BMJ Open

Comparisons of the short-term effectiveness and safety of surgical treatment for neovascular glaucoma: a systematic review and network meta-analysis

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To cite: Lin P, Zhao Q, He J, *et al*. Comparisons of the short-term effectiveness and safety of surgical treatment for neovascular glaucoma: a systematic review and network meta-analysis. *BMJ Open* 2022;**12**:e051794. doi:10.1136/bmjopen-2021-051794

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-051794).

Received 31 March 2021
Accepted 04 April 2022

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ABSTRACT

Objective To compare the effectiveness and safety of the six interventions for neovascular glaucoma.

Design A systematic review and network meta-analysis.

Methods Randomised controlled trials and cohort studies which compared the six interventions in neovascular glaucoma were identified using the following databases searched up to 1 September 2020: PubMed, Cochrane Library, Embase and Web of Science. The quality assessment was conducted by using the Cochrane risk of bias tool and the Newcastle-Ottawa scale. The primary outcome measure was the weighted mean differences for intraocular pressure reduction. Secondary one was ORs for success rate. Outcome measures were reported with a 95% CI and p<0.05 was considered statistically significant. Network meta-analysis was performed using Stata V.15.0.

Results Twenty-three studies involving a total of 1303 patients were included. The types of surgical treatments included Ahmed glaucoma valve (AGV) implant surgery, AGV combined with intravitreal anti-vascular endothelial growth factor (AGV +IVAV), cyclophotocoagulation (CPC), cyclocryotherapy (CCT), trabeculectomy with mitomycin (Trab(MMC)) and Trab(MMC) combined with IVAV (Trab(MMC)+IVAV). Network meta-analysis showed that in comparison with AGV, AGV +IVAV (MD=4.74, 95% CI 1.04 to 8.45) and Trab(MMC)+IVAV (MD=6.19, 95% CI 0.99 to 11.40) showed a favourable effect in intraocular pressure reduction (IOPR) 6 months after surgery. Compared with CCT, AGV (OR=−0.17, 95% CI −0.53 to −0.05), AGV +IVAV (OR=−0.10, 95% CI −3.48 to −1.19), CPC (OR=−0.12, 95% CI −0.53 to −0.05), Trab(MMC) (OR=3.54, 95% CI 1.15 to 10.91) and Trab(MMC)+IVAV (OR=5.78, 95% CI 2.29 to 14.61) showed a superior impact in success rate. The order of efficacy as best intervention ranked as follows: Trab(MMC)+IVAV (IOPR 6 months after surgery, surface under the cumulative ranking (SUCRA)=88.1), CPC (IOPR 12 months after surgery, SUCRA=81.9), AGV +IVAV (IOPR 12 months after surgery, SUCRA=79.9) and AGV +IVAV (success rate, SUCRA=92.7). Adverse events were also summarised in detail.

Conclusion In the treatment of neovascular glaucoma, AGV+IVAV and CPC were more effective in IOPR and success rate than the other four interventions. Additionally, AGV+IVAV is superior to CPC concerning the success rate in the long-term treatment. However, considering the limitations of this review, more high-quality trials, especially those surgical interventions not mentioned in this review, should be carried out in the future to further confirm the current findings.

Strengths and limitations of this study

⇒ To the best of our knowledge, this is the most comprehensive network meta-analysis which includes all the available data of comparative studies and evaluates different aspects of different therapeutic strategies.
⇒ The effectiveness and the safety were assessed with rigorous inclusion criteria, leading to more convincing results.
⇒ In terms of intraocular pressure reduction, we selected the common follow-up time point between all studies to reduce bias, including 6 months and 12 months.
⇒ There was no common time point of data concerning success rate, we used information available at the final follow-up for statistical analysis.

INTRODUCTION

Neovascular glaucoma (NVG) is a potentially blinding, refractory glaucoma, which is characterised by neovascularisation in iris or anterior chamber angle.[1] NVG manifests as dramatic elevation of intraocular pressure (IOP), severe ocular pain and vision loss, influencing the quality of life in patients adversely. It is secondary to various ocular ischaemic diseases, such as diabetic retinopathy, central retinal vein occlusion and ocular ischaemic syndrome.[2] With a high prevalence of diabetes and vascular disease, the incidence of NVG is increasing steadily, accounting for more than 30% of refractory glaucoma and becomes an occupational health issue.[1]

The therapy for NVG is twofold. First, the underlying cause needs controlling, usually by panretinal photocoagulation (PRP) or intravitreal vascular endothelial growth factor (VEGF) inhibitors, aiming at reduction of ischaemic drive that induces formation of new blood vessels. The second key aspect is the successful IOP management.[3] When medication of decreasing IOP are insufficient, surgery is regarded as the first-line choice for NVG, but complicated by higher failure rates and more difficult tissue anatomy than in primary glaucoma.[4] Thus, its treatments have been paid high attention to in glaucoma.

Currently, glaucoma drainage devices (GDDs),[5] filtering surgery,[6] cyclodestructive surgery,[7] combined with PRP or IVAV, are routinely used surgical treatment modalities for NVG,[8 9] which present with a certain effectiveness and increase the diversity of treatment strategies.[10] Many authors verified the effectiveness of these treatment modalities.[11 12] Nevertheless, there is no sufficient evidence of superiority of one over another. Some systematic review and meta-analyses have been published to evaluate the effectiveness and safety of these combination of treatment modalities for NVG. Two meta-analyses reported the effect of intravitreal bevacizumab injection before AGV implantation, which indicated higher surgical success rate.[13 14] However, because of the limitations of the traditional pairwise meta-analysis, it is difficult to determine which one is the best management of NVG in the modalities.

In recent years, network meta-analysis has been developed. Compared with traditional pairwise meta-analysis, it allows for combining of data related to multiple treatments, comparison of interventions based on indirect information and generating a ranking of treatment arms according to the efficacy.[15] A latest network meta-analysis suggested that trabeculectomy with mitomycin and interferon was the most likely to improve the success rate in treatment of NVG,[16] followed by glaucoma valve; however, there was an inevitable insufficiency of evidence to determine the optimal surgical interventions since intraocular pressure reduction (IOPR) and adverse events were not mentioned in the analysis. The significant heterogeneity of follow-up time also indicated different degrees of bias in the analysis, which may affect the assessment of surgical success. In addition, the result of loop-specific approach showed a certain local inconsistency signifying that the findings related to trabeculectomy should be interpreted cautiously.

