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Comparative Efficacies of 13 Surgical Interventions for Primary Congenital Glaucoma in Children: A Network Meta-Analysis of Randomized Clinical Trials

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Highlights

• The comparative efficacies of surgical interventions for primary congenital glaucoma remain inconclusive.

• *Illuminated microcatheter-assisted circumferential trabeculotomy* was superior to *conventional partial trabeculotomy* in both intraocular pressure reduction and success rate.

- *Illuminated microcatheter-assisted circumferential trabeculotomy* was ranked as the most efficacious intervention in terms of success rate.
- Primary congenital glaucoma-surgical interventions can be ranked by efficacy and such ranking may be used to facilitate clinical decision-making.

Data statement

All data generated or analyzed during this study are included in this article.

ABSTRACT

BACKGROUND: Timely and proper intraocular pressure (IOP) management is vital to prevention of visual impairment in children with primary congenital glaucoma (PCG). Although various surgical interventions have been proposed, no well-founded evidence exists on their comparative efficacies. We aimed to compare the efficacies of surgical interventions for PCG.

METHODS: We searched relevant sources up to April 4, 2022. Randomized controlled trials (RCTs) entailing surgical interventions for PCG in children were identified. A network meta-analysis (NMA) was performed, comparing 13 surgical interventions: *Conventional partial trabeculotomy ([CPT] control)*, *240-degree trabeculotomy*, *Illuminated microcatheter-assisted circumferential trabeculotomy (IMCT)*, *Viscocanalostomy*, *Visco-circumferential-suture-trabeculotomy*, *Goniotomy*, *Laser goniotomy*, *Kahook dual blade ab-interno trabeculectomy*, *Trabeculectomy with mitomycin C*, *Trabeculectomy with modified scleral bed*, *Deep sclerectomy*, *Combined trabeculectomy-trabeculotomy with mitomycin C*, and *Baerveldt implant*. The main outcomes were mean IOP reduction and surgical success rate at postoperative 6 months. The mean differences (MDs) or odds ratios (ORs) were analyzed by a random-effects model, and the efficacies were ranked by *P*-score. We appraised the RCTs using the Cochrane risk-of-bias (ROB) tool (PROSPERO: CRD42022313954).

RESULTS: Sixteen (16) RCTs were eligible for NMA, including 710 eyes of 485 participants and 13 surgical interventions, which formed a network of 14 nodes comprising both single interventions and intervention combinations. *IMCT* was superior to *CPT* in both IOP reduction (MD [95% CI], -3.10 [-5.50 to -0.69]) and surgical success rate (OR [95% CI], 4.38 [1.61 to 11.96]). The MD and OR comparing the other surgical interventions and intervention combinations with *CPT* were not statistically significant. The *P*-scores ranked *IMCT* as the most efficacious surgical intervention in terms of success rate (*P*-score = 0.777). Overall, the trials had a low-to-moderate ROB.

CONCLUSION: This NMA indicated that *IMCT* is more effective than *CPT* and might be the most efficacious of the 13 surgical interventions for management of PCG.

Keywords: Primary congenital glaucoma; Surgical intervention; Efficacy; Randomized Clinical trial; Network meta-analysi

1. INTRODUCTION

Primary congenital glaucoma (PCG) is an optic neuropathy with high intraocular pressure (IOP) characterized by anomalous development of the anterior chamber angle [1]. PCG accounts for up to 18% of all cases of childhood blindness [2-6]. This disease's blinding and progressive nature [7] necessitates management that is both timely and proper.

The definitive PCG management approach is surgery, mostly because, for pediatric patients, treatment with medication is poorly tolerated over the long term and less effective than for adults [1, 8]. As PCG's principal pathology is in the anterior chamber angle, two procedures generally are used: goniotomy or trabeculotomy. Both of these address the issue of angle anomaly and increase aqueous outflow by directly connecting Schlemm's canal to the anterior chamber [8]. Other types of surgical interventions, such as filtering surgery, glaucoma drainage devices and cyclodestructive procedures, also have been proposed [8], with the result that there is considerable heterogeneity in PCG management, even among experts.

Various randomized controlled trials (RCTs) therefore have been done to compare surgical interventions' efficacies for PCG in pediatric patients [9-24]. Determining their comparative efficacies remains difficult, however, due specifically to the lack of head-to-head comparisons. Moreover, the current accumulated evidence is limited to pairwise comparisons between specific interventions [25] and lacks comprehensive all-interventions comparisons. Consequently, there is still no well-founded evidence supporting a given intervention's outstanding efficacy for PCG management.

Network meta-analysis (NMA), as an extension of the traditional meta-analysis, enables intervention comparison based on not only direct evidence, but also indirect evidence (i.e., from interventions that are not directly compared) [26]. Furthermore, intervention hierarchies can be obtained using valid methods of statistical inference [27]. Thus motivated, we performed an NMA on RCTs to assess the comparative efficacies of surgical interventions for PCG in pediatric patients

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2. METHODS

The protocol of this systematic review was prospectively registered at PROSPERO (CRD42022313954) [28] and has been published [29]. This NMA has been reported in accordance with and is fully compliant with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), Supplemental Digital Content 1, http://links.lww.com/JS9/A163, Supplemental Digital Content 2, http://links.lww.com/JS9/A164 2020 [30] and AMSTAR 2, Supplemental Digital Content 3, http://links.lww.com/JS9/A165 (Assessing the methodological quality of systematic reviews) Guidelines [31].

2.1. Eligibility Criteria for Present Review

RCTs that had compared the efficacies of surgical interventions for PCG in pediatric patients were included. There were no restrictions on any surgical intervention types. Editorials, case reports as well as comments, abstracts and letters were excluded. Studies that had only compared different application methods (e.g., exposure time, concentration) of the same adjunctive substance such as antimetabolite (e.g., mitomycin C [MMC], 5-fluorouracil) and bevacizumab (e.g., IOP-lowering effect of 'trabeculectomy (TLE) with MMC application for 2 minutes' *vs.* 'TLE with MMC application for 4 minutes') were also excluded; the reason for the exclusion was that the main purpose of this study was to compare the IOP-lowering effect of the surgical technique itself. In addition, the detailed application methods of adjuncts differed among studies.

