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Protocol for systematic review and network meta-analysis of comparative effectiveness of surgical interventions for primary congenital glaucoma

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ABSTRACT

Introduction Primary congenital glaucoma (PCG), a type of childhood glaucoma, is primarily treated surgically to lower intraocular pressure (IOP). Failure to intervene could result in partial, or even total, blindness. Various surgical intervention types have been proposed for PCG, though the evidence on comparative effectiveness remains limited. The current protocol is an ongoing network meta-analysis enabling comparative investigation of surgical interventions for which randomised controlled trials (RCTs) are available. Our aim is to systematically compare the efficacy of various types of surgical intervention for patients with PCG.

Methods and analysis Studies of interest will assess the effects of those surgical interventions on surgery-naïve children (age <18 years) suffering PCG. RCTs regardless of language or publication date will be searched from three electronic databases (Cochrane Central Register of Controlled Trials, Embase and MEDLINE) from 4 April 2022. Two reviewers will screen, first, titles and abstracts, followed by full-text papers, for useful data that they will extract. The primary outcome measure will be the IOP-lowering effect of a given surgical intervention. The two reviewers also will assess the internal validity of studies using the relevant and domain-based risk-of-bias assessment tool. Overall evidence quality will be assessed according to the Confidence in Network Meta-Analysis approach and will be presented in summarised form with network diagrams. For enhanced visualisation of the included interventions' effects, forest plots will be constructed. Pairwise effect sizes also will be calculated based on the evidence that is available in the network.

Ethics and dissemination This work will synthesise evidence obtained from published studies, and as such, no ethics review or approval will be required. A paper presenting the findings will be submitted to a peer-reviewed scientific journal for publication.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The network meta-analysis (NMA) design will enable comparative investigation of all surgical primary congenital glaucoma interventions for which sufficient randomised controlled trials are available.
⇒ This NMA potentially allows for hierarchical and clinically meaningful representation of surgical interventions for lowering of intraocular pressure.
⇒ This work would not exclude the potential influence of skill differentials among trial-participating surgeons.
⇒ The sample size as well as the number of studies included may be inadequate, and, as such, a network of intervention arms might not be formed.

INTRODUCTION

Paediatric glaucoma is a group of potentially blinding conditions characterised by elevated intraocular pressure (IOP) and subsequent damage to the optic nerve.[1] Primary congenital glaucoma (PCG) is glaucoma diagnosed in infants <24 months[2] and is not associated with systemic or ocular abnormalities other than isolated malformation of the trabecular meshwork.[3]

A number of surgical techniques and their IOP-lowering effects have been treated in the literature.[4] Angle surgery (goniotomy or trabeculotomy) is the generally accepted treatment standard and primary intervention for PCG.[5] However, PCG management varies considerably in its approaches, even among recognised expert practitioners. Two systematic reviews have examined the effectiveness of PCG patients' surgical interventions.[6 7] They commend the 360-degree circumferential trabeculotomy as offering greater potential utility for surgical success relative to conventional trabeculotomy. However, there remains very little evidence of meaningful difference between combined trabeculectomy-trabeculotomy (CTT) and the alternative routine conventional trabeculotomy or viscotrabeculotomy vs routine conventional trabeculotomy. Overall, there remains insufficient evidence justifying recommendation of any surgical intervention over another or others.