Therefore, aiming to add more sufficient evidence, we performed a network meta-analysis involving more specific outcome measurements including IOPR, success rate and adverse events to evaluate the comparative effectiveness and safety of different surgical treatment, to help ophthalmologist better make treatment strategies for patients with NVG. We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting checklist and the Meta-Analyses of Observational Studies in Epidemiology reporting checklist.

MATERIAL AND METHODS

Data sources

A medical literature search was performed in the following databases from their inception through 1 September 2020: PubMed, Web of Science, the Cochrane Library and Embase. Different from Dong's network meta-analysis,[16] we neglected the Chinese database due to the lower quality of literature retrieved. There are no restrictions regarding publication year, language or methodological filter on these studies. The searching was performed using medical subject headings and keywords, including 'neovascular glaucoma', 'neovascular', 'rubeosis and iris', 'rubeosis iridis', 'neovascularization and iris', 'rubeotic glaucoma', 'congestive and glaucoma', 'haemorrhagic', 'hemorrhagic', 'NVG', 'NVI' and 'NVA'. The details of search strategy are showed in online supplemental appendix 1 to 4. Two reviewers searched literatures, reviewed the titles and abstracts of articles independently to select the potential ones and tried contacting authors. The full texts of the selected articles were checked based on inclusion and exclusion criteria, and the divergent articles were checked by a third reviewer.

Inclusion criteria

Studies were included according to the following criteria: (1) study type: randomised controlled trials (RCTs) or cohort studies; (2) population: patients were diagnosed as NVG by symptoms, signs and examination; (3) intervention: controlled study of different therapeutic strategies related to different surgeries; and (4) outcome variables: at least one of the outcome measures was required.

Exclusion criteria

The following studies were excluded if (1) follow-up time was <6 months; (2) trials with a small sample size of (n<10); (3) drug dose-related study; (4) comparative studies of similar surgical procedures, such as trabeculectomy versus modified trabeculectomy; (5) abstracts from conferences and full texts without raw data available for retrieval, literature reviews, letters and duplicate publications.

Outcome measure

The primary outcome was the mean difference in IOPR after surgery, with or without antiglaucoma medication. When authors reported the mean and SD of the IOPR, we used these directly. If not available, we computed them as follows: $IOPR=IOP_{baseline} - IOP_{endpoint}$, $SD_{IOPR} = (SD^2_{baseline} + SD^2_{endpoint} - SD^2_{baseline} \times SD^2_{endpoint})^{1/2}$. In order to reduce bias, we preferably selected the common follow-up time point between all studies: mean IOPR 6 months after surgery and mean IOPR 12 months after surgery. In case 12-month data were not reported, we used the latest reported outcome data or the data closest to 12 months.[17] The secondary outcomes were the rates of surgical success, using the definitions used by authors of individual studies. In case there was no common time

point of data concerning success rate, we used information available at the final follow-up for statistical analysis.

Data extraction

Two investigators independently worked for data extraction, and they collected the following information: (1) basic characteristics, including author name, study design, publication year, age and gender of patients, intervention, sample size, stages of NVG, outcomes and follow-up; (2) clinical outcomes, including IOPR 6 months after surgery, IOPR 12 months after surgery and success rate.

Quality assessment

The quality assessment of RCTs was conducted by using the Cochrane risk of bias tool, and cohort studies using the Newcastle-Ottawa scale. Quality assessment was independently carried out by two reviewers, and disagreements were checked by a third reviewer.

Statistical analysis

A network meta-analysis was carried out using Stata V.15.0. Continuous variables (IOPR 6 months after surgery and IOPR 12 months after surgery) were analysed using mean difference (MD) and its 95% credible interval (CI), while dichotomous variables (success rate) using OR. At the beginning of our network meta-analysis, pairwise meta-analyses were performed, then 'mvmeta' package was used to perform the plots of different comparisons, the rankplots based on probabilities and the surface under the cumulative ranking (SUCRA) for different endpoints. Furthermore, node-splitting analysis and loop-specific approach were used to evaluate inconsistency, and the Grades of Recommendations Assessment, Development and Evaluation (GRADE) was used to evaluate the importance of the outcomes.

RESULTS

Identification of the relevant studies

9658 articles were identified in our initial search, from which 2624 articles were excluded for duplications, and 6606 were excluded by reading titles and abstracts. In the remaining 428 articles, full texts were obtained to check eligibility, in which 39 studied were excluded because of non-comparative study, 168 studies were excluded for wrong intervention or comparator and 198 studies were excluded because of lacking of clinical data. Finally, 23 studies were included in our final analysis (online supplemental appendix 5). Figure 1 shows the selection process for relevant studies.

Characteristics of the included studies

The review involved 1303 patients and the sample size ranged from 20 to 170 cases. Four studies were RCTs and 19 were cohort studies. Twenty-two studies were two-arm studies, and one was three-arm study. In

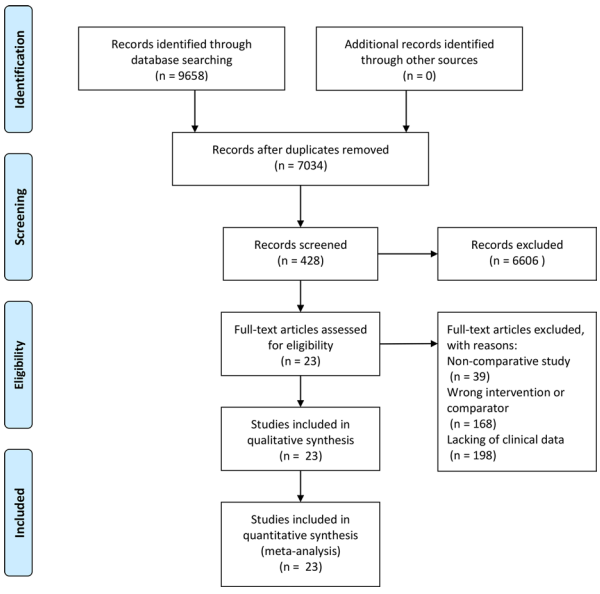

Figure 1 Flow chart of the study selection procedure.