2.2. Search Methods for Identification of Studies

We systematically searched the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, PubMed, and EMBASE from inception to April 4, 2022. Our search strategies were developed in collaboration with an academic librarian expert in systematic review, and are based on established terminology such as MESH and EMBASE search terms. The following keywords were included: *Congenital*, *Glaucoma*, *Surgery*, and *Children*. We also screened the World Health Organization (WHO) International Clinical Trials Registry Platform, *clinicaltrials.gov*, and references from published papers to identify additional relevant studies. No language-based restrictions were imposed on our electronic searches. The complete search strategies are available in **Supplementary Appendix 1, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**.

2.3. Study Selection

To identify pertinent articles, the titles and abstracts of those retrieved were exported to Endnote (version X9; Thomson Reuters), wherein duplicates were removed. The remaining titles and abstracts were assessed by two investigators (DK/YJL) independently for eligibility, and for the eligible ones, the relevant full-text articles were retrieved. Then, the same two investigators independently assessed those articles for final eligibility. Eligibility classification discrepancies were resolved through discussion, consensus, or, when needed, third-party (YKK) adjudication.

2.4. Data Collection and Risk-of-Bias Assessment

For each of the trials, two individuals (DK/AH) independently extracted data and then entered it (electronic format) into Microsoft Access 2016 (Microsoft Corporation, Redmond, WA, USA). Any conflicting data entries were identified using an algorithm. The trial characteristics of interest were: (1) study ID (name of first author, year of publication), (2) country of study, (3) length of follow-up, (4) inclusion of participants with history of surgery, (5) surgical interventions, (6) number of eyes (participants), (7) baseline mean age, (8) baseline mean IOP, (9) postoperative 6-month and 1-year mean IOP reduction, and (10) surgical success rate.

Trial quality was evaluated using a revised tool for assessment of risk of bias (ROB) in randomized trials (RoB 2) [27]. The five domains of bias evaluated were as follows: randomization process, adherence to assigned interventions, missing outcome data, outcome measurement bias, and reported-results bias. Each domain was rated as: low ROB, “some concerns” or high ROB. Any domain’s worst ROB was used to determine the overall ROB. In the evaluation, we referred to the Cochrane Database of Systematic Reviews (CDSR) [25] for previously published articles’ contents that had been confirmed through communication with the authors. ROB was assessed by two investigators (YJL/YKK) independently, any discrepancies being resolved via discussion.

2.5. Definitions Used in Categorization of Surgical Interventions

To improve interpretability and, thereby, support decision-making, we grouped the surgical intervention arms into the 13 categories that follow: (1) *Conventional partial trabeculotomy ([CPT] control)*, (2) *240-degree trabeculotomy (240° trabeculotomy)*, (3) *Illuminated microcatheter-assisted circumferential trabeculotomy (IMCT)*, (4) *Viscocanalostomy (VC)*, (5) *Visco-circumferential-suture-trabeculotomy (VCST)*, (6) *Goniotomy*, (7) *Neodymium-YAG laser goniotomy (laser goniotomy)*, (8) *Kahook dual blade ab-interno*

trabeculectomy (KDB trabeculectomy), (9) *Trabeculectomy with mitomycin C (TM)*, (10) *Trabeculectomy with modified scleral bed (TmS)*, (11) *Deep sclerectomy (DS)*, (12) *Combined trabeculectomy-trabeculotomy with mitomycin C (CTTM)*, and (13) *Baerveldt implant* (**Table 1**). Each surgical intervention is described in detail in **Supplementary Table 1, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**.

2.6. Outcomes

The primary outcome measure was the amount of mean IOP reduction at postoperative 6 months; in a large number of RCTs on PCG surgical interventions, the postoperative observation period was 6 months (as indicated in **Table 2**), and so the standard for a primary outcome was set at 6 months for this study. When comparing interventions A and B, stated IOP values representing intervention A/B difference were compared; a negative mean difference (MD), therefore, indicated the superiority of intervention A (i.e., a lower IOP). Results of intention-to-treat analyses were extracted preferentially. If postoperative 6-month data were not available, we adopted the data closest in terms of time point.

The secondary outcome measure was surgical success rate at postoperative 6 months, as defined based on each study's definition (e.g., proportion of eyes showing IOP equal to or less than a given value, without any signs of glaucoma progression or serious visual complications). All of the definitions can be found in **Supplementary Table 2, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**. We applied qualified success rates to the analysis; in cases where such data were not available, we used the complete (absolute) values instead. Also, if no distinction between complete (absolute) and qualified success was provided, we applied the reported surgical success rate.

2.7. Data Synthesis

We compared the effects of the competing surgical interventions on the primary outcome (i.e., postoperative 6-month mean IOP reduction) according to the MD with 95% confidence intervals (CIs). As for the secondary outcome (i.e., postoperative 6-month surgical success rate), the odds ratio (OR) was calculated by dividing intervention group 1's success proportion by that of intervention group 2. To combine direct evidence with indirect, an NMA was performed with the R software package "netmeta" (version 4.0.4; The R Foundation, Vienna, Austria), which applies a frequentist method based on a graph-theoretical approach according to the electrical network theory [32, 33]. The "netmeta" function takes within-study correlation into account by reweighting, using the Laplacian matrix and its pseudoinverse, all of each multi-

arm study's comparisons based on back-calculation of variances [34]. Because the included studies were small in number and heterogeneous, we applied random-effects models [35].

2.8. Data Analysis

We ranked the interventions by *P*-score, which is the most frequent analogue of the surface under the cumulative ranking curve (SUCRA) [33]. The *P*-score, as valued between 0 and 1, is the probability that a certain treatment is among the best ones [27, 36].