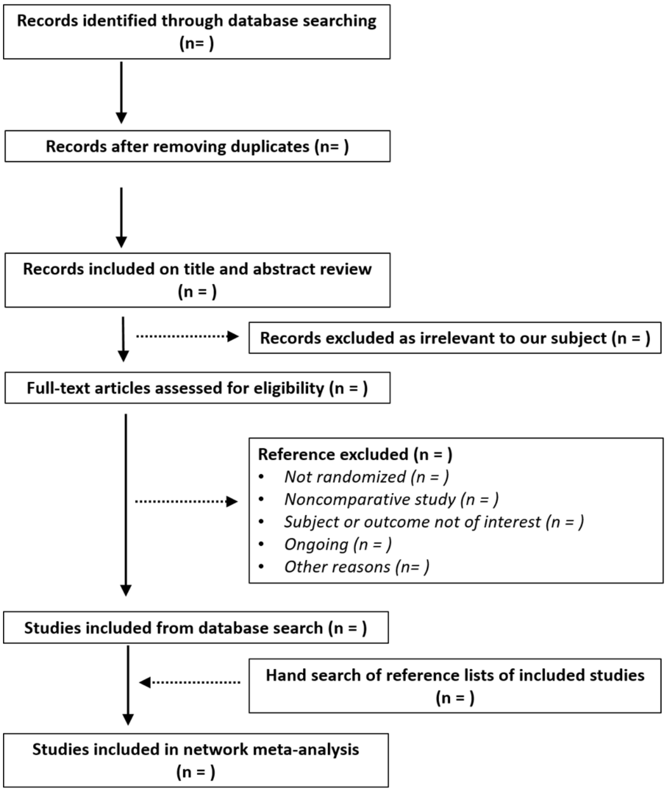

Figure 1 PRISMA flow diagram of study-selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Traditional (ie, meta-analytic) pairwise investigation of single interventions has proved impossible, as they vary by study, and randomised controlled trials (RCTs) have been insufficient in number to make possible the evaluation of each of the different types of intervention. Traditional meta-analyses also are limited by unavailability of a sufficient number of pairwise comparisons of interventions.[8] Therefore, it is difficult to interpret the entire available body of evidence: either RCTs are available only for certain surgical interventions or the evidence is limited for certain other interventions. For many surgical intervention types, furthermore, there are simply no direct comparisons available.

Network meta-analysis (NMA), however, is a protocol that allows for efficacy comparison of different interventions.[9 10] Simply, creation of a pairwise RCT network enables the use of any and all evidence, direct or indirect, for efficacy determinations.[11] For PCG, NMA enables comparative analysis of all surgical interventions for which sufficient RCTs are available, which utility compares favourably with traditional systematic review and meta-analysis, by which only two interventions can be analysed. With the NMA design; moreover, available interventions' efficacies can be ranked.

The protocol presented in these pages is an ongoing NMA design for systematic effectiveness comparison of various types of surgical intervention for IOP-lowering of paediatric PCG patients. The main research question was: What are the efficacies of the different types of surgical intervention for IOP lowering? The above-stated objective—efficacy evaluation of the different surgical intervention types—will allow for generation of a clinically meaningful intervention hierarchy.

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for protocols is followed by this protocol.[12] The NMA results will be reported in accordance with the PRISMA statement and the PRISMA extension for network meta-analyses (PRISMA-NMA).[13 14]

Eligibility criteria

The eligibility criteria for study inclusion in the NMA are as follows: (1) any RCTs indicating IOP-lowering effects of any surgical intervention for surgery-naïve paediatric patients (age <18 years) with PCG; (2) any surgical intervention or control-treatment or no-treatment group, as a comparator; (3) studies reporting secondary results (eg, visual field test, adverse event results) other than IOP-lowering effects; (4) availability in full-text format.

Categorisation of studies

For improved interpretability and better decision-making support thereby, surgical intervention arms will be categorised. By an iterative, 'review of relevant RCTs with discussion' process, 12 categories for the proposed NMA have been identified: (A) conventional partial trabeculotomy, (B) CTT with mitomycin C, (C) illuminated microcatheter-assisted circumferential trabeculotomy, (D) Kahook dual blade ab-interno trabeculectomy, (E) trabeculectomy with mitomycin C, (F) viscocanalostomy, (G) visco-circumferential-suture-trabeculotomy, (H) conventional partial trabeculotomy with viscocanalostomy, (I) goniotomy, (J) neodymium-doped yttrium aluminium garnet (Nd-YAG) laser goniotomy, (K) Baerveldt implant and (L) 240-degree trabeculotomy. And as for the reference arm, it will be conventional partial trabeculotomy.

Information sources

RCTs will be searched in three electronic databases (Cochrane Central Register of Controlled Trials, Embase and MEDLINE), with no publication-date limitation. The WHO International Clinical Trials Registry Platform as well as *clinicaltrials.gov* also will be screened.

Search strategy

Our search strategies were developed with the help of an academic librarian who is an expert in systematic review and are based on established terminology such as MESH and Embase search terms, as available. The following keywords were included: *congenital*, *glaucoma*, *surgery*, *children*. The search strategy was first developed for the MEDLINE database and was then adjusted in order to meet the other databases' conditions. The full-search strategies are provided in online supplemental appendix.