our study, the types of surgical treatments included Ahmed glaucoma valve (AGV), AGV combined with intravitreal anti-vascular endothelial growth factor (AGV +IVAV), cyclophotocoagulation (CPC), cyclocryotherapy (CCT), trabeculectomy with mitomycin (Trab(MMC)) and Trab(MMC) combined with IVAV (Trab(MMC)+IVAV). To be more understandable, we explained the meaning of acronyms in table 1. Eight studies compared AGV with AGV +IVAV, three studies compared AGV with CPC, three compared AGV +IVAV with Trab(MMC)+IVAV, two compared CCT with Trab(MMC)+IVAV, five compared Trab(MMC) with Trab(MMC)+IVAV, one compared AGV with Trab(MMC) and one compared AGV with Trab(MMC)+IVAV. Three hundred and eight patients were included in AGV groups, 309 patients in AGV +IVAV groups, 67 patients in CPC groups, 53 patients in CCT groups, 235 patients in Trab(MMC) groups and 355 patients in Trab(MMC)+IVAV groups. In terms of the criteria of IOPR, 14 trials employed the criteria of IOPR 6 months after surgery and 12 trials used the criteria of IOPR 12 months after surgery. As summarised in online supplemental appendix 6, 21 trials used heterogeneous criteria of success rate defined by authors of individual studies. The baseline characteristics of each study are presented in table 2.

Quality assessment

In four RCTs, one study did not state the method of randomisation in details and three studies employed computer random number for randomisation. Only one study mentioned the blinding method. All of the RCTs had complete data. The risk of bias summary is shown in online supplemental appendix 7. In terms of the cohort studies, based on the Newcastle-Ottawa quality assessment scale, one study scored 9 points,

Table 1 The acronyms of the included surgical treatments

Acronym	Surgical treatment
AGV	Ahmed glaucoma valve implant surgery
IVAV	Intravitreal anti-vascular endothelial growth factor
AGV+IVAV	AGV combined with IVAV
CPC	Cyclophotocoagulation
CCT	Cyclocryotherapy
Trab(MMC)	Trabeculectomy with mitomycin
Trab(MMC)+IVAV	Trab(MMC) combined with IVAV

eight studies scored 8 points, five studies scored 7 points and five studies scored 6 points (online supplemental appendix 8).

The results of meta-analysis

The results of pairwise meta-analysis are demonstrated in online supplemental appendix 9. Figure 2 shows the network of eligible comparisons for IOPR 6 months after surgery, IOPR 12 months after surgery and success rate, and figure 3 shows the results of network meta-analysis.

Fourteen studies involving 882 eyes reported IOPR 6 months after surgery (figure 2). When compared with AGV, AGV +IVAV (MD=4.74, 95% CI 1.04 to 8.45) and Trab(MMC)+IVAV (MD=6.19, 95% CI 0.99 to 11.40) showed a significantly higher IOPR 6 months after surgery, but no significant difference was found between AGV +IVAV(MD=−1.45, 95% CI −5.93 to 3.03) and Trab(MMC)+IVAV. Meanwhile, no significant difference was found among the other interventions.

Thirteen studies involving 681 eyes and 14 comparisons reported IOPR 12 months after surgery (figure 2). As illustrated in figure 3, no significant difference was found in IOPR 12 months after surgery.

In terms of success rate, 20 studies involving 21 comparisons and 1098 eyes were merged for analysis (figure 2). Compared with CCT, the interventions including AGV (OR=−0.17, 95% CI −0.53 to −0.05), AGV +IVAV (OR=−0.10, 95% CI −0.31 to −0.03), CPC (OR=−0.12, 95% CI −0.53 to −0.03), Trab(MMC) (OR=3.54, 95% CI 1.15 to 10.91) and Trab(MMC)+IVAV (OR=5.78, 95% CI 2.29 to 14.61) presented with a significantly higher success rate. Additionally, the success rate in AGV +IVAV was significantly higher than that in AGV (OR=1.71, 95% CI 1.12 to 2.61) and Trab(MMC) (OR=−0.34, 95% CI −0.78 to −0.15), and no significant difference was found between the latter two treatments. However, no significant difference was found among the other interventions.

The plots of probability and SUCRA are illustrated in online supplemental appendix 10. Table 3 shows that Trab(MMC)+IVAV had the highest probability to be the best intervention in IOPR 6 months after surgery while AGV+IVAV ranking behind. CPC and AGV+IVAV had the highest probability to be the best intervention in IOPR 12 months after surgery, and AGV+IVAV had the highest probability to be the best intervention in success rate, respectively.

Consistency analysis

Node-splitting analysis was performed to evaluate the inconsistency by comparing direct and indirect effects, indicating no significant inconsistency (online supplemental appendix 11) and the results were reliable. In addition, the results of loop-specific approach showed no significant inconsistency in the comparisons of closed circles in outcomes of IOPR (12 mo) and success rate, but significant inconsistency in IOPR (6mo) (table 4).

GRADE for the outcome measurements

We summarised the GRADE judgements in online supplemental appendix 12. According to the suggestions of GRADE workgroups, we combined the evidences of direct and indirect comparisons and chose a higher level, and the results demonstrated the evidences provided in this review were moderate, low or very low.

Adverse events

In the included studies, 23 reported adverse events. Twenty studies reported 225 cases of hyphema, in which 70 occurred in the AGV group, 67 in the Trab(MMC) group, 38 in the AGV +IVAV group, 29 in the Trab(MMC)+IVAV group, 13 in the CCT group and 8 in the CPC group. Ten studies reported 73 cases of corneal oedema, in which 31 occurred in the CCT group, 20 in the AGV group, 14 in the CPC group, 5 in the AGV +IVAV group and 3 in the Trab(MMC) group. Eleven studies reported hypotony, in which 24 eyes occurred in the AGV +IVAV group, 17 in the Trab(MMC)+IVAV group, 16 in the AGV group, 7 in the Trab(MMC) group and 3 in the CPC group. Shallow anterior chamber was reported in 13 studies, including 42 cases in the AGV +IVAV group, 20 in the AGV group, 11 in the Trab(MMC)+IVAV group and 10 in the Trab(MMC) group.