We assessed the cross-study heterogeneity of effect estimates and the study heterogeneity effects on pooled effect estimate using Q statistics and I^2 statistics, respectively [37, 38]. Inconsistency (i.e., non-agreement of direct with indirect intervention effects) [39] was evaluated using Separating Indirect from Direct Evidence (SIDE; a.k.a. node-splitting) [40]. We assessed NMA-estimate confidence by a semi-automated web application (Confidence in Network Meta-analysis [CINeMA]; Institute of Social and Preventive Medicine) [41, 42]. A comparison-adjusted funnel plot with an accompanying Egger's test for asymmetry was used to assess cross-study bias (i.e., publication bias) in NMA [43]. Statistical significance was recorded for cases where the 2-sided α level was less than 0.05.

For the purposes of a sensitivity analysis, we repeated an NMA (1) for the primary outcome by excluding studies that had included patients with a history of previous surgery and (2) for the mean IOP reduction at postoperative 1 year.

3. RESULTS

3.1. Search Results

Our systematic search uncovered 1,186 articles of which 1,162 were unique reports, and, after excluding reports based on scrutiny of titles and abstracts, 58 full-text articles were retrieved. Upon full evaluation of these citations, 16 RCTs, comprising a total of 710 eyes of 485 participants, were deemed to have met the NMA inclusion criteria. **Fig. 1** is a flowchart of the process of selection for inclusion in our study. The excluded studies along with the rationales for their exclusion are provided in **Supplementary Appendix 2, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**.

3.2. Study Characteristics

The characteristics of the 16 RCTs included in the NMAs are provided in **Table 2**. Study duration (i.e., follow-up duration) ranged from 6 to 60 months, and the baseline mean IOP ranged from 16.4 to 34.0 mmHg. Nine studies had been conducted in Egypt [9-13, 15, 17, 19, 20], 3 in India [16, 18, 21], and one each in Brazil [14], Lebanon [22], Saudi Arabia [23], and the USA [24]. Twelve (12) studies [9-12, 15-18, 20-22, 24] included only patients lacking any surgical history, whereas 4 [13, 14, 19, 23] also included such patients. A schematic of the ROB assessment across all of the studies included in our analysis is provided in **Supplementary Appendix 3, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**. Overall, the trials were determined to have a low-to-moderate ROB.

3.3. Primary Outcome: Intraocular Pressure Reduction

The total of 13 surgical interventions formed a 14-node network of both single interventions and intervention combinations (**Fig. 2**). As shown in **Fig. 3A**, *IMCT* effected a greater IOP reduction than did *CPT*, when combined in the NMA (MD, -3.10; 95% CI, -5.50 to -0.69, *P*-score = 0.752; **Supplementary Appendix 4, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**). However, the amounts of IOP reduction of the other 10 single surgical interventions and those of the two surgical intervention combinations were not significantly different from that of *CPT*, wherein *TmS* showed the lowest MD, followed by *TM*, *Baerveldt implant*, *Laser goniotomy*, *240° trabeculotomy*, *CTTM + DS*, *CTTM*, *KDB trabeculectomy*, *Goniotomy*, *CPT + VC*, *VCST*, and *VC* (**Fig. 3A**). For illustration of the head-to-head comparisons, a net league table is provided in the form of **Supplementary Fig. 1A, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**.

3.4. Secondary Outcome: Surgical Success Rate

Fifteen (15) studies [9-21, 23, 24] had reported success rates, entailing 13 intervention nodes (**Supplementary Fig. 2, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**). Complete (absolute) success rates were used in two studies [13, 17] in which qualified success rate data were not available. Also, 4 studies [10, 20, 23, 24] reported success rates without any distinction between complete (absolute) and qualified success. Of the present comparison's interventions, *IMCT* showed a significantly higher success rate than that for *CPT* when combined in the NMA (OR, 4.38; 95% CI, 1.61 to 11.96; **Fig. 3B**). However, comparisons of others' success rates with that of *CPT* were not statistically significant, with ORs ranging from 1.42 (*CPT + VC*) to 3.47 (*VCST*) (**Fig. 3B**). A net league table representative of the head-to-head comparison is shown in **Supplementary Fig. 1B, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**. According to the *P*-scores, *IMCT* (*P*-score = 0.777) was the most efficacious surgical intervention as well (**Supplementary Appendix 4, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**).

3.5. Examination of Network Model and Validity of Results

Our network model revealed moderate heterogeneity across studies for primary outcome (I^2 = 50.6%). Within-design heterogeneity was not significant (P = 0.208), though between-design inconsistency was borderline-significant (P = 0.087). When a full design-by-treatment random-effects model was assumed, the Q value was low (Q = 2.41), and the between-design inconsistency ceased to be significant (P = 0.120; **Supplementary Table 3, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**). The SIDE analysis showed no disagreement (inconsistency) between the direct estimates and the indirect ones (all Ps ≥ 0.05; **Supplementary Table 4, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**). The comparison-adjusted funnel plot, which evaluated the risk of publication bias incurred in the NMA (**Supplementary Fig. 3, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**), showed a relatively even distribution, which is to say, no bias to either side. This was corroborated by the Egger's test, which indicated no significance (P = 0.34). These findings, overall, indicated a low probability of small-study effects in the present network model. As for the primary outcome (i.e., IOP reduction), we examined the overall evidence certainty within the all-comparison network, and found it to be widely distributed from very low to moderate (**Supplementary Appendix 5, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**).

3.6. Sensitivity Analyses

In our analysis of mean IOP reduction at postoperative 6 months, which excluded studies that had included patients with a surgery history (**Fig. 4A**), *IMCT* showed a greater IOP reduction than did *CPT*, when combined in the NMA (MD, -3.05; 95% CI, -5.99 to -0.12; **Fig. 4B**, *P*-score = 0.761; **Supplementary Appendix 4, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**). The amounts of mean IOP reduction of the others, however, were not significantly different from that of *CPT*, with MDs ranging from -5.60 (*TmS*) to -0.25 (*KDB trabeculectomy)* (**Fig. 4B**). For illustration of head-to-head comparisons, a net league table is provided in the form of **Supplementary Fig. 4A, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**.

