to the optic nerve depends on the extent of IOP elevation

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(Quigley et al. 1980). Reduction of IOP both decreases the incidence rate of POAG and delays progression of POAG (Sommer et al. 1991; Heijl et al. 2002; Kass et al. 2002). In clinical practice, medications and surgeries may help decrease IOP and prevent progression of the disease. Unless contraindicated, drug initial therapy, and potential cost, side-effects, and dosing schedules may influence medication choice.

Medical treatments act to decrease IOP in three main ways: increase outflow of aqueous humour, decrease secretion of aqueous humour and decrease intra-ocular volume. Prostaglandins (PGA), AA, BB, CAI and miotics (MIO) are the drugs most widely used to treat POAG. Previous meta-analysis demonstrated that medical treatment was effective in prevention of visual field loss (Maier et al. 2005). However, different drugs decrease IOP through various mechanisms, thus leading to different efficacies with regard to lowering IOP. Monotherapy, dual therapy and occasionally, triple therapy have all been carried out on patients. The wide variety of drug treatment options makes it difficult for doctors to choose a specific regimen. Previous meta-analyses have compared the IOP lowering efficacy of drugs such as latanoprost and timolol, among others (Denis et al. 2007; Stewart et al. 2008), but these comparisons have been carried out between only a limited number of regimens because data from randomized controlled trials involve limited types of drugs. A previous network meta-analysis compared the treatment effect of several PGAs, AAs, BBs and placebo (van der Valk et al. 2009), but its data focused on comparisons among the use of single drugs. To elucidate the IOP lowering effect of different categories and combinations of drugs, this study describes a network meta-analysis comparing and ranking all categories of medications for medical treatment of POAG.

Materials and Methods

Data sources and searches

The study was registered in PROSPERO database with an ID of CRD42017067235. PubMed, EMBASE and clinicaltrials.gov were searched

for relevant studies published during 1970 till now. A complete search strategy of PubMed search was contained in File S1. Search terms were composed of keywords in combination with both MeSH terms and text words. The search terms included PGA, AA, BBs, CAI and POAG. A filter was applied for randomized controlled trials. There was no limitation on language or publication date. Eligible studies were identified by manually checking the reference lists of the included studies.

Study selection

Two authors (F-L and WB-H) independently reviewed the abstracts identified in the search to identify possible eligible studies and eligible studies were selected based on the result from both authors. Studies were included in this review based on the following criteria. (i) Studies must be randomized controlled trials. (ii) Trials must compare the above-mentioned antiglaucoma regimens in glaucoma patients. (iii) Duration of trials must be at least 3 months. (iv) Different categories or combinations of medicines must be used in different groups of patients, and only one type of regimen can be used during the trial by one group of patients. (v) Trials must report on the outcomes of interest (see below). We excluded trials that included patients undergoing triple therapy or surgical therapy (including laser iridotomy). Studies not providing direct results of Δ IOP (change of mean diurnal IOP from the baseline to the end of the study) were excluded because calculation of Δ IOP based on other provided data led to inaccurate estimation of Δ IOP, thus increasing the inconsistencies between studies. Figure S1 shows the literature search process in detail.

Patient involvement

There was no patient involvement in this study.

Data extraction and quality assessment

Two authors independently extracted the data. Disagreements were resolved through discussions with two other researchers. Extracted data included the characteristics of the studies, baseline characteristics of the patients and characteristics of the treatment.

Combinations of two medications were classified into fixed combination and concomitant use of drugs. The network meta-analysis does not distinguish between these two strategies. Previous studies showed fixed combination of two drugs leads to IOP lowering effects comparable to concomitant use of both components (Hughes et al. 2005; Schuman et al. 2005). The primary outcome of this study was the efficacy of each regimen, including mean Δ IOP during the study, percentage of IOP decrease (relative reduction of IOP) and number of patients reaching an IOP lower than 18 mmHg by the end of the study. The secondary outcome was the tolerance analysis, including the number of patients experiencing hyperaemia during the trial. Two authors independently assessed the quality of evidence using Cochrane's Collaboration tool for evaluating study bias (Higgins et al. 2011). Details about the methodologies of the included studies and a graph of publication bias are provided in Table S5 and Figure S18, respectively.

Statistical analysis

The primary analysis compared each treatment group against the prostaglandin group, which was chosen as the reference group. We also performed mixed comparison of all other possible comparators. Inconsistency in the network model was estimated using the inconsistency factors (difference between direct and indirect treatment effect estimates) and their uncertainty (using loop-specific heterogeneity estimates). The presence of small-study effects was assessed using a 'comparison-adjusted' funnel plot (Chaimani et al. 2013). It suggests no evidence of small-study effects in the network if all studies lay symmetrically around the zero line of the comparison-adjusted funnel plot (Chaimani et al. 2013). We use rankograms to show the rank of each treatment in decreasing IOP or the chance of causing hyperaemia. The surface under the cumulative ranking curve (SUCRA), which is a simple transformation of the mean rank, was used to provide a hierarchy of the treatments (Salanti et al. 2011; Bangalore et al. 2014). Larger SUCRA values indicate higher rank of the treatment (Salanti et al. 2011; Bangalore et al. 2014). In addition, a clustered ranking

plot was constructed using SUCRA values for efficacy (Δ IOP) and safety (hyperaemia) outcomes to obtain information on meaningful groups of treatments that maximize benefits for efficacy and safety outcomes.