Meanwhile, tube exposure or occlusion was reported in nine studies, including 23 cases in the AGV group and 17 in the AGV +IVAV group. Encapsulated plate was reported in six studies, including 19 eyes in the AGV group and 12 in the AGV +IVAV group. Bleb leak was reported in six studies, including six cases in the Trab(MMC) group, six in the Trab(MMC)+IVAV group and two in the AGV +IVAV group. Phthisis bulbi was reported in four studies, including six eyes in the AGV group and two in the Trab(MMC) group.

Moreover, five studies reported 24 cases of vitreous haemorrhage, in which 10 occurred in the Trab(MMC) group, 7 in the Trab(MMC)+IVAV group, 6 in the AGV group and 1 in the AGV +IVAV group. Choroidal effusion or detachment was reported in 11 studies, including 21 cases in the Trab(MMC)+group, 18 in the Trab(MMC) group, 12 in the AGV group and 10 in the AGV +IVAV group. Two studies reported two cases with retinal detachment in the AGV group.

Table 2 The characteristics of the included studies

References	Study design	Interventions	Age (MD, SD)	Gender (Male/female)	Sample size No. Patients	Sample size No. Eyes	Outcomes	Mean follow-up (months)	Anti-VEGF	Combine PRP
Ma *et al*[25]	OCT	AGV vs AGV +IVAV	58.78 (13.09) vs 57.60 (13.56)	27/25	N/A	32 vs 20	*	15	Bevacizumab	Yes
Mahdy *et al*[18]	RCT	AGV vs AGV +IVAV	56 (4.3) vs 55 (1.3)	23/17	20 vs 20	20 vs 20	†‡*	18	Bevacizumab	Yes
Zhou *et al*[26]	OCT	AGV vs AGV +IVAV	57.89 (11.51) vs 54.40 (13.68)	36/17	28 vs 25	28 vs 25	†‡*	15.36 (4.53) vs 15.08 (5.14)	Bevacizumab	Yes
Kang *et al*[27]	OCT	AGV vs AGV +IVAV	54.3 (10.8) vs 54.8 (13.0)	22/5	13 vs 14	13 vs 14	*	6	Bevacizumab	Yes
Arcieri *et al*[19]	RCT	AGV vs AGV +IVAV	62.40 (11.78) vs 59.25 (8.05)	24/16	20 vs 20	20 vs 20	†‡*	28.2 (8.04) vs 25.8 (8.04)	Bevacizumab	Yes
Kwon and Sung[28]	OCT	AGV vs AGV +IVAV	57(18) vs 59(10)	56/14	25 vs 45	25 vs 45	‡*	27(14) vs 26(16)	Bevacizumab	Yes
Li *et al*[29]	OCT	AGV vs AGV +IVAV	57.49 (8.42) vs 58.06 (7.33)	46/34	34 vs 46	34 vs 46	*	6	Ranibizumab	N/A
Kong *et al*[30]	OCT	AGV vs AGV +IVAV vs AGV +IVAV	54.24 (11.05) vs 53.00 (12.32) vs 54.00 (12.74)	43/25	21 vs 26 vs 21	21 vs 26 vs 21	†‡*	12	Ranibizumab; conbercept	N/A
Yildirim *et al*[31]	RCT	AGV vs CPC	57.2 (10.3) vs 60.0 (11.7)	35/31	33 vs 33	33 vs 33	†‡*	24	No	N/A
Liu and Tong[32]	OCT	AGV vs CPC	57.30 (12.88) vs 56.44 (13.16)	27/19	24 vs 22	31 vs 26	†	6	No	N/A
Choy *et al*[33]	RCT	AGV vs CPC	62.8 (11.0) vs 61.3 (13.5)	13/6	12 vs 8	12 vs 8	‡*	31.0 (15.4) vs 28.5 (17.9)	No	Yes
Zhang *et al*[34]	OCT	AGV+IVAV vs Trab(MMC)+IVAV	57.5 (12.5) vs 57.0 (11.5)	12/10	12 vs 10	13 vs 10	‡	26	Bevacizumab	Yes
Sun *et al*[35]	OCT	AGV+IVAV vs Trab(MMC)+IVAV	52.42 (12.78)	23/22	23 vs 22	23 vs 22	†‡*	12	Ranibizumab	Yes
Gao and Liu[36]	OCT	AGV+IVAV vs Trab(MMC)+IVAV	56.25 (9.98) vs 54.75 (11.10)	49/27	36 vs 40	36 vs 40	†‡*	12	Ranibizumab	Yes
Du and Yang[37]	OCT	CCT vs Trab(MMC)+IVAV	57.6 (13. 4)	31/15	23 vs 23	23 vs 23	†‡*	12	Bevacizumab	Yes
Wang and Wang[38]	OCT	CCT vs Trab(MMC)+IVAV	45.5 (4.6) vs 44.5 (6.3)	33/27	30 vs 30	30 vs 30	†‡*	12 (0.3)	Ranibizumab	Yes
Saito *et al*[39]	OCT	Trab(MMC) vs Trab(MMC)+IVAV	61(14) vs 60(13)	33/19	32 vs 20	32 vs 20	*	28(13) vs 12(5)	Bevacizumab	Yes
Takihara *et al*[40]	OCT	Trab(MMC) vs Trab(MMC)+IVAV	60.0 (10.4) vs 60.3 (11.6)	44/6	30 vs 20	33 vs 24	†‡*	25.3 (9.8) vs 15.2 (3.6)	Bevacizumab	Yes
Lee *et al*[41]	OCT	Trab(MMC) vs Trab(MMC)+IVAV	52.73 (11.27) vs 56.53 (11.86)	38/20	26 vs 32	26 vs 32	*	12	Bevacizumab	Yes
Yu *et al*[42]	OCT	Trab(MMC) vs Trab(MMC)+IVAV	54.88 (4.19) vs 55.71 (4.23)	48/42	42 vs 48	42 vs 48	†*	6	Conbercept	Yes
Song[43]	OCT	Trab(MMC) vs Trab(MMC)+IVAV	59.25 (5.51) vs 58.73 (5.44)	91/79	82 vs 88	82 vs 88	†	6	Conbercept	N/A
Shen *et al*[44]	OCT	AGV vs Trab(MMC)	54.0 (15.6) vs 59.65 (15.8)	19/21	20 vs 20	20 vs 20	‡*	31.1 (24.5) vs 25.0 (19.7)	No	N/A