A total of 12 studies [9-18, 20, 22] with 9 intervention nodes were included in our analysis of mean IOP reduction at postoperative 1 year (**Fig. 4C**). The *IMCT* effected a greater IOP reduction than did *CPT* (MD, -2.43; 95% CI, -4.15 to -0.72), while the others showed no significant differences with that of *CPT*, with MDs ranging from -2.44 (*Baerveldt implant*) to -0.74 (*240° trabeculotomy*) (**Fig. 4D**). A net league table is provided in the form of **Supplementary Fig. 4B, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**. According to the *P*-scores, *IMCT* (*P*-score = 0.864) was the most efficacious intervention (**Supplementary Appendix 4, Supplemental Digital Content 4, http://links.lww.com/JS9/A166**).

4. DISCUSSION

This NMA including 16 RCTs represents a comprehensive synthesis of data on the comparative efficacies of different types of surgical interventions for PCG. We found that for pediatric patients with PCG, *IMCT* is more effective than *CPT*, and that it might be the most efficacious among the total of 13 surgical interventions in terms of both IOP reduction and surgical success rate.

In a traditional pairwise meta-analysis of surgical interventions for PCG, Gagrani et al. [25] likewise showed that mean IOP may be lower with *IMCT* than with *CPT* at 6 and 12 months. The evidence on the comparative efficacies of the other surgical interventions, however, was limited due to either a complete lack of studies or an insufficient number. A total of only 7 studies, comprising 3 different pairwise comparisons, were included in their analysis, since the comparisons were limited to specific, direct-evidence-based ones. Going beyond this limitation, our NMA enabled both direct and indirect comparisons between interventions, exploiting all available evidence across the network while preserving within-trial randomization.

The results of our NMA revealed that *IMCT* is more efficacious than *CPT* in both IOP reduction and surgical success rate, though the reasons have yet to be elucidated. There are two possible explanations. First, a greater extent of angle opening in *IMCT* than in *CPT* could lead to a larger amount of aqueous drainage, resulting in greater IOP reduction and correspondingly higher surgical success rate. Whereas *CPT* opens the angle partially, usually 100 to 120 degrees, *IMCT* effects 360 degrees of circumferential angle opening [8]. Second, during *IMCT*, the illuminated microcatheter tip is continuously visible transsclerally throughout the Schlemm's canal passage. The visibility of the tip might minimize the risk of misdirection and false passage [44], thereby contributing to better surgical outcomes.

IMCT was identified, in the built-up hierarchies of the interventions, as the most efficacious surgical intervention with regard to surgical success rate, as it was in the sensitivity analyses on mean IOP reduction at postoperative 1 year. In most of the head-to-head comparisons between *IMCT* and the others (other than *CPT*), however, the differences did not reach statistical significance. Therefore, given the evidence gathered to date, the superiority of *IMCT* over other interventions (other than *CPT*) is not yet clear and needs further investigation.

Several study limitations merit further discussion. First, the relatively small sample size in each trial might have incurred a small-study effect, which refers to the phenomenon that smaller trials show different, often larger, treatment effects than larger ones [45]. The wide CI in studies with small sample sizes also should be taken into account when interpreting the results. Second, subgroup analyses by characteristics such as ethnicity, geographic location, disease severity, or age of onset were not feasible due to

inaccessibility to individual patient data or an insufficient number of trials. It has been reported that PCG incidence varies greatly with race, ethnicity, and level of consanguinity in the community [46]. Moreover, the prognosis of children with PCG has been known to differ according to age of onset [47, 48]. Further studies examining other confounding factors are required in order to fully evaluate the comparative efficacies of surgical interventions for PCG. Third, the cross-trial definitions of surgical success rate and follow-up period were inconsistent, which differences might limit the inter-study comparability. We had attempted to perform subgroup analyses according to the surgical success criteria. However, the number of studies in each subgroup included was relatively small for meaningful analyses. Outcome measures for future research should be standardized so as to improve comparability of studies. Fourth and finally, studies investigating the effect of adjunct usage itself (e.g., IOP-lowering effect of 'TLE with MMC' *vs*. 'TLE without MMC') in surgical intervention could not be included in the final analysis, because their study design or participants was not compliant with the current study's eligibility criteria.

Notwithstanding these limitations, our study is of value, especially in light of the difficulties inherent in performing RCTs on PCG (due to its rarity), the reported incidence of which is known to range from 1:10,000 to 1:20,000 live births [46, 49-51] and to be higher in consanguineous populations (1:1,250 in Slovakian gypsies [51], 1:2,500 in Saudi Arabia [52], and 1:3,300 in Andhra Pradesh, India [53]). Currently, among practitioners, there is no consensus on the surgical approach to PCG, which uncertainty may hinder their decision-making and performance with respect to the optimal treatment modality for each patient. We believe that our NMA could form the basis for establishment of evidence-based guidelines for management of PCG.

The findings of the current study indicate several directions for future research. First, larger, multi-ethnic, and multi-country RCTs with long-term follow-ups are required to further accumulate evidence on the efficacy of surgical interventions for PCG. Second, utilization of a standardized reporting system for surgical outcomes is needed to improve comparability between studies. Third, studies comparing the complications of surgical interventions would also provide valuable information for practitioners on patient management, particularly regarding safety issues. Fourth and finally, investigations gathering evidence on the cost-effectiveness of surgical interventions or the quality of life of patients/caregivers would be worthwhile.

5. CONCLUSIONS

This NMA of RCTs indicated that *IMCT* is more effective than *CPT* and, moreover, that it might be the most efficacious of the 13 surgical interventions for PCG. These findings would provide comprehensive evidence for determination of optimal treatment strategies for PCG in clinical practice.

Conflict of interest statement

None declared.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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Fig. 1. Flow diagram of study selection process for inclusion in network meta-analysis.