Sensitivity analysis

The robustness of the results was assessed using sensitivity analyses. Studies that tend to be the source of inconsistency underwent sensitivity analysis. Sensitivity analyses were carried out by excluding the studies causing heterogeneity and performing network meta-analysis again on all remaining studies to determine whether the results change.

Results

The literature search returned 1253 studies. Abstract review resulted in the exclusion of 1146 articles because they were not randomized controlled trials or crossover design studies or otherwise failed to meet inclusion criteria. After full-text review, 72 studies were included in the statistical analysis (see Supplemental Reference List). Of these 72 studies, 50 were included in the network meta-analysis of Δ IOP, while 54 studies were used in the network meta-analysis of hyperaemia. Studies included in our research covered 19 916 patients. Table S1 provides the baseline characteristics of the included trials.

Efficacy outcomes

Change of intra-ocular pressure

The change in IOP was assessed in 50 studies, involving 12 different regimens. The results from 9345 patients were available for analysis. Figure S2 shows the network plot for Δ IOP. For monotherapy using PGA as reference, PGA showed the strongest IOP decreasing effect. Compared to PGA, BB showed relatively weaker IOP lowering effect followed by AA [mean difference (MD): 1.59 (0.98, 2.21)] and CAI [MD: 2.44 (1.82, 3.05)]. For dual therapy, regimens composed of a combination of PGA and another medicine (i.e., PGA + AA, PGA + BB and PGA + CAI) demonstrated more powerful IOP lowering efficacy, while combinations of two non-PGA drugs were less effective in controlling IOP than

PGA alone. All combinations of non-PGA drugs showed similar efficacy in IOP control. Table 1 shows the complete results. The probability analysis resulted in the following hierarchy for IOP lowering effect: PGA + AA, followed by PGA + CAI, PGA + BB, and PGA and other regimens, as shown in Figure 1.

Percentage of IOP reduction

Because the baseline values of IOP are different between studies and may influence the value of IOP reduction during the study, we also used relative IOP reduction as a standard to determine the IOP lowering effect of different regimens. The relative values were then estimated using the baseline value and the reduction from baseline as follows: $IOPR\% = IOPR/IOP_{baseline}$ and $SD_{IOPR\%} = SD_{IOPR}/IOP_{baseline}$ (Cheng et al. 2009). The network meta-analysis includes 50 studies and 9345 patients. Figure S3 shows the network plot of relative IOP reduction. Similar to the results of Δ IOP, PGA contributed to the largest relative IOP reduction among monotherapy regimens, while dual therapy regimens produced greater results than either of its components alone. Dual therapy regimens containing PGA performed better than other regimens. Table 1 shows the complete results of MD with 95% confidence intervals. Based on the probability analysis, the hierarchy for IOP lowering effect was PGA + AA followed by PGA + BB, PGA + CAI, and PGA and other regimens, as shown in Figure 2.

Number of patients achieving IOP \leq 18 mmHg

Number of patients with IOP \leq 18 mmHg was assessed for 14 studies, involving eight different regimens. Data from 6092 patients were available for analysis. Figure S4 shows the network plot for the result of this analysis. Of the monotherapies, patients using PGA alone showed the highest proportion of patients achieving IOP lower than 18 mmHg. Compared to PGA, AA [OR: 0.29 (0.13, 0.64)], BB [OR: 0.32 (0.19, 0.56)] and CAI [OR: 0.22 (0.08, 0.62)] contributed to fewer patients reaching IOP of 18 mmHg. Dual therapy did not show an advantage over PGA in this analysis. No statistical significance was found in comparison between PGA

and any dual therapy regimen. Table 2 lists the results. Figure 3 shows the rankograms, which should be interpreted carefully. Prostaglandin analogue (PGA) ranks the highest, but PGA and other dual therapy regimens actually have similar ability to decrease IOP below 18 mmHg.

Safety outcomes

Hyperaemia

Most of the adverse events in patients receiving medications to lower IOP have a relatively low incidence rate. This study collected data on the incidence rate of hyperaemia. Data from 54 studies, covering 17 162 patients, are included in the network meta-analysis of hyperaemia. Figure S5 shows the network plot for hyperaemia. Table 3 displays the results. Treatment with PGA led to more severe hyperaemia than any other monotherapy regimen, while BBs have the smallest effect on the incidence of hyperaemia. Most dual therapy regimens containing PGA also lead to serious hyperaemia, except for PGA + AA. Regimens containing BB but not PGA have better performance in causing hyperaemia. Figure 4 shows the rankograms.

Ocular discomfort

Data from 36 studies covering 9966 patients are included in the network meta-analysis of ocular discomfort (including burning, itching, tearing and foreign body sensation of the eyes). Figure S6 shows the network plot for ocular discomfort. Table S2 displays the results, and Figure S7 shows the rankograms.

Efficacy versus safety

Figure 5 presents all treatments ordered by their relative ranks for efficacy on the y -axis and safety on the x -axis. We found that the combination of PGA with another medication is more efficacious in lowering IOP than both other combinations without PGA and monotherapy. Monotherapy with PGA is more effective than any other medication used alone in controlling IOP. However, addition of PGA to a dual drug regimen is usually associated with higher incidence of hyperaemia, while BBs showed the lowest risk of causing hyperaemia.