Continued

Table 2 Continued

References	Study design	Interventions	Age (MD, SD)	Gender (Male/female)	Sample size		Outcomes	Mean follow-up (months)	Anti-VEGF	Combine PRP
					No. Patients	No. Eyes				
Liu *et al*[45]	OCT	AGV vs Trab(MMC)+IVAV	56.7 (13.6) vs 62.3 (10.8)	21/16	19 vs 18	19 vs 18	†*	6	Ranibizumab	N/A

*Success rate.
†Intraocular pressure reduction 6 months after surgery.
‡Intraocular pressure reduction 12 months after surgery.
AGV, Ahmed glaucoma valve implant surgery; AGV+IVAV, AGV combined with IVAV; CCT, cyclocryotherapy; CPC, cyclophotocoagulation; IVAV, intravitreal anti-VEGF; MMC, mitomycin; OCT, observational cohort study; PRP, panretinal photocoagulation; RCT, randomised controlled trial; Trab(MMC), trabeculectomy with MMC; Trab(MMC)+IVAV, Trab(MMC) combined with IVAV; VEGF, vascular endothelial growth factor.

Besides, nine studies reported anterior segment inflammation, 20 cases occurred in the AGV +IVAV group, 19 in the AGV group, 16 in the CCT group, 11 in the CPC group and 1 in the Trab(MMC)+IVAV group. Ocular pain was reported in five studies, in which 36 cases in the CCT group, 18 in the CPC group, 8 in the AGV group, 5 in the Trab(MMC) group, 2 in the AGV +IVAV group and 2 in the Trab(MMC)+IVAV group. Two studies reported ocular atrophy, two cases occurred in the CPC group and one in the Trab(MMC) group.

Regarding to adverse events, we supplemented extra data of complications (online supplemental appendix 13) and summarised them in table 5.

DISCUSSION

This is the first network meta-analysis to evaluate the efficacy and safety of the six widely used treatment modalities for NVG. The focus of our work is on more specific outcome measurements, with stricter inclusion criteria and less bias, which is very different from Dong's work. First, we regrettably found that most of Dong's included studies were of poor quality as well as some extraction errors and failed to meet our inclusion criteria. Studies with follow-up time which was not mentioned or less than 6 months were excluded, and only two included studies in our meta-analysis were the same as Dong's.[18 19] Meanwhile, since application of panretinal photocoagulation, laser peripheral iridotomy and anti-scarring drugs were common as adjunctive treatments, they could not be compared as stand-alone interventions. Due to similar principles of reducing VEGF, bevacizumab, ranibizumab and conbercept were classified as anti-VEGF inhibitors in our analysis.[20] By reason of the foregoing, compared with Dong's network meta-analysis,[16] our inclusion criteria were more rigorous, leading to more convincing results.

The results demonstrated that in the six interventions, the effectiveness of CCT was the worst, and the effectiveness of AGV+IVAV was better than the other five interventions in success rat, but similar as CPC in IOPR 12 months after surgery. Besides, the effectiveness of Trab(MMC)+IVAV was the best among the six interventions in IOPR 6 months after surgery.

In terms of the rank of probability for the six interventions, it is reasonable that AGV +IVAV demonstrated a highest probability to be the best intervention in success rate. The insertion of GDD implants has been considered as an option with lower risk of failure than conventional filtering surgery for treating NVG.[5] Among GDDs, Ahmed possesses even higher acceptance and popularity and has been widely used by an increasing number of surgeons.[21] In this review, only AGV was included, we neglected other glaucoma valve-related studies in reason that there is no sufficient studies of comparison of each different types of GDDs. In regard to this, several authors conducted reviews and found no evidence of superiority of one over another in treatment of glaucoma.[5 22 23] Meanwhile, CPC and AGV +IVAV had an advantage over other

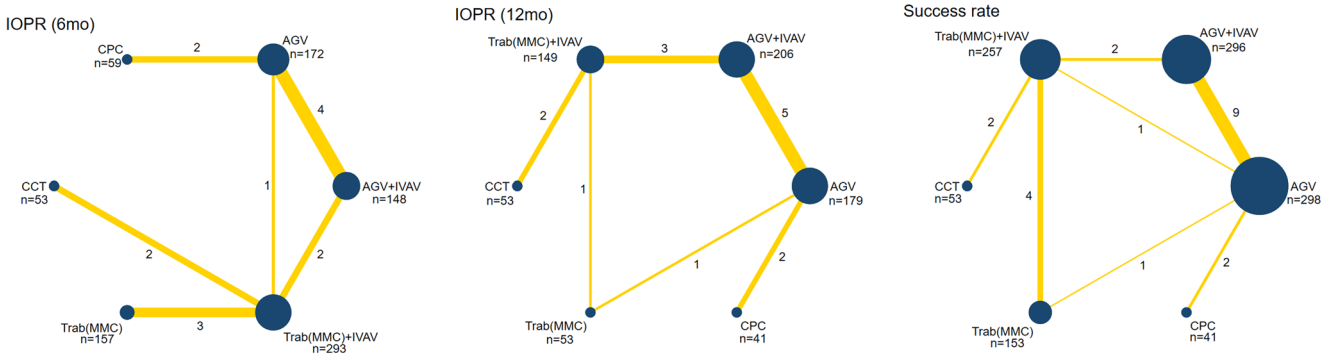

Figure 2 Network of treatment comparisons (Note: width of the lines is proportional to the number of trials comparing every pair of treatments. Size of each circle is proportional to the sample size of interventions. For example, in success rate, '9' represents the number of comparisons between AGV group and AGV+IVAV group, 'n=257' represents the sample size of Trab(MMC)+IVAV group). AGV, Ahmed glaucoma valve implant surgery; AGV+IVAV, AGV combined with IVAV; CCT, cyclocryotherapy; CPC, cyclophotocoagulation; IOPR, intraocular pressure reduction; IVAV, intravitreal anti-vascular endothelial growth factor; mo, months; Trab(MMC), trabeculectomy with mitomycin; Trab(MMC)+IVAV, Trab(MMC) combined with IVAV

four interventions in IOPR 12 months after surgery. The fact that two studies in the CPC groups were RCTs and patients with similar visual acuity were selected in the non-RCT, avoids create a potential selection bias, since cyclodestructive procedures are normally an option for advanced NVG with limited visual acuity, whereas AGVs are usually implanted in patients with better prognosis and visual potential.[24] Therefore, AGV +IVAV was superior to CPC concerning the success rate.