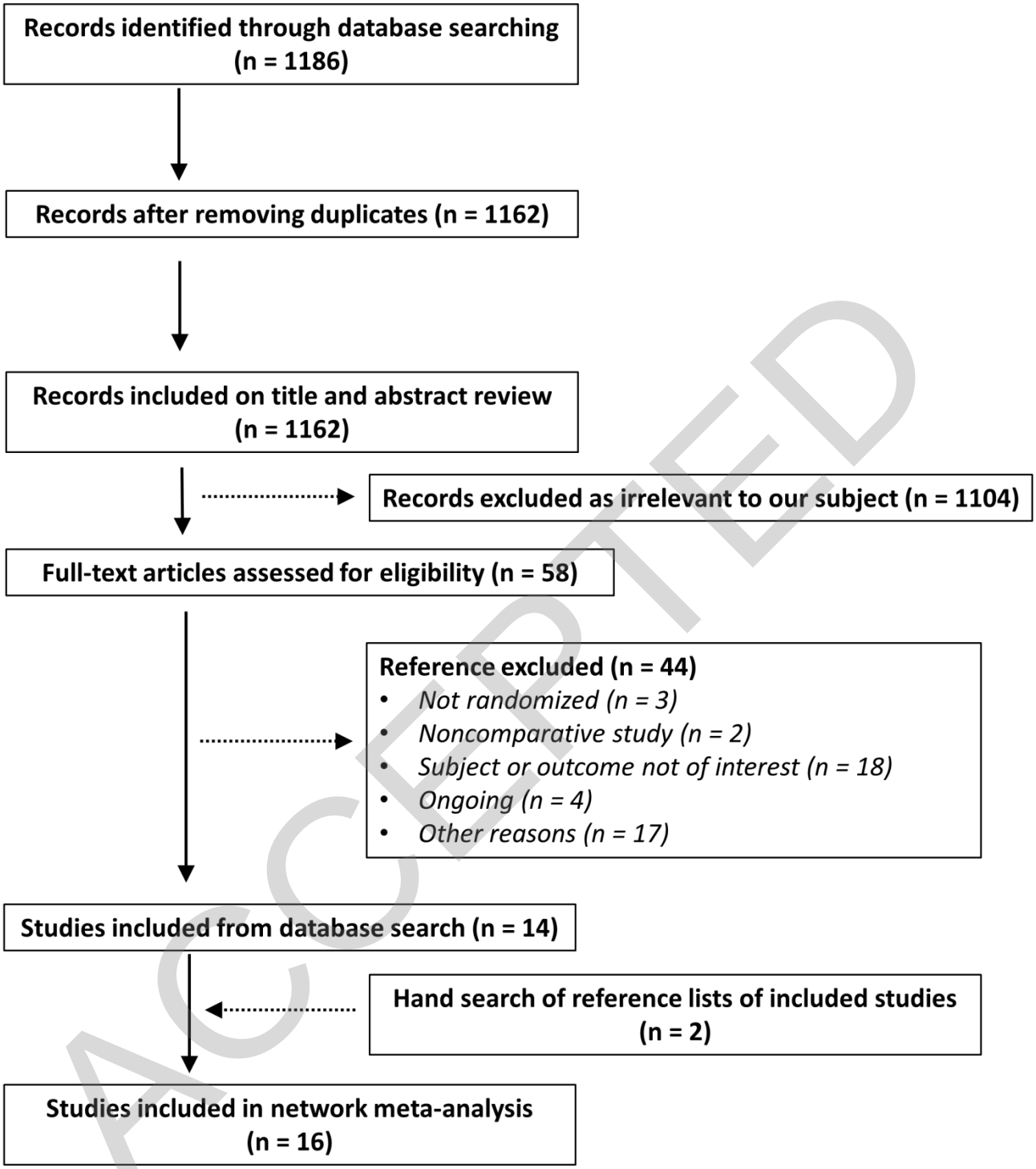

Fig. 2. Network plot of primary outcome. Surgical interventions, with direct comparisons, are linked by lines, with the width of the lines being proportional to the number of trials comparing each pair of interventions. The size of each node is proportional to the number of eyes of participants (i.e., sample size) randomly assigned to each intervention. Green lines indicate direct comparisons with *Conventional partial trabeculotomy (CPT)*; blue indicates direct comparisons with *Combined trabeculectomy-trabeculotomy with mitomycin C (CTTM)*; gray indicates direct comparisons between other interventions. DS = deep sclerectomy; IMCT = illuminated microcatheter-assisted circumferential trabeculotomy; KDB = Kahook dual blade; TmS = trabeculectomy with modified scleral bed; TM = trabeculectomy with mitomycin C; VC = viscocanalostomy; VCST = visco-circumferential-suture-trabeculotomy.