Table 1. Results of Δ IOP and relative reduction of IOP. Comparison of different regimens using mixed-comparison model on effect of IOP lowering.

| | | | | | | | | | | | | | | | | | | | | | | | | |
|--------------------|----------------------|----------------------|-----------------------|----------------------|---------------------|---------------------|-----------------------|----------------------|----------------------|------------------------|----------------------------|----------------------|----------------------|------------------------|----------------------|-------------------------|---------------------|-------------------------|---------------------|------------------------|---------------------|-------------------------|-------------------|------------------------|
| PGA | -6.07 (-8.53, -3.61) | -5.94 (-7.61, -4.27) | -9.10 (-11.55, -6.65) | 3.48 (-1.43, 8.39) | 3.60 (1.47, 5.73) | 2.17 (-1.74, 6.08) | 1.23 (-2.83, 5.29) | -1.95 (-6.91, 3.00) | -1.43 (-3.62, 0.77) | -2.43 (-6.08, 1.23) | -18.55 (-24.39, -12.70) | | | | | | | | | | | | | |
| 1.59 (0.98, 2.21) | AA | 0.13 (-2.41, 2.68) | 9.55 (4.19, 14.91) | 9.67 (6.60, 12.74) | 8.24 (3.75, 12.73) | 6.68 (1.70, 11.66) | 4.12 (-0.61, 8.84) | 4.64 (1.57, 7.72) | 3.65 (-0.67, 7.96) | -12.47 (-18.82, -6.13) | | | | | | | | | | | | | | |
| 1.53 (1.11, 1.95) | -0.06 (-0.70, 0.57) | BB | -3.03 (-5.78, -0.28) | -3.16 (-5.74, -0.58) | CAI | 12.58 (7.26, 17.90) | PGA + AA | -2.95 (-4.23, -1.66) | -2.52 (-3.28, -1.75) | -2.45 (-3.02, -1.88) | -3.36 (-4.11, -2.61) | -3.56 (-4.79, -2.33) | -2.62 (-3.85, -1.40) | -1.87 (-3.06, -0.67) | -2.19 (-2.89, -1.48) | -2.21 (-3.17, -1.24) | 1.16 (-0.37, 2.70) | 5.02 (3.13, 6.91) | 4.52 (3.02, 6.02) | 4.73 (2.93, 6.52) | 3.79 (1.99, 5.59) | 3.03 (1.15, 4.92) | 3.35 (1.84, 4.85) | |
| 2.44 (1.82, 3.05) | 0.84 (0.17, 1.52) | 0.91 (0.27, 1.55) | 12.58 (7.26, 17.90) | 12.70 (9.70, 15.70) | 11.27 (6.84, 15.69) | 9.70 (4.81, 14.59) | 7.15 (2.43, 11.87) | 7.67 (4.81, 10.53) | 6.67 (2.43, 11.87) | -9.45 (-15.79, -3.11) | -22.02 (-29.66, -14.39) | -11.70 (-0.11) | -6.03 (-9.81, 2.24) | -22.15 (28.37, -15.92) | -4.59 (-9.59, 0.40) | -20.71 (-27.75, -13.68) | -3.03 (-8.44, 2.38) | -19.15 (-26.51, -11.79) | -0.47 (-6.54, 5.59) | -16.59 (-24.26, -8.93) | -1.00 (-4.67, 2.68) | -17.12 (-23.36, -10.87) | BB + MIO | -16.12 (-23.01, -9.23) |
| -1.42 | -3.01 (-4.39, -1.64) | -2.95 | PGA + AA | 0.12 (-4.48, 4.72) | -1.31 (5.57, 2.95) | -2.87 (-8.99, 3.24) | -5.43 (-12.29, 1.43) | (-9.71, -0.11) | -5.03 (-7.27, -2.79) | -3.60 (-10.32, 2.08) | -4.12 (-2.56 (-9.11, 3.99) | (-6.26, 2.19) | AA + CAI | 0.52 (-4.70, 5.75) | BB + CAI | -0.02 (-0.86, 0.82) | 3.37 (1.78, 4.98) | PLA | | | | | | |
| (-2.68, -0.16) | -2.52 (-3.28, -1.75) | -2.45 (-3.02, -1.88) | 0.50 (-0.70, 1.69) | PGA + BB | -1.43 (-4.80, 1.93) | -3.00 (-7.22, 1.23) | -5.55 (-10.82, -0.29) | -3.60 | -3.60 | -4.12 | -2.56 (-9.11, 3.99) | (-6.26, 2.19) | AA + CAI | 0.76 (-0.90, 2.41) | BB + CAI | -0.02 (-0.86, 0.82) | 3.37 (1.78, 4.98) | PLA | | | | | | |
| (-1.45, -0.40) | -2.72 (-3.96, -1.47) | -2.65 (-3.79, -1.51) | 0.29 (-0.72, 1.31) | -0.20 (-1.21, 0.81) | 0.74 (-0.33, 1.81) | 1.49 (0.16, 2.82) | 1.17 (0.61, 1.73) | 1.36 (0.05, 2.66) | 0.42 (-0.88, 1.72) | -0.34 (-1.80, 1.13) | -0.02 (-0.86, 0.82) | 3.35 (1.84, 4.85) | | | | | | | | | | | | |
| -1.13 | -1.78 (-3.03, -0.53) | -1.72 (-2.86, -0.57) | 1.23 (-0.34, 2.80) | 1.99 (0.24, 3.74) | 1.67 (0.43, 2.91) | 1.65 (0.22, 3.08) | 1.16 (0.30, 2.01) | 4.52 (3.02, 6.02) | 5.02 (3.13, 6.91) | 4.73 (2.93, 6.52) | 3.79 (1.99, 5.59) | 3.03 (1.15, 4.92) | 3.35 (1.84, 4.85) | | | | | | | | | | | |
| (-0.34) | -1.02 (-2.22, 0.17) | -0.96 (-2.23, 0.31) | 0.29 (-0.72, 1.31) | 1.49 (0.16, 2.82) | 1.17 (0.61, 1.73) | 1.65 (0.22, 3.08) | 1.16 (0.30, 2.01) | 4.52 (3.02, 6.02) | 5.02 (3.13, 6.91) | 4.73 (2.93, 6.52) | 3.79 (1.99, 5.59) | 3.03 (1.15, 4.92) | 3.35 (1.84, 4.85) | | | | | | | | | | | |
| (-1.35, 0.67) | -1.02 (-2.22, 0.17) | -0.96 (-2.23, 0.31) | 0.29 (-0.72, 1.31) | 1.49 (0.16, 2.82) | 1.17 (0.61, 1.73) | 1.65 (0.22, 3.08) | 1.16 (0.30, 2.01) | 4.52 (3.02, 6.02) | 5.02 (3.13, 6.91) | 4.73 (2.93, 6.52) | 3.79 (1.99, 5.59) | 3.03 (1.15, 4.92) | 3.35 (1.84, 4.85) | | | | | | | | | | | |
| 0.57 (-0.69, 1.82) | -1.34 (-2.10, -0.58) | -1.28 (-1.86, -0.70) | 1.23 (-0.34, 2.80) | 1.99 (0.24, 3.74) | 1.67 (0.43, 2.91) | 1.65 (0.22, 3.08) | 1.16 (0.30, 2.01) | 4.52 (3.02, 6.02) | 5.02 (3.13, 6.91) | 4.73 (2.93, 6.52) | 3.79 (1.99, 5.59) | 3.03 (1.15, 4.92) | 3.35 (1.84, 4.85) | | | | | | | | | | | |
| 0.25 (-0.29, 0.79) | -1.36 (-2.34, -0.38) | -1.30 (-2.16, -0.44) | 1.23 (-0.34, 2.80) | 1.99 (0.24, 3.74) | 1.67 (0.43, 2.91) | 1.65 (0.22, 3.08) | 1.16 (0.30, 2.01) | 4.52 (3.02, 6.02) | 5.02 (3.13, 6.91) | 4.73 (2.93, 6.52) | 3.79 (1.99, 5.59) | 3.03 (1.15, 4.92) | 3.35 (1.84, 4.85) | | | | | | | | | | | |
| 0.23 (-0.56, 1.02) | -1.36 (-2.34, -0.38) | -1.30 (-2.16, -0.44) | 1.23 (-0.34, 2.80) | 1.99 (0.24, 3.74) | 1.67 (0.43, 2.91) | 1.65 (0.22, 3.08) | 1.16 (0.30, 2.01) | 4.52 (3.02, 6.02) | 5.02 (3.13, 6.91) | 4.73 (2.93, 6.52) | 3.79 (1.99, 5.59) | 3.03 (1.15, 4.92) | 3.35 (1.84, 4.85) | | | | | | | | | | | |
| 3.60 (2.19, 5.01) | 2.01 (0.47, 3.54) | 2.07 (0.60, 3.54) | 1.16 (-0.37, 2.70) | 5.02 (3.13, 6.91) | 4.52 (3.02, 6.02) | 4.73 (2.93, 6.52) | 3.79 (1.99, 5.59) | 3.03 (1.15, 4.92) | 3.35 (1.84, 4.85) | | | | | | | | | | | | | | | |