But it is noteworthy that Trab(MMC)+IVAV unexpectedly showed superiority in IOPR 6 months after surgery more than other five interventions. We think the reasons may be attributed to the following aspects. First of all, in this review most of trials have a small sample size, and the number of comparisons was small. As shown in figure 4, the contribution plot of IOPR 6 months after surgery showed Trab(MMC)+IVAV accounted for a large proportion, demonstrating the small sample size influenced the total effect and final outcomes adversely (figure 4). In addition, the funnel plots of IOPR 6 months after surgery showed the potential report bias (figure 5). Moreover, the results of loop-specific approach showed a significant inconsistency existed in IOPR 6 months after surgery, which means the results of indirect comparisons were not consistent with those of direct ones; two comparisons concluded different conclusions in IOPR 6 months after surgery. Subsequently, the findings in favour of Trab(MMC)+IVAV should be interpreted cautiously. Besides, in respect of IOPR 12 months after surgery and success rate, Trab(MMC)+IVAV showed inferiority to AGV+IVAV, CPC and AGV. As mainstream consideration, it shared a low long-term effectiveness mainly due to neovascular membrane obstruction in the filtering passage or external scarring and conjunctival fibrosis

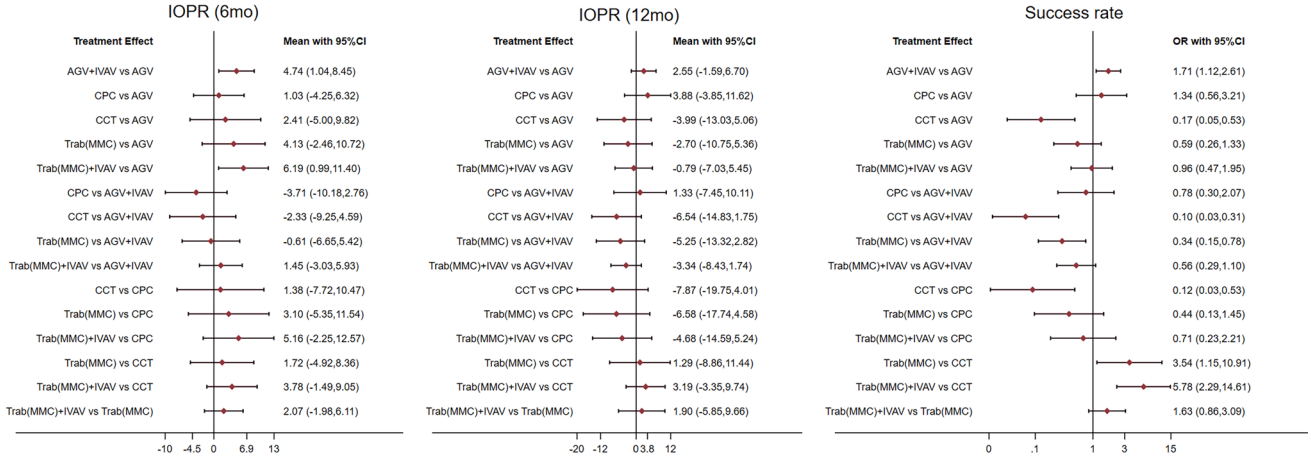

Figure 3 The results of network meta-analysis. AGV, Ahmed glaucoma valve implant surgery; AGV+IVAV, AGV combined with IVAV; CCT, cyclocryotherapy; CPC, cyclophotocoagulation; IOPR, intraocular pressure reduction; IVAV, intravitreal anti-vascular endothelial growth factor; mo, months; Trab(MMC), trabeculectomy with mitomycin; Trab(MMC)+IVAV, Trab(MMC) combined with IVAV.

Table 3 The results of SUCRA and probability

Treatments/outcomes	SUCRA	PrBest	Mean rank
IOPR (6mo)			
AGV	14.5	0.001	5.3
AGV+IVAV	68.9	0.213	2.6
CPC	30.1	0.054	4.5
CCT	39.6	0.057	4
Trab(MMC)	58.8	0.128	3.1
Trab(MMC)+IVAV	88.1	0.547	1.6
IOPR (12mo)			
AGV	48.2	0.014	3.6
AGV+IVAV	79.9	0.304	2
CPC	81.9	0.59	1.9
CCT	18.2	0.022	5.1
Trab(MMC)	28.2	0.042	4.6
Trab(MMC)+IVAV	43.6	0.029	3.8
Success rate			
AGV	54.3	0.002	3.3
AGV+IVAV	92.7	0.663	1.4
CPC	73.7	0.303	2.3
CCT	0.4	0	6
Trab(MMC)	25	0.002	4.8
Trab(MMC)+IVAV	53.9	0.03	3.3

Data are probability in the rows of 'SUCRA' and 'PrBest'.
AGV, Ahmed glaucoma valve implant surgery; AGV+IVAV, AGV combined with IVAV; CCT, cyclocryotherapy; CPC, cyclophotocoagulation; IOPR (6mo), intraocular pressure reduction 6 months after surgery; IOPR (12mo), intraocular pressure reduction 12 months after surgery; IVAV, intravitreal anti-vascular endothelial growth factor; PrBest, the best probability (from 0 to 1); SUCRA, surface under the cumulative ranking; Trab(MMC), trabeculectomy with mitomycin; Trab(MMC)+IVAV, Trab(MMC) combined with IVAV.