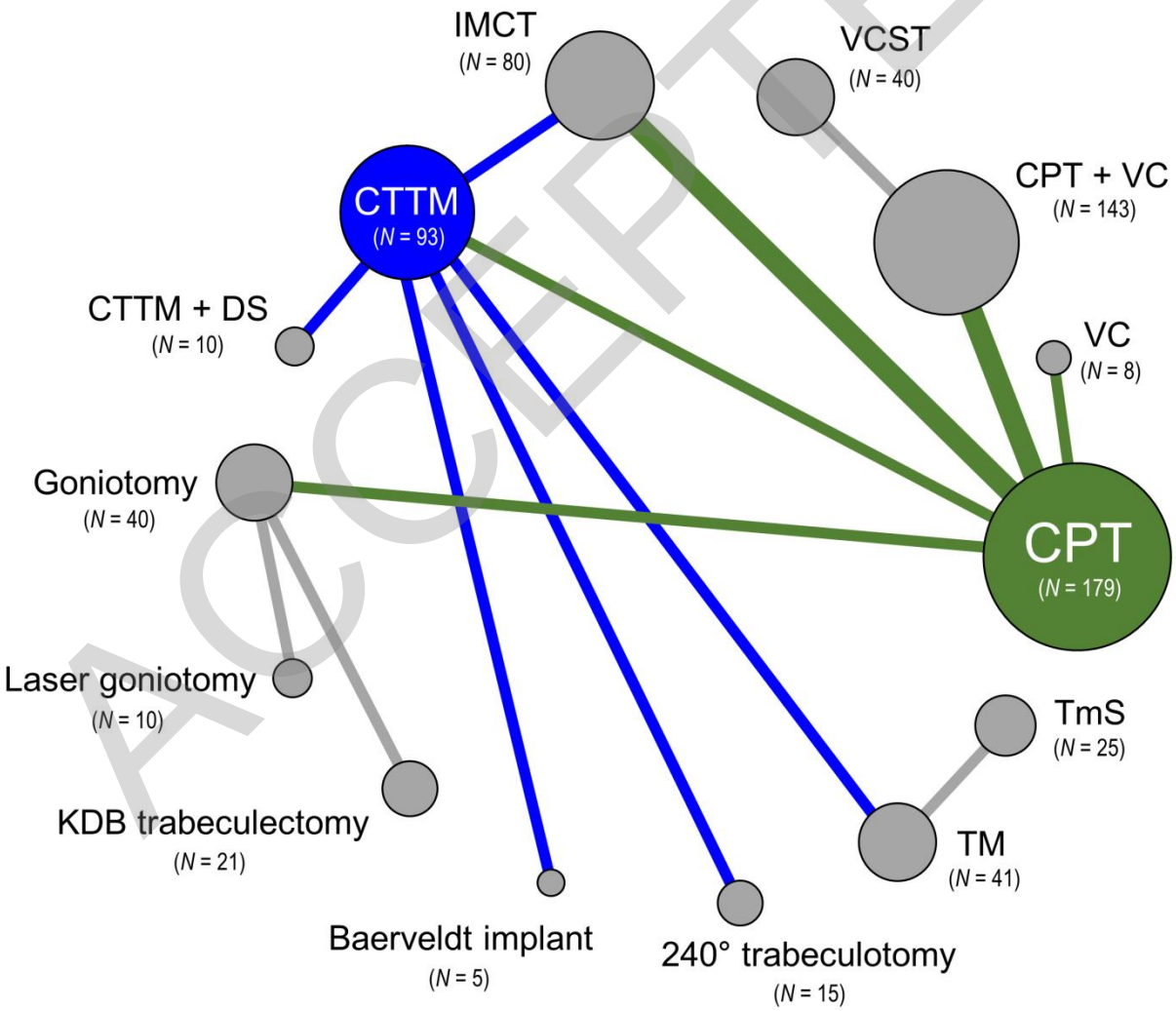

Fig. 3. Forest plots of primary and secondary outcomes. **A,** Mean intraocular pressure (IOP) reduction at postoperative 6 months. **B,** Surgical success rate. Each surgical intervention was compared with *Conventional partial trabeculotomy (CPT)*, which was the reference group. CI = confidence interval; CTTM = combined trabeculectomy-trabeculotomy with mitomycin C; DS = deep sclerectomy; IMCT = illuminated microcatheter-assisted circumferential trabeculotomy; KDB = Kahook dual blade; MD = mean difference; OR = odds ratio; TmS = trabeculectomy with modified scleral bed; TM = trabeculectomy with mitomycin C; VC = viscocanalostomy; VCST = visco-circumferential-suture-trabeculotomy.