Treatment.

Δ IOP.

Relative reduction of IOP.

MD indicates mean difference.

AA = α -2 adrenergic agonist, BB = beta-blocker, CAI = carbonic anhydrase inhibitors, IOP = intra-ocular pressure, PGA = prostaglandin analogue, PLA = placebo.

Interestingly, the combination of PGA with AA also showed an acceptably low rate of hyperaemia, even better than BBs alone. Prostaglandin analogues (PGA) + AA lies closest to the diagonal line of the graph, indicating that it achieves good IOP lowering effect while causing less hyperaemia.

Direct comparison

Traditional pairwise meta-analysis was performed for any possible group of comparisons. Most of the results of direct comparison were the same as the results from the network meta-analyses. However, several comparisons showed different point estimates, but the confidence interval generally overlapped. Detailed results of the pairwise meta-analysis are provided in Table S3.

Sensitivity analysis and publication bias

Loop-specific sensitivity analysis showed different results for different outcomes. Loop 02-04-09 (AA-CAI-AA + CAI) in Δ IOP and relative IOP reduction showed heterogeneity with a lower limit of 0.56 (see Figures S8 and S9). We then performed a network meta-analysis of the outcomes above excluding study Aung2014, which was the only study involving comparison regimens 02, 04 and 09. The results did not quite change after exclusion of study Aung2014 (Table S4). For the results on hyperaemia, loop 02-03-04 (AA-BB-CAI) showed a slight heterogeneity with a lower limit of 0.16 (see Figure S10). Similarly, results of ocular discomfort showed a slight heterogeneity in loop 05-06-07 (PGA + AA-PGA + BB-PGA + CAI) with a lower limit of 0.23 (see Figure S11). The rare incidence of the adverse events above and the small number of studies involving these regimens were determined to be the source of the heterogeneity. No heterogeneity was detected in results of the number of patients achieving IOP \leq 18 mmHg (see Figure S12). None of the funnel plots of outcomes (Δ IOP, relative IOP reduction, hyperaemia, number of patients achieving IOP \leq 18 mmHg and ocular discomfort) showed significant asymmetry (Figures S13-S17).