promoted by VEGF, even with antimetabolites such as mitomycin C or 5-fluorouracil.[6 8]

Moreover, as shown in table 5, we had some interesting findings on adverse events. First, complications including corneal oedema, anterior segment inflammation, ocular pain and ocular atrophy were reported more in CPC and CCT cases than others. Second, hyphema was reported more in AGV, CPC, CCT and Trab(MMC) cases, whereas was less in AGV +IVAV and Trab(MMC)+IVAV cases, which indicated that combined surgery with IVAV may decrease the incidence of hyphema. Third, low IOP and shallow anterior seem to occur more in AGV +IVAV cases, may be due to the strong filterability of the implant at the beginning. Fourth, drainage tube related complications including tube exposure, tube occlusion and encapsulated plate occurred more often in AGV cases than those in AGV +IVAV cases, which demonstrated that anti-VEGF may improve surgical success rate of AGV. Additionally, bleb leak, vitreous haemorrhage and choroidal detachment were reported more in Trab(MMC) and Trab(MMC)+IVAV cases, and combined surgery with IVAV improved surgical effect; Last, it is worth noting that phthisis bulbi was reported in AGV and Trab(MMC) cases while retinal detachment was reported in AGV cases, although the incidence of these complications appeared low. However, there were some differences in the adverse events included in each study, the results need to be interpreted with caution.

Our review has two methodological strengths. In this research network meta-analysis was carried out to compare the direct and indirect effect of the four treatments, and the SUCRA plot was performed to estimate the ranks of interventions, which may facilitate ophthalmologist to make treatment strategies correctly. However, our review has its disadvantages. First, the evidence from GRADE for included outcomes was relatively low. Only four randomised studies were retrieved, whereas the remaining were non-randomised comparative studies. Second, there was a certain heterogeneity in follow-up time when observing 12-month postoperative IOP. We followed the recommendations of the European Glaucoma Society, which states that the latest reported outcome data or the data closest to 12 months could be reported in case 12-month data were not reported.[17] Third, heterogeneous definitions of the success criteria challenges the validity of our analysis and conclusions. Fourth, the number and sample size of retrieved studies are small, which may affect the interpretation of the results. Fifth, only three outcomes were analysed in our research, more outcomes such as best corrected visual

Table 4 Loop-specific approach

Outcome	Loop	ROR	Z_value	P_value	95% CI	Loop_Heterog_tau2
IOPR (6mo)	AGV-AGVI-TrabI	6.490	0.85	0.395	(0.00 to 21.45)	25.666
IOPR (12mo)	AGV-AGVI-Trab-TrabI	0.123	0.013	0.990	(0.00 to 19.05)	24.326
Success rate	AGV-Trab-TrabI	1.574	1.343	0.179	(0.00 to 3.87)	0
	AGV-AGVI-TrabI	1.282	1.16	0.246	(0.00 to 3.45)	0.066

Loop-specific approach is used to check the inconsistency which aims at the closed loop. In this analysis, ROR is close to 1, indicating no significant difference between direct and indirect effects.
AGV, Ahmed glaucoma valve implant surgery; AGVI, AGV+ IVAV; IVAV, intravitreal anti-vascular endothelial growth factor; MMC, mitomycin; ROR, reporting odds ratio; Trab, trabeculectomy; Trab, Trab(MMC); TrabI, Trab(MMC)+IVAV.

Table 5 Adverse events

	AGV (n=213 eyes)	AGV+IVAV (n=269 eyes)	CPC (n=33 eyes)	CCT (n=53 eyes)	Trab(MMC) (n=182 eyes)	Trab(MMC)+IVAV (n=278 eyes)
Corneal oedema	20 (9.4%)	5 (1.9%)	14 (42.4%)	31 (58.5%)	3 (1.6%)	—
Hyphema	70 (32.9%)	38 (14.1%)	8 (24.2%)	13 (24.5%)	67 (36.8%)	29 (10.4%)
Low intraocular pressure	16 (7.5%)	24 (8.9%)	3 (9.1%)	—	7 (3.8%)	17 (6.1%)
Shallow anterior	20 (9.4%)	42 (15.6%)	—	—	10 (5.5%)	11 (4.0%)
Vitreous haemorrhage	6 (2.8%)	1 (0.4%)	—	—	10 (5.5%)	7 (2.5%)
Choroidal detachment	12 (5.6%)	10 (3.7%)	—	—	18 (9.9%)	21 (7.6%)
Retinal detachment	2 (0.9%)	—	—	—	—	—
Tube exposure	11 (5.2%)	12 (4.5%)	—	—	—	—
Tube occlusion	12 (5.6%)	5 (1.9%)	—	—	—	—
Encapsulated plate	19 (8.9%)	12 (4.5%)	—	—	—	—
Phthisis bulbi	6 (2.8%)	—	—	—	2 (1.1%)	—
Bleb leak	—	2 (0.7%)	—	—	6 (3.3%)	6 (2.2%)
Anterior segment inflammation	19 (8.9%)	20 (7.4%)	11 (33.3%)	16 (30.2%)	—	1 (0.4%)
Ocular pain	8 (3.8%)	2 (0.7%)	18 (54.5%)	36 (67.9%)	5 (2.7%)	2 (0.7%)
Ocular atrophy	—	—	2 (6.1%)	—	1 (0.5%)	—

AGV, Ahmed glaucoma valve implant surgery; AGV+IVAV, AGV combined with IVAV; CCT, cyclocryotherapy; CPC, cyclophotocoagulation; IVAV, intravitreal anti-VEGF; MMC, mitomycin; Trab(MMC), trabeculectomy with MMC; Trab(MMC)+IVAV, Trab(MMC) combined with IVAV; VEGF, vascular endothelial growth factor.

acuity and numbers of anti-glaucoma medications were also relevant but not analysed, because no sufficient data were reported in the included studies. Sixth, since most of the primary ocular diseases leading to NVG were diabetic retinopathy and retinal vein occlusion (online supplemental appendix 14), which may do better than ocular ischaemic syndrome cases or others, the results should be interpreted cautiously due to this potential confounding factor. Finally, the included studies only consisted of six interventions, more surgical treatment should be carried out in the upcoming studies to allow future systematic reviews and meta-analysis. These limitations may affect the final outcomes. In addition, data of each adverse event was insufficient, so the safety of the six treatments could not be evaluated by SUCRA in this review.