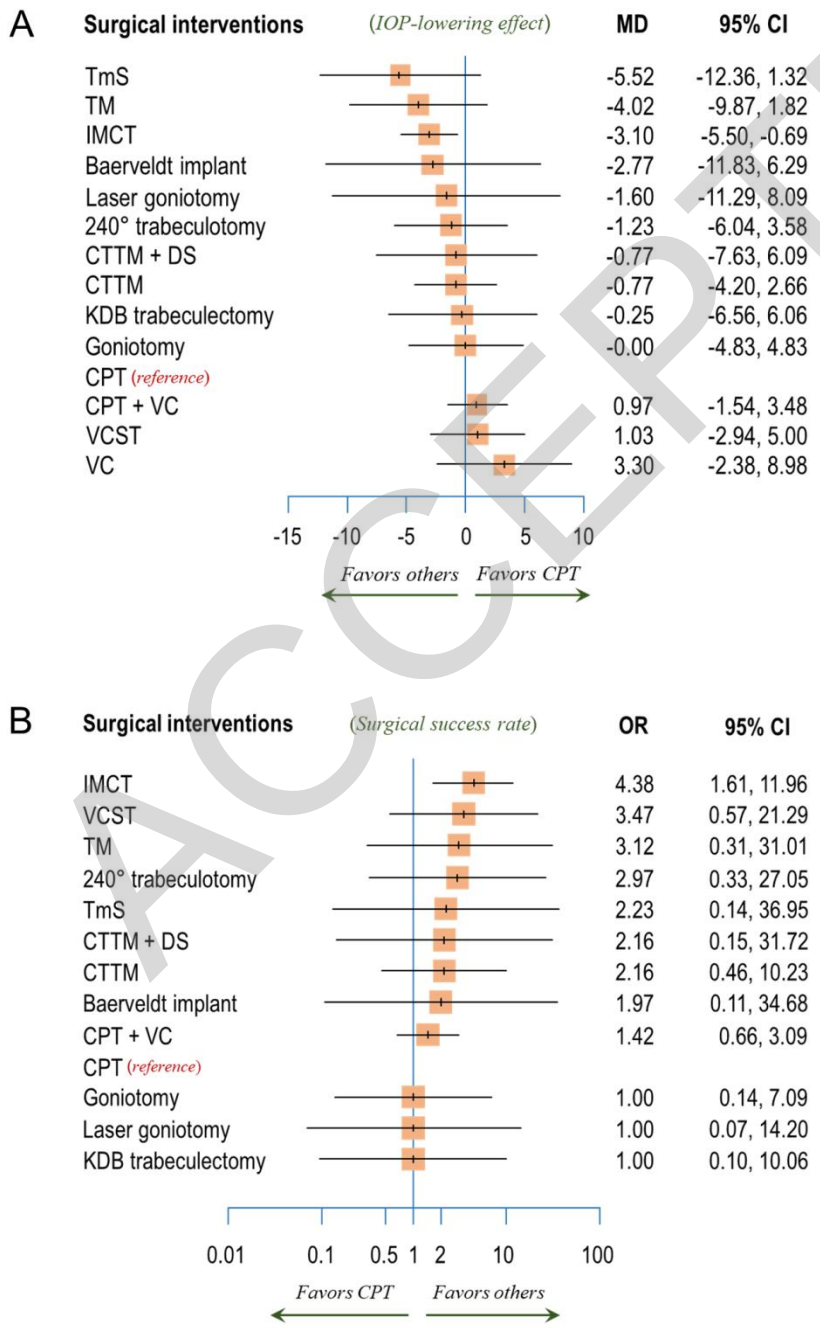

Fig. 4. Network plots and forest plots for sensitivity analyses. **A, B,** Mean intraocular pressure (IOP) reduction at postoperative 6 months, excluding studies that had included patients with history of previous surgery. **C, D,** Mean IOP reduction at postoperative 1 year. In the forest plots, each surgical intervention was compared with *Conventional partial trabeculotomy (CPT)*, which was the reference group. CI = confidence interval; CTTM = combined trabeculectomy-trabeculotomy with mitomycin C; DS = deep sclerectomy; IMCT = illuminated microcatheter-assisted circumferential trabeculotomy; KDB = Kahook dual blade; MD = mean difference; TmS = trabeculectomy with modified scleral bed; TM = trabeculectomy with mitomycin C; VC = viscocanalostomy; VCST = visco-circumferential-suture-trabeculotomy.

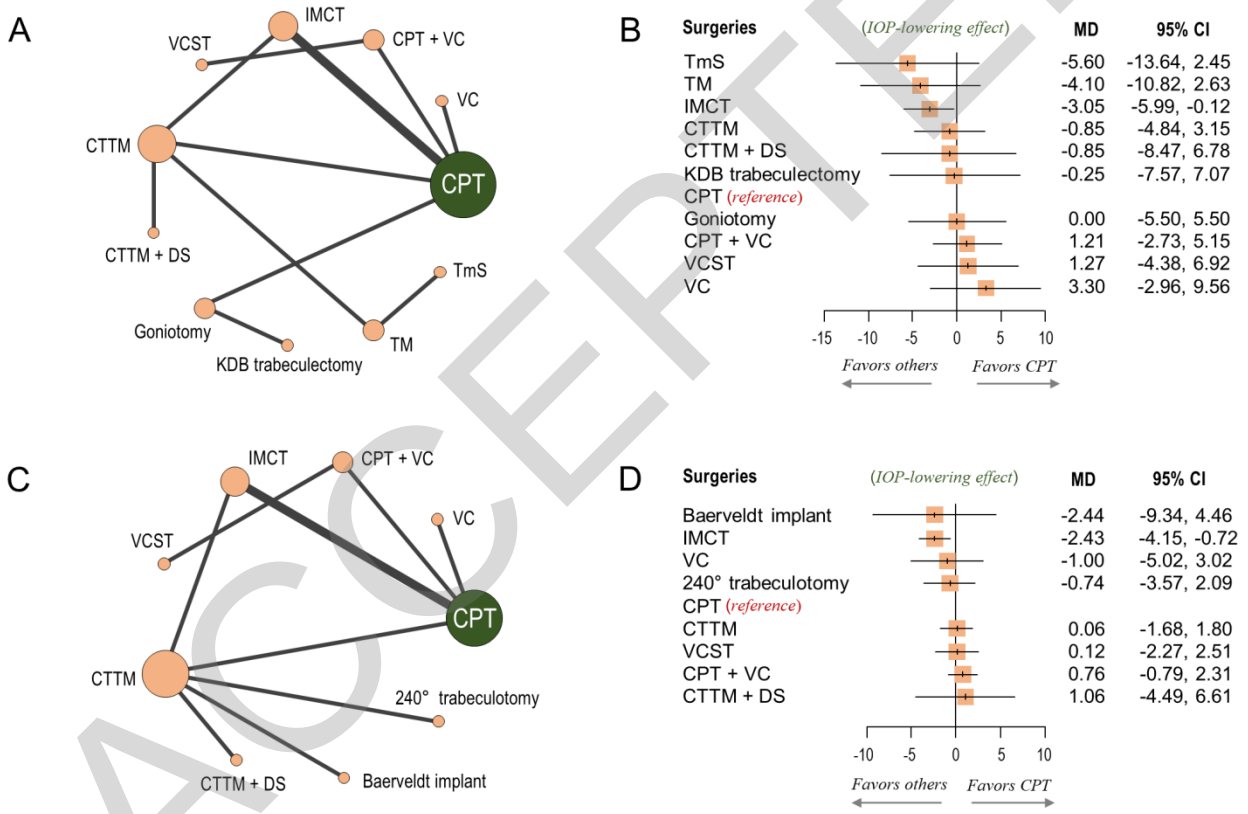

Table 1. Classifications, types and designated terms of surgical interventions.

Classification	Type	Designated Term
Angle surgery	Conventional partial trabeculotomy	CPT
	240-degree trabeculotomy	240° trabeculotomy
	Illuminated microcatheter-assisted circumferential trabeculotomy	IMCT
	Viscocanalostomy	VC
	Visco-circumferential-suture-trabeculotomy	VCST

	Goniotomy	Goniotomy
	Neodymium-YAG laser goniotomy	Laser goniotomy
	Kahook dual blade ab-interno trabeculectomy	KDB trabeculectomy
Filtering surgery	Trabeculectomy with mitomycin C	TM
	Trabeculectomy with modified scleral bed	TmS
	Deep sclerectomy	DS
Combined surgery	Combined trabeculectomy-trabeculotomy with mitomycin C	CTTM
Glaucoma drainage device	Baerveldt implant	Baerveldt implant

Table 2. Characteristics of studies included in meta-analysis.