Discussion

This network meta-analysis has three major findings: (i) PGAs are the most

Table 2. Comparison of different regimens mixed-comparison model on number of patients achieving IOP≤18 mmHg.

| | | | | | | | | | |
|-------------------|-------------------|-------------------|--------------------|-------------------|--------------------|-------------------|----------|--|--|
| PGA | | | | | | | | | |
| 0.29 (0.13, 0.64) | AA | | | | | | | | |
| 0.32 (0.19, 0.56) | 1.11 (0.47, 2.60) | BB | | | | | | | |
| 0.22 (0.08, 0.62) | 0.77 (0.22, 2.66) | 0.69 (0.25, 1.90) | CAI | | | | | | |
| 0.90 (0.51, 1.59) | 3.08 (1.26, 7.52) | 2.77 (1.58, 4.86) | 4.01 (1.38, 11.64) | PGA + BB | | | | | |
| 0.15 (0.02, 1.04) | 0.52 (0.07, 4.02) | 0.47 (0.07, 3.21) | 0.67 (0.08, 5.68) | 0.17 (0.03, 1.06) | PGA + CAI | | | | |
| 0.59 (0.22, 1.60) | 2.03 (0.70, 5.86) | 1.83 (0.70, 4.77) | 2.65 (0.69, 10.14) | 0.66 (0.25, 1.71) | 3.93 (0.49, 31.34) | AA + BB | | | |
| 0.76 (0.27, 2.15) | 2.61 (0.75, 9.03) | 2.35 (0.88, 6.31) | 3.40 (1.08, 10.72) | 0.85 (0.32, 2.27) | 5.05 (0.62, 40.87) | 1.29 (0.35, 4.76) | BB + CAI | | |

Treatment.

IOP≤18 mmHg.

AA = α-2 adrenergic agonist, BB = beta-blocker, CAI = carbonic anhydrase inhibitors, PGA = prostaglandin analogue, PLA = placebo.

effective in lowering IOP among the monotherapy regimens, while dual therapy containing PGA and another medication, for instance, AA, are similar in efficacy for IOP lowering to use of PGA alone. (ii) In achieving a target IOP, PGA performs as well as dual therapy regimens. PGAs are still better than any other monotherapy in this respect. (iii) BBs and dual therapy regimens containing BB but not PGAs carry the lowest risk of causing hyperaemia, while the risk is highest for PGAs among all the monotherapies. Prostaglandin analogues (PGA) + BB and PGA + CAI also cause hyperaemia more often than BB alone. However, PGA + AA performs at least as well as BB in this respect. A previous study compared medical versus surgical treatments of POAG, concluding that both treatments could lower IOP and reduce the risk for optic nerve damage over the short to medium term. However, which treatments are the best to prevent visual disability and improve patient-reported outcomes are not known (Boland et al. 2013). Some previous traditional meta-analyses (Zhang et al. 2001; Fung et al. 2007; Cheng et al. 2009) and one previous network meta-analysis (van der Valk et al. 2009) are aligned with our findings and showed that PGAs are better than other single medications at lowering IOP. Comparisons of dual therapy with other regimens are rare. The results from this network meta-analysis fill this gap.

Prostaglandin analogues (PGA) and BBs in eye-drop form are the most frequently used initial treatment to lower IOP in patients with glaucoma. Prostaglandin analogues (PGA) are the most effective drugs at lowering IOP and can be considered as initial medical therapy unless other considerations

such as cost, side-effects, intolerance or patient refusal preclude their use (Ophthalmology AAO 2015). Other agents in addition to PGAs and BBs include α2-AAAs, MIO, and topical and oral CAI. Side-effects and effectiveness influence the choice of regimen for maximal effectiveness and tolerance to achieve the desired IOP reduction for each patient. For patients with POAG, PGA is the recommended first choice when considering cost-effectiveness and IOP lowering efficacy because PGA also provides acceptable clinical tolerability. PGAs decrease IOP by increasing the outflow of aqueous humour, which is suitable for preservation of normal function of the aqueous humour. However, for patients with severe hyperaemia, BBs may be a better option despite its lower ability to control IOP. Considering the influence of BB on the cardiovascular and respiratory systems, they are not recommended for people with cardiac disease or asthma. Moreover, the results of our network meta-analysis are mostly based on clinical data at a follow-up time of 3 months. One study showed that after long-term use of BB, additional medications are needed to acquire ideal IOP control. For long-term treatment, PGAs or surgery may be better options than BBs alone. Addition of another drug to PGA produces a moderate effect on IOP lowering but still does not help with hyperaemia. Although our results showed that PGA + AA can reduce the incidence of hyperaemia, this may be due to two reasons: first, the sample size of patients using PGA + AA is relatively small, resulting in a likely underestimate of its effect on the incidence of hyperaemia; second, alpha-2 AAs can cause vasoconstriction, thus relieving the extent of hyperaemia. If

PGA + AA causes less hyperaemia because of its vasoconstriction effect, then it would be an excellent choice for treatment of glaucoma. The efficacy of AA and CAI to lower IOP is relatively weak, but the addition of these two drugs to PGA or BB strengthens the effect the former drug. It may be best to use AA or CAI in combination with other drugs but not alone.