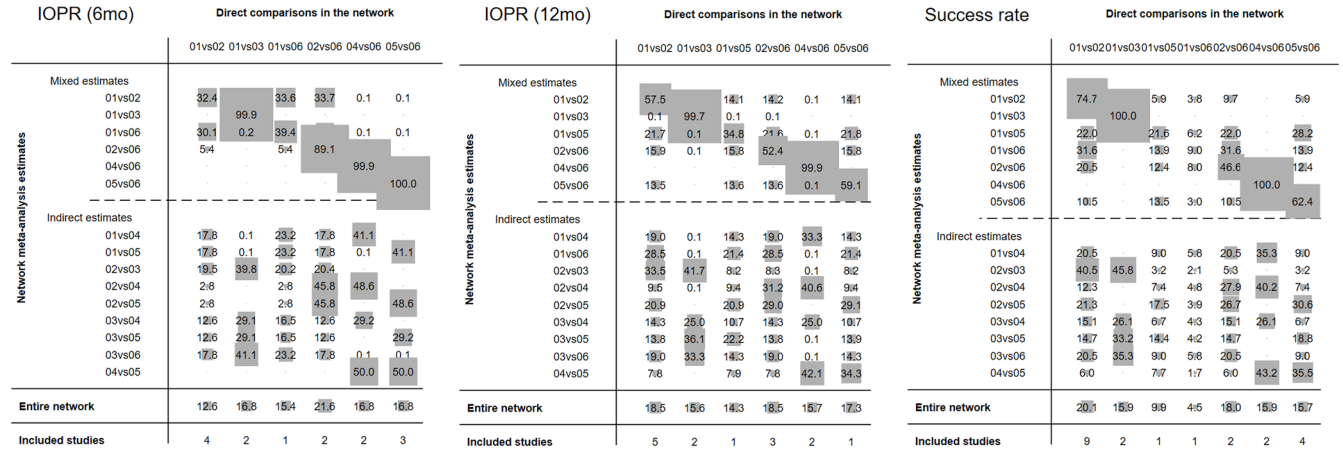

Figure 4 The contribution plots of each outcome (Note: 01=AGV, 02=AGV+IVAV, 03=CPC, 04=CCT, 05=Trab(MMC), and 06=Trab(MMC)+IVAV). AGV, Ahmed glaucoma valve implant surgery; AGV+IVAV, AGV combined with IVAV; CCT, cyclocryotherapy; CPC, cyclophotocoagulation; IOPR, intraocular pressure reduction; IVAV, intravitreal anti- vascular endothelial growth factor; mo, months; Trab(MMC), trabeculectomy with mitomycin; Trab(MMC)+IVAV, Trab(MMC) combined with IVAV.

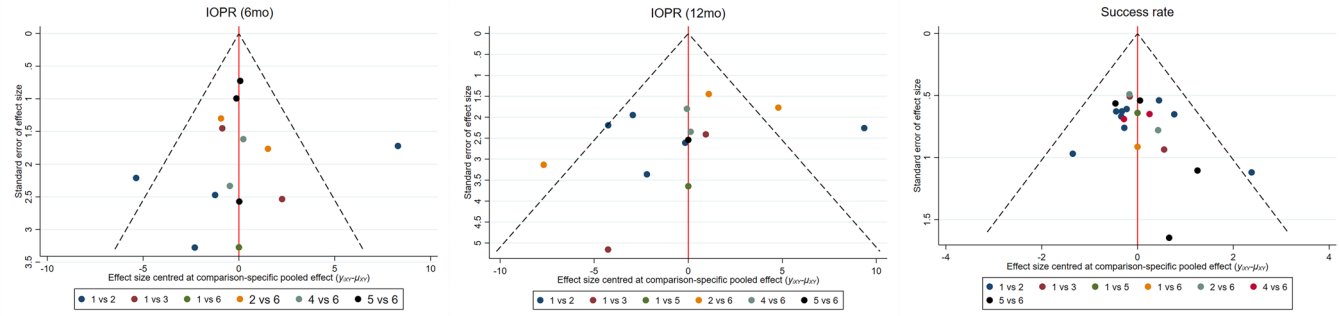

Figure 5 The funnel plots of each outcome (Note: 1=AGV, 2=AGV+IVAV, 3=CPC, 4=CCT, 5=Trab(MMC), and 6=Trab(MMC)+IVAV). AGV, Ahmed glaucoma valve implant surgery; AGV+IVAV, AGV combined with IVAV; CCT, cyclocryotherapy; CPC, cyclophotocoagulation; IOPR, intraocular pressure reduction; IVAV, intravitreal anti- vascular endothelial growth factor; mo, months; Trab(MMC), trabeculectomy with mitomycin; Trab(MMC)+IVAV, Trab(MMC) combined with IVAV.

CONCLUSION

In conclusion, our review suggested, among the six interventions, AGV+IVAV and CPC were superior to the other four interventions, and the effectiveness of CCT was the worst in the treatment of NVG. Additionally, AGV+IVAV is superior to CPC concerning the success rate in the long-term treatment. However, considering the limitations of this study, more high-quality trials, especially those surgical interventions not mentioned in this review, should be carried out in the future to further confirm the current conclusions.

Acknowledgements We thank Haoyu Chen from Department of Ophthalmology, Joint Shantou International Eye Center Shantou University and the Chinese University of Hong Kong, for his editorial assistance.

Contributors PL conceived the study, drafted the protocol, collected data, performed the statistical analysis and wrote the manuscript. QZ participated in data extraction and data analysis. JH, WF and WH contributed to assembly of data, the quality assessment and data interpretation. ML revised the manuscript, accepted full responsibility for the work of the study, had access to the data, and controlled the decision to publish as the guarantor. All authors have read and approved the final version of the manuscript.

Funding This work was supported by Science and Technology Plan Projects of Shenzhen, China (grant number: JCYJ20160428144848002).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as online supplementary information. All included articles could be downloaded from the website https:// pubmed.ncbi.nlm.nih.gov/.

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