Study ID	Country	Follow-up Duration (months)	Inclusion of Participants with History of Surgery	Surgical Interventions (study arm)	Number of Eyes (Participants) Randomized	Baseline Mean Age (months)	Baseline Mean IOP (mmHg)	Postoperative 6-Month Mean IOP Reduction (mmHg)	Postoperative 1-Year Mean IOP Reduction (mmHg)	Surgical Success Rate (%)[a]
Elwehidy et al, 2022	Egypt	36	No	VCST	84 (49)	4.8 (2.1)	29.1 (3.3)	17.9 (3.0)	17.7 (3.0)	94.6
				CPT + VC		4.9 (1.7)	29.9 (3.2)	18.0 (2.8)	17.1 (2.8)	87.8
Elhilali et al, 2021	Egypt	12	No	KDB trabeculectomy	42 (29)	9.1 (9.6)	24.4 (6.8)	10.1 (6.0)	12.6 (6.0)	57.1[b]
				Goniotomy		6.3 (3.9)	23.1 (3.7)	9.9 (3.3)	10.3 (3.3)	57.1[b]
Elwehidy et al, 2021	Egypt	60	No	CPT + VC	154 (92)	5.0 (2.3)	26.5 (2.9)	15.0 (2.5)	14.4 (2.5)	89.7
				CPT		5.0 (2.9)	27.9 (3.1)	16.2 (2.7)	15.2 (2.7)	85.5
Bor'i et al, 2020	Egypt	14 (13–22)[c]	No	TmS	50 (25)	2.5 (0.5)	31.6 (4.9)	18.6 (4.3)	16.1 (4.3)	84.0
				TM		2.5 (0.5)	32.1 (4.0)	17.1 (3.5)	15.0 (3.6)	88.0
Wagdy, 2020	Egypt	12	Yes	240° trabeculotomy	30 (30)	14.1 (2.3)	28.2 (1.7)	14.0 (1.9)	14.3 (1.8)	93.3[d]
				CTTM		14.2 (3.1)	28.1 (3.5)	13.5 (3.1)	13.5 (3.1)	86.7[d]
Rolim-de-Moura et al, 2020	Brazil	12	Yes	Baerveldt implant	13 (13)	40.8 (31.7)	22.8 (5.9)	10.6 (6.4)	10.6 (5.2)	100.0
				CTTM		28.6 (17.7)	23.7 (7.3)	8.6 (8.0)	8.1 (6.7)	100.0
El Sayed et al, 2017	Egypt	24	No	IMCT	62 (62)	5.6 (4.8)	25.1 (6.4)	13.3 (5.7)	13.2 (5.5)	89.3
				CPT		4.4 (3.8)	22.3 (5.2)	7.9 (5.1)	9.5 (4.8)	56.3
Shakrawal et al, 2017	India	12	No	IMCT	40 (31)	6.5 (3.9)	24.7 (3.9)	14.7 (3.5)	15.2 (3.4)	90.0
				CPT		10.2 (5.4)	24.6 (3.3)	12.2 (2.9)	12.9 (2.9)	70.0
Khalil et al, 2016	Egypt	36	No	CPT	28 (28)	6.5 (3.9)	24.1 (1.9)	12.7 (4.2)	14.1 (1.8)	85.7[d]
				CTTM		5.6	24.1	11.6	13.6	85.7[d]

						(4.0)	(1.8)	(4.5)	(1.8)	
Temkar et al, 2015	India	12	No	IMCT	60 (30)	6.6 (5.7)	21.8 (9.8)	10.4 (8.9)	10.2 (8.6)	93.3
				CTTM		6.6 (5.7)	21.7 (8.9)	10.7 (8.0)	10.1 (7.8)	93.3
ElSheikha et al, 2015	Egypt	6	Yes	CPT + VC	41 (31)	6.8 (6.5)	23.5 (5.4)	6.1 (6.4)	NA	66.7
				CPT		6.9 (5.7)	24.3 (4.4)	6.4 (6.4)	NA	60.0
Bayoumi, 2012	Egypt	12	No	CTTM	20 (20)	4.7 (2.0)	16.7 (4.3)	10.9 (4.0)	11.8 (3.7)	100[b]
				CTTM + DS		7.0 (3.8)	16.4 (8.4)	10.9 (7.4)	10.8 (7.3)	100[b]
Reddy et al, 2011	India	6	No	CTTM	32 (18)	<24.0	24.9 (6.8)	9.0 (5.9)	NA	75.0
				TM		<24.0	27.3 (4.6)	12.3 (5.0)	NA	81.3
Noureddin et al, 2006	Lebanon	12	No	CPT	16 (8)	3.4 (4.1)	34 (2.6)	20.5 (4.2)	18.4 (3.8)[e]	NA
				VC		3.4 (4.1)	32.3 (4.1)	17.2 (5.8)	19.4 (4.0)[e]	NA
Senft et al, 1989	Saudi Arabia	9.5 (2-15)[c]	Yes	Goniotomy	20 (10)	5.7 (3.9)	28.4 (4.6)	4.8 (7.8)[f]	NA	40.0[b]
				Laser goniotomy		5.7 (3.9)	29.5 (11.0)	6.4 (10.1)[f]	NA	40.0[b]
Anderson, 1982	USA	34	No	Goniotomy	18 (9)	<9.0	NA	NA[g]	NA	66.6[b]
				CPT		<9.0	NA	NA[g]	NA	66.6[b]

CPT = conventional partial trabeculotomy; CTTM = combined trabeculectomy-trabeculotomy with mitomycin C; DS = deep sclerectomy; IMCT = illuminated microcatheter-assisted circumferential trabeculotomy; IOP = intraocular pressure; KDB = Kahook dual blade; NA = not available; TmS = trabeculectomy with modified scleral bed; TM = trabeculectomy with mitomycin C; VC = viscocanalostomy; VCST = visco-circumferential-suture-trabeculotomy.

Data on age, IOP and surgical success rate were rounded to one decimal place, if applicable.

[a] Adopted data for the closest point in time to postoperative 6 months in cases where their data are not available.

[b] No distinction between complete (absolute) and qualified success.

[c] Average follow-up duration (range).

[d] Complete (absolute) surgical success rate.

[e] Adopted postoperative 16-month IOP data due to lack of 1-year data.

[f] Adopted IOP data following surgical intervention (measurement period not specified).

[g] Adopted average IOP value for all of the other included CPT studies' postoperative 6-month data due to lack of data (applied identical values for both interventions, considering their identical surgical success rates).