Some trials considered in our study showed contradictory results, which may have influenced the results of our study. In analysis of hyperaemia, several differences were observed between pairwise meta-analyses and network meta-analyses. These seem to be caused primarily by rare events or small-study sample size. For instance, when comparing the incidence of hyperaemia between PGA and AA, the network meta-analysis showed that PGA led to high incidence rate of hyperaemia as a statistically significant result. However, in the traditional pairwise meta-analysis, the result was not very close to statistical significance, with an OR of 0.94 (0.48, 1.82). Stewart2006 considered only 28 patients and thus reported an opposite result of the other two studies, causing high heterogeneity. Because the study sample is too small, its result is easily affected by the small-study effect. Thus, AA may still be a better treatment when considering incidence of hyperaemia.

Limitations

This study has several limitations. First, the study populations of some regimens are too small. For example, only one study, with a study population of 516, compared PGA with placebo. Thus, results about placebo are very likely influenced by the small sample size. For the dual PGA + AA

Table 3. Comparison of different regimens mixed-comparison model on incidence of hyperaemia.

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|-------------------|----|-------------------|----|--------------------|-----|--------------------|----------|---------------------|----------|-------------------|-----------|-------------------|---------|-------------------|----------|-------------------|----------|-------------------|----------|-------------------|--------------------|--------------------|-----|-------------------|
| PGA | 0.65 (0.38, 1.12) | AA | 0.35 (0.21, 0.59) | BB | 1.61 (0.70, 3.71) | CAI | 0.41 (0.11, 1.53) | PGA + AA | 5.55 (2.09, 14.76) | PGA + BB | 1.86 (0.80, 4.33) | PGA + CAI | 0.24 (0.07, 0.75) | AA + BB | 0.62 (0.17, 2.30) | AA + CAI | 0.32 (0.11, 0.93) | BB + CAI | 0.64 (0.18, 2.30) | BB + MIO | 2.02 (0.77, 5.25) | 0.80 (0.06, 10.97) | 0.40 (0.03, 6.04) | PLA | |
| | 0.23 (0.17, 0.32) | | 0.57 (0.25, 1.31) | | 0.65 (0.22, 1.90) | | 2.25 (0.92, 5.52) | | 10.32 (2.97, 35.84) | | 0.44 (0.20, 0.97) | | 0.20 (0.07, 0.60) | | 0.84 (0.43, 1.64) | | 0.32 (0.11, 0.93) | | 0.64 (0.18, 2.30) | | 2.02 (0.77, 5.25) | | 0.80 (0.06, 10.97) | | 0.40 (0.03, 6.04) |
| | 0.37 (0.16, 0.87) | | 0.23 (0.03, 0.73) | | 1.28 (0.69, 2.37) | | 4.19 (1.22, 14.38) | | 2.45 (0.70, 8.61) | | 1.16 (0.43, 3.11) | | 0.40 (0.12, 1.39) | | 2.62 (0.89, 7.70) | | 0.32 (0.11, 0.93) | | 0.64 (0.18, 2.30) | | 2.02 (0.77, 5.25) | | 0.80 (0.06, 10.97) | | 0.40 (0.03, 6.04) |
| | 0.15 (0.05, 0.44) | | 1.28 (0.69, 2.37) | | 3.63 (2.38, 5.52) | | 0.99 (0.37, 2.67) | | 6.42 (1.60, 25.70) | | 0.37 (0.18, 0.76) | | 0.40 (0.12, 1.39) | | 2.62 (0.89, 7.70) | | 0.32 (0.11, 0.93) | | 0.64 (0.18, 2.30) | | 2.02 (0.77, 5.25) | | 0.80 (0.06, 10.97) | | 0.40 (0.03, 6.04) |
| | 0.84 (0.56, 1.25) | | 2.39 (0.84, 6.81) | | 6.74 (2.62, 17.33) | | 2.60 (0.95, 7.13) | | 2.05 (0.61, 6.94) | | 0.83 (0.33, 2.08) | | 0.40 (0.12, 1.39) | | 2.62 (0.89, 7.70) | | 0.32 (0.11, 0.93) | | 0.64 (0.18, 2.30) | | 2.02 (0.77, 5.25) | | 0.80 (0.06, 10.97) | | 0.40 (0.03, 6.04) |
| | 1.56 (0.61, 3.96) | | 0.57 (0.27, 1.20) | | 1.60 (0.79, 3.26) | | 0.83 (0.33, 2.08) | | 4.14 (1.09, 15.76) | | 0.75 (0.30, 1.85) | | 0.40 (0.12, 1.39) | | 2.62 (0.89, 7.70) | | 0.32 (0.11, 0.93) | | 0.64 (0.18, 2.30) | | 2.02 (0.77, 5.25) | | 0.80 (0.06, 10.97) | | 0.40 (0.03, 6.04) |
| | 0.37 (0.18, 0.77) | | 1.48 (0.66, 3.34) | | 4.19 (1.65, 10.63) | | 1.68 (0.52, 5.46) | | 1.64 (0.10, 26.72) | | 0.30 (0.02, 4.03) | | 0.16 (0.01, 2.48) | | 0.67 (0.05, 9.45) | | 0.26 (0.02, 3.63) | | 0.64 (0.18, 2.30) | | 2.02 (0.77, 5.25) | | 0.80 (0.06, 10.97) | | 0.40 (0.03, 6.04) |
| | 0.87 (0.34, 2.21) | | 0.47 (0.22, 1.00) | | 1.34 (0.69, 2.60) | | 1.68 (0.52, 5.46) | | 1.64 (0.10, 26.72) | | 0.30 (0.02, 4.03) | | 0.16 (0.01, 2.48) | | 0.67 (0.05, 9.45) | | 0.26 (0.02, 3.63) | | 0.64 (0.18, 2.30) | | 2.02 (0.77, 5.25) | | 0.80 (0.06, 10.97) | | 0.40 (0.03, 6.04) |
| | 0.31 (0.16, 0.60) | | 0.96 (0.35, 2.63) | | 2.70 (1.08, 6.77) | | 1.68 (0.52, 5.46) | | 1.64 (0.10, 26.72) | | 0.30 (0.02, 4.03) | | 0.16 (0.01, 2.48) | | 0.67 (0.05, 9.45) | | 0.26 (0.02, 3.63) | | 0.64 (0.18, 2.30) | | 2.02 (0.77, 5.25) | | 0.80 (0.06, 10.97) | | 0.40 (0.03, 6.04) |
| | 0.62 (0.26, 1.52) | | 0.96 (0.35, 2.63) | | 2.70 (1.08, 6.77) | | 1.68 (0.52, 5.46) | | 1.64 (0.10, 26.72) | | 0.30 (0.02, 4.03) | | 0.16 (0.01, 2.48) | | 0.67 (0.05, 9.45) | | 0.26 (0.02, 3.63) | | 0.64 (0.18, 2.30) | | 2.02 (0.77, 5.25) | | 0.80 (0.06, 10.97) | | 0.40 (0.03, 6.04) |
| | 0.25 (0.02, 3.32) | | 0.38 (0.03, 5.07) | | 1.07 (0.08, 14.32) | | 0.67 (0.06, 7.75) | | 1.64 (0.10, 26.72) | | 0.30 (0.02, 4.03) | | 0.16 (0.01, 2.48) | | 0.67 (0.05, 9.45) | | 0.26 (0.02, 3.63) | | 0.64 (0.18, 2.30) | | 2.02 (0.77, 5.25) | | 0.80 (0.06, 10.97) | | 0.40 (0.03, 6.04) |