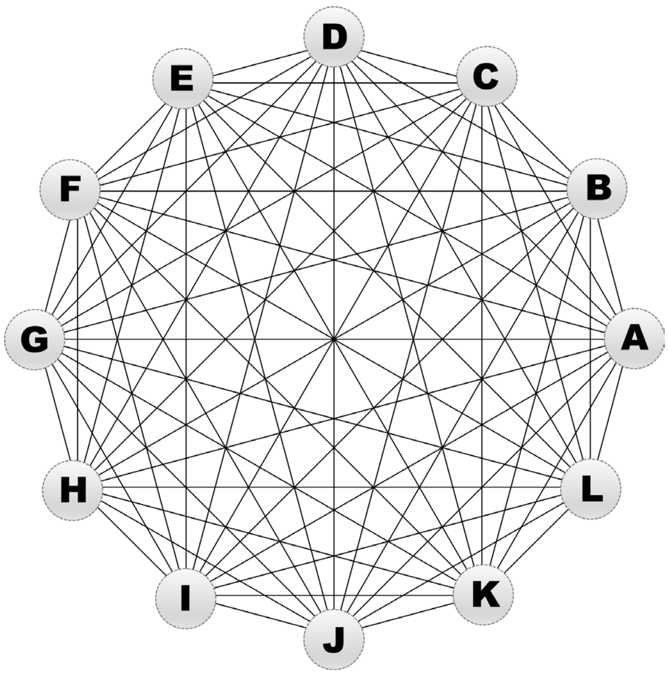

Figure 2 All possible network connections (pairwise comparisons, lines) with 12 nodes (ie, interventions A–L): (A) conventional partial trabeculotomy, (B) combined trabeculectomy-trabeculotomy with mitomycin C, (C) illuminated microcatheter-assisted circumferential trabeculotomy, (D) Kahook dual blade ab-interno trabeculectomy, (E) trabeculectomy with mitomycin C, (F) viscocanalostomy, (G) visco-circumferential-suture-trabeculotomy, (H) conventional partial trabeculotomy with viscocanalostomy, (I) goniotomy, (J) neodymium-doped yttrium aluminium garnet (Nd-YAG) laser goniotomy, (K) Baerveldt implant and (L) 240-degree trabeculotomy.

For systematic reviews and meta-analyses that are prospectively identified (the reference lists of which could include potentially relevant studies), manual searches will be conducted so as to identify any of missed by the electronic searches. The analysed studies will include data on PCG surgical interventions, regardless of language, publication date or country. The planned overall start date for our study is 4 April 2022, and we aim to finish it within 6 months after the initiation.

Selection process

Two reviewers will independently screen titles and abstracts in order to identify studies that are potentially eligible. For each study so identified, the two reviewers will then review its full text, again independently. A third reviewer will resolve any disagreements in either of the two stages just outlined above. Inter-rater agreement will be reported as the Cohen's kappa coefficient (κ). For studies reported in multiple papers, the paper reporting the most complete effectiveness analysis will be chosen. The complete stepwise process will be represented by PRISMA flowchart (figure 1).

Data collection and management

For extraction and recording of study data, the two reviewers will use a standardised extraction table preagreed to by all of the authors.

Data items

The extracted data will include study characteristics (eg, author, year, country), participant characteristics (eg, sample size, age, sex, history of previous surgery), types of surgical intervention as well as timing of follow-up assessment. Means and SDs of primary outcome (ie, IOP) measured at the baseline, along with the time points after and closest to the end of the treatment, will be extracted so as to accommodate predicted cross-study treatment-duration variation.

Where studies reporting more than two surgical interventions (or control groups) both of which could have been independently included in the NMA, data will be extracted from all study arms. For example, if one RCT encompasses three treatment arms (A, B and C), data will be extracted from all three.

For primary outcomes where mean±SE are reported, SDs will be calculated based on the formula $SD=SE\times\sqrt{n}$. Where medians or IQRs are reported, the methods described by Wan *et al* will be employed for computation of means and SDs.[15] Where means and 95% CIs are reported, SDs will be calculated based on the formula $SD=\sqrt{n}\times(\text{upper 95\% CI limit}-\text{lower 95\% CI limit})/t$, t being the t-distribution value for the 95% CI of a sample distribution having dfs that are equal to the group sample size−1. If a paper provides insufficient data, they will be obtained, if possible, from the corresponding author. All of the extracted data will be tabulated.