Treatment.
Hyperaemia.

AA = α -2 adrenergic agonist, BB = beta-blocker, CAI = carbonic anhydrase inhibitors, MIO = miotics, PGA = prostaglandin analogue, PLA = placebo.

regimen, although four studies provided data about its efficacy and safety, the overall population involved is still relatively small. Thus, it is reasonable to suspect that the unpredictable result of hyperaemia with PGA + AA did not quite reflect the clinical condition. After all, there was no evidence of this result being affected by small sample size. Second, this study considered the effect of medications on IOP and hyperaemia. However, diagnosis of POAG and evaluation of POAG progression depend on visual field tests. Results of visual field changes may better reflect functional changes of glaucoma. However, most of the randomized controlled trials did not provide data on visual field changes. In the future, long-term, large-scale trials are needed to evaluate the parameters of visual field changes. Third, this study groups all PGAs, for example, latanoprost, bimatoprost and treats them in the same way. All data of different PGAs are combined in this network meta-analysis. However, there were studies showing that bimatoprost or travoprost is more effective at lowering IOP than latanoprost and cause less hyperaemia and studies reporting opposite results also exist (Noecker et al. 2003; Parrish et al. 2003; Konstas et al. 2005). Thus, we consider that the combination of different PGAs will not cause heterogeneity in the network meta-analysis. This topic is worth studying in future clinical trials. Fourth, we did not explore the effect of triple therapy on IOP control or tolerance. Previous studies involving triple therapies have showed contradictory results (Baiza-Duran et al. 2012; Garcia-Lopez et al. 2014). Some studies showed that triple therapy provides stronger IOP lowering effect, while some studies show that it is weaker than dual therapy. Thus, triple therapy deserves further study. Fifth, event rates in one or both treatment arms of some studies are too low or even equal to zero. This caused some of our results to show wide confidence intervals for several treatment comparisons. Sixth, most of the studies selected have pharmaceutical industry involved, either acting as sponsors or providing statistical service, etc. Previous studies and reviews summarized that industrial funding may have influence on conclusions of clinical trials, and ophthalmologists should carefully determine if

results from other clinical trials could guide their clinical practice (Rossetti et al. 1993; Alasbali et al. 2009). Thus, we tried to perform meta-analysis only including studies without pharmaceutical industry involvement. However, we failed because of limited number of studies. Finally, some patient characteristics and methodological qualities, such as age, sex, and race as well as selection bias or performance bias, might be potential sources of heterogeneity between studies, influencing the final results. To assess the influence of these factors on our research, meta-regression or subgroup analysis may help. However, in network meta-analyses, the power of meta-regression or subgroup analysis is weaker than for traditional pairwise meta-analysis. In addition, considering the complex comparison network between all regimens, using meta-regression or subgroup analysis to check the bias may not be helpful. Future studies are needed to determine whether these factors have substantial influence on treatment outcomes.

Conclusions

Our network meta-analysis showed that among the monotherapy regimens, PGAs provide the best IOP lowering effect. However, a combination of PGA and other drugs leads to better IOP decrease. Combination of BB and another non-PGA drug may have less ocular side-effects than PGA alone. In clinical practice, when considering regimens for IOP lowering, not only the IOP lowering efficacy but also the incidence of adverse events should be considered.

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Fax: +86-20-87333271
Email: zhangxl2@mail.sysu.edu.cn

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

- Figure S1.** Flow chart of literature search.
- Figure S2.** Network plots of eligible comparisons for network meta-analysis of Δ IOP. The size of nodes is proportional to the total sample size of each treatment and the width of lines is proportional to the number of studies compared in every pair of treatments.
- Figure S3.** Network plots of eligible comparisons for network meta-analysis of relative reduction of IOP. The size of nodes is proportional to the total sample size of each treatment and the width of lines is proportional to the number of studies compared in every pair of treatments.
- Figure S4.** Network plots of eligible comparisons for network meta-analysis of incidence of hyperemia. The size of nodes is proportional to the total sample size of each treatment and the width of lines is proportional to the number of studies compared in every pair of treatments.
- Figure S5.** Network plots of eligible comparisons for network meta-analysis of number of patients achieving IOP \leq 18mmHg. The size of nodes is proportional to the total sample size of each treatment and the width of lines is proportional to the number of studies compared in every pair of treatments.
- Figure S6.** Network plots of eligible comparisons for network meta-analysis of ocular discomfort. The size of nodes is proportional to the total sample size of each treatment and the width of lines is proportional to the number of studies compared in every pair of treatments.
- Figure S7.** Ranking of medical treatments based on incidence of ocular discomfort. PGA, prostaglandin analog; AA, alpha-2 adrenergic agonist; BB, beta-blocker; CAI, carbonic anhydrase inhibitors; PLA, placebo.
- Figure S8.** Loop specific sensitivity analysis of Δ IOP. 95%CI with a lower limit reaching 0 means that no heterogeneity exists between included studies. The code for each regimen is as follows: 1. PGA 2. AA 3. BB

- 4. CAI 5. PGA+AA 6. PGA+BB 7. PGA+CAI 8. AA+BB 9. AA+CAI 10. BB+CAI 11. BB+MIO.
- Figure S9.** Loop specific sensitivity analysis of relative reduction of IOP. 95%CI with a lower limit reaching 0 means that no heterogeneity exists between included studies. The code for each regimen is as follows: 1. PGA 2. AA 3. BB 4. CAI 5. PGA+AA 6. PGA+BB 7. PGA+CAI 8. AA+BB 9. AA+CAI 10. BB+CAI 11. BB+MIO.
- Figure S10.** Loop specific sensitivity analysis of incidence of hyperemia. 95%CI with a lower limit reaching 0 means that no heterogeneity exists between included studies. The code for each regimen is as follows: 1. PGA 2. AA 3. BB 4. CAI 5. PGA+AA 6. PGA+BB 7. PGA+CAI 8. AA+BB 9. AA+CAI 10. BB+CAI 11. BB+MIO.
- Figure S11.** Loop specific sensitivity analysis of ocular discomfort. 95%CI with a lower limit reaching 0 means that no heterogeneity exists between included studies. The code for each regimen is as follows: 1. PGA 2. AA 3. BB 4. CAI 5. PGA+AA 6. PGA+BB 7. PGA+CAI 8. AA+BB 9. AA+CAI 10. BB+CAI 11. BB+MIO.
- Figure S12.** Loop specific sensitivity analysis of number of patients achieving IOP \leq 18mmHg. 95%CI with a lower limit reaching 0 means that no heterogeneity exists between included studies. The code for each regimen is as follows: 1. PGA 2. AA 3. BB 4. CAI 5. PGA+AA 6. PGA+CAI 7. AA+BB 8. BB+CAI.
- Figure S13.** Assessment of publication bias: funnel plot of analysis for Δ IOP.
- Figure S14.** Assessment of publication bias: funnel plot of analysis for relative reduction of IOP.
- Figure S15.** Assessment of publication bias: funnel plot of analysis for incidence of hyperemia.
- Figure S16.** Assessment of publication bias: funnel plot of analysis for number of patients achieving IOP \leq 18mmHg.
- Figure S17.** Assessment of publication bias: funnel plot of analysis for ocular discomfort.
- Figure S18.** Graph of risk of bias assessments for RCTs included in this study.
- Table S1.** Baseline Characteristics of studies included in network meta-analysis.
- Table S2.** Results of ocular discomfort. Comparison of different regimens using mixed-comparison model on effect of IOP lowering.
- Table S3.** Results of pairwise meta-analysis of different regimens.
- Table S4.** Results of network meta-analyses of Δ IOP and relative reduction of IOP after exclusion of study Aung2014.
- Table S5.** Summary of methodological quality of included studies.
- File S1.** Search terms for Pubmed Search.

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Correspondence:
Xiulan Zhang
State Key Laboratory of Ophthalmology
Zhongshan Ophthalmic Center
Sun Yat-sen University
Guangzhou
510060, China
Tel: +86-20-87330484