Outcomes and prioritisation

The primary outcome is IOP change between the baseline and follow-up, measured as defined in each study. The secondary outcome is the surgical intervention success rate assessed by dichotomous (success/failure) or discrete data (proportion of success or failure over a specific time period).

Risk of bias in individual studies

The two reviewers will assess the included studies' internal validity (ie, risk of bias) according to the domain-based risk-of-bias assessment tool most relevant, and the results will be provided in graphical format as recommended in the Cochrane handbook. A third reviewer will resolve any disagreements.

Data synthesis

The characteristics of the included trials will be summarised and then tabulated. Summarisation will entail using a network diagram, within which each node will represent an intervention class (see, again, the inclusion criteria), and the node size will be proportional to the number of patients receiving treatment. The effects of two interventions' pairwise comparison will be shown as edges interconnecting nodes, the edge line thickness representing pairwise comparison weight. A contribution matrix will indicate the influence of the individual comparisons as well as that of direct and indirect evidence on the overall effects' summary. If quantitative synthesis is inappropriate, a narrative synthesis will be conducted.

Assessment of transitivity and meta-biases

It is expected that the surgical interventions for PCG, as identified in the preliminary search, will all be jointly randomisable in principle; this attribute will meet the transitivity assumption. For all comparisons of interventions in the network, inferences will be based on direct evidence (ie, pairwise RCTs), indirect evidence (ie, effect B–C derived from A–B and A–C comparisons), or a combination of both direct and indirect evidence.

Network meta-analysis

Under the assumption of the cross-study similarity of the effect-modifier distribution, frequentist NMA will be performed (see proposed closed network geometry, figure 2). After all of the available evidence in the network is obtained, pairwise effect sizes will be calculated.[16] Effect measures for treatments that are not already compared in a pairwise RCT can be compared indirectly by applying a common comparator to them.[8 17 18] Considering that interventions can vary for given characteristics, the sample used in each study may slightly differ; therefore, a random effect model will be used to generate pooled standardised effect sizes. The corrected effect size (Hedges' g) will be used, so as to allow for inclusion of smaller studies.[19] For ranking of the mixed (direct and indirect) effect sizes as well as 95% CIs for all of the treatment combinations in the network, network forest plots, interval plots and league tables will be employed.

Detection of heterogeneity and assessment of inconsistency

Heterogeneity will be reported based on 95% prediction intervals and I^2. Forest plots will be visually examined to identify any obvious inconsistency between the direct and indirect treatment effects (loop consistency); any such inconsistency might indicate non-satisfaction of the assumption of transitivity. In cases where there is significant heterogeneity detected, inconsistency will be evaluated using the node-splitting approach, one comparison at a time.[20] Also, comparison-adjusted funnel plots will be used for visual inspection and assessment of small-study effects as well as for assessment of potential publication bias.[21]

Confidence in cumulative evidence

Overall evidence quality will be assessed by the Confidence in Network Meta-Analysis (CINeMA) approach based on study limitations, imprecision, heterogeneity, indirectness and publication bias; CINeMA is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework but with some conceptual and semantic differences.[22] It covers six domains: (1) within-study bias (ie, impact of risk of bias in included studies), (2) reporting bias (ie, publication and other reporting bias), (3) indirectness, (4) imprecision, (5) heterogeneity and (6) incoherence.[23] For within-study bias and indirectness, the reviewer's input at the study level is required. Then, CINeMA assigns to each domain, according to user-defined rules, judgments at three levels (no concerns, some concerns, major concerns). The cross-domain judgments will be summarised to show four levels of confidence for each relative treatment effect, and these levels will correspond to standard GRADE assessments (very low, low, moderate, high).

Statistical analyses

Statistical package R will be used for all of the statistical analyses.[24] The netmeta R-package will be used for performing and reporting of the NMA. P-scores will be applied to indicate the treatment efficacy ranking. For creation of the visual nodes-and-connections network, the *forest.netmeta* function of the netmeta package will be employed.

Patient and public involvement

No patients or members of the public will be directly involved. Only data already reported in the literature, along with the aforementioned sources, will be used in this study.

ETHICS AND DISSEMINATION

This work will synthesise evidence from already published studies, and, therefore, will not require any ethics review or approval. A paper presenting the findings will be submitted to a peer-reviewed scientific journal for publication, and the results will be reported based on the PRISMA statement as well as the PRISMA-NMA guidelines.

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