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Protocol for a systematic review and network meta-analysis comparing the efficacy and safety of benzalkonium chloride-preserved, alternatively preserved and preservative-free eyedrops in the treatment of glaucoma

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ABSTRACT

Introduction The primary therapeutic approach to glaucoma involves the long-term use of intraocular pressure (IOP)-lowering eyedrops. However, the prevalent use of benzalkonium chloride (BAK) as a preservative in glaucoma eyedrops has been associated with ocular side effects, prompting a demand for alternatively preserved (AP) or preservative-free (PF) eyedrops. Studies comparing various preservatives have shown conflicting evidence concerning the safety of BAK-preserved (BP) eyedrops, some studies indicating no notable concerns and others reporting adverse effects. The current protocol concerns a network meta-analysis enabling systematic investigation of the IOP-lowering efficacy and safety profiles of BP, AP and PF eyedrops in patients with glaucoma for whom randomised controlled trials (RCTs) are available.

Methods and analysis This study will evaluate the IOP-lowering effects of glaucoma eyedrops, comparing formulations with and without preservatives in patients with glaucoma. A systematic search for RCTs, regardless of language or publication date, will be conducted across three electronic databases (Cochrane search engine, Embase and MEDLINE) from 1 March 2024. Two reviewers will conduct a sequential screening of titles and abstracts, followed by full-text papers, to extract useful data. The two reviewers will also assess the internal validity of studies using the relevant and domain-based risk of bias assessment tool. Overall evidence quality will be assessed using the Confidence in Network Meta-Analysis approach and presented in summarised form with network diagrams. Forest plots will be generated for enhanced visualisation of the included glaucoma eyedrops' effects, and pairwise effect sizes will be calculated based on available evidence in the network.

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The network meta-analysis (NMA) design will enable comparative investigation of all glaucoma eyedrops for which sufficient randomised controlled trials are available.
⇒ This NMA has the potential to provide a hierarchical and clinically meaningful representation of the intraocular pressure-lowering efficacy and safety of glaucoma eyedrops, particularly with respect to preservatives.
⇒ There exists a potential risk of publication bias (ie, the greater likelihood of studies with positive results being published relative to those with negative results) affecting the comprehensiveness of the evidence base.

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INTRODUCTION

The primary treatment for glaucoma usually involves the long-term use of intraocular pressure (IOP)-lowering eyedrops.[1] In the process of IOP reduction, ideal medications are required, which should be effective not only in lowering IOP but also in being highly tolerable and minimally interfering in a patient's life. However, medical management of glaucoma is associated with ocular side effects, which often are attributable to the preservatives present in glaucoma eyedrops.

To prolong the shelf-life of multidose bottles and prevent contamination, preservatives are commonly added. Among the preservatives, benzalkonium chloride (BAK) is the most used in ophthalmic solutions.[2] However, BAK toxicity on the ocular surface has been reported in several studies, leading to an increasing demand for alternatively

preserved (AP) or preservative-free (PF) eyedrops.[2 3] A previous in vitro study comparing the adverse effects of different preservatives on cultured ocular epithelial cells showed that replacement of BAK with polyquad or sofZia resulted in significantly higher percentages of live conjunctival and corneal cells compared with BAK.[4] Also, in a large-scale European observational study involving 9658 patients, all recorded ocular symptoms, and signs were significantly more frequent in patients taking preserved medications than in those taking PF formulations.[5] Conversely, Tressler *et al*[6] addressed, in a systematic 2011 review, the issue of BAK-preserved (BP) eyedrops, having assessed both clinical and preclinical studies and finding no reason for concerns over efficacy or safety. More recently, Hedengran *et al*[7] reviewed the efficacy and safety of BP eyedrops relative to AP and PF eyedrops and reported no significant differences between BP and AP or PF eyedrops. Given the conflicting evidence concerning these eyedrops, there is a need for a comprehensive systematic review of current clinical studies comparing these formulations in terms of their IOP-lowering effects and safety profiles in patients with glaucoma.

Traditional meta-analysis primarily concentrates on direct pairwise comparisons, estimating cumulative effects through the combination and comparison of specific interventions. However, assessing the comparative effectiveness of various interventions becomes challenging, especially in the absence of studies providing direct head-to-head evidence.[8 9] Network meta-analysis (NMA), an extension of traditional meta-analysis, enables the comparison of interventions that have never been directly compared by incorporating both direct and indirect comparison. Moreover, with NMA, intervention hierarchies can be constructed using valid methods of statistical inference.[10–12]

The protocol presented in these pages outlines an NMA design for systematic comparison of glaucoma eyedrops with various types of preservatives. The main research question was: Does (IOP)-lowering efficacy differ among glaucoma eyedrops containing different preservatives? Additionally, we compared ocular surface status and patients' adherence based on the differently preserved glaucoma eyedrops.

METHODS AND ANALYSIS

This protocol is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13] The NMA results, correspondingly, will be reported based on the PRISMA statement and PRISMA extension for network meta-analyses (PRISMA-NMA).[14 15]

Eligibility criteria

The eligibility criteria for inclusion in the NMA are as follows: (1) any randomised controlled trials (RCTs) involving IOP-lowering eyedrops in patients with either glaucoma or ocular hypertension; (2) any IOP-lowering eyedrops, control-treatment or no-treatment group, as a comparator; (3) reports including secondary results (eg, visual field test, adverse event results) other than IOP-lowering effects; (4) availability of study in full-text format.

Exclusion criteria

Studies with fewer than 10 participants per group will be excluded from our analysis. Trials assessing combination medical therapies will also be excluded, as these treatments are typically prescribed for patients who have not responded to a single first-line therapy. While no restrictions will be placed on the minimum or maximum duration of treatment, included studies must have followed participants for at least 28 days postrandomisation to assess outcomes. Crossover trials and studies conducted on paediatric populations will not be eligible.

Categorisation of studies

For improved interpretability and better decision-making thereby, IOP-lowering eyedrop arms will be categorised. According to the study aim, the proposed NMA has been categorised 12-fold: (1) BP prostaglandin analogue, (2) BP beta-blocker, (3) BP alpha-2 adrenergic agonist, (4) BP carbonic anhydrase inhibitor, (5) AP prostaglandin analogue, (6) AP beta-blocker, (7) AP alpha-2 adrenergic agonist, (8) AP carbonic anhydrase inhibitor, (9) PF prostaglandin analogue, (10) PF beta-blocker, (11) PF alpha-2 adrenergic agonist and (12) PF carbonic anhydrase inhibitor. The reference arm, meanwhile, will include participants either untreated or placebo-treated.

Information sources

RCTs will be searched within three electronic databases (Cochrane Central Register of Controlled Trials, Embase and MEDLINE) without any limitation as to the publication date. The WHO International Clinical Trials Registry Platform and ClinicalTrials.gov will also be screened to identify unpublished studies and minimise potential publication and selection biases.

Search strategy

We developed our search strategies with the assistance of an academic librarian, an expert in systematic review; we based them on established terminology, such as MeSH (Medical Subject Headings) and Embase search terms, as available. The keywords included were: *benzalkonium chloride, preservative and glaucoma*. The search strategy was initially developed for the MEDLINE database and then adjusted to meet the other databases' conditions. The full-search strategies are provided in the online supplemental appendix 1.

For prospective identification of systematic reviews and meta-analyses (the reference lists of which might include potentially relevant studies) missed by the electronic searches, manual searches will be conducted. The analysed studies, regardless of language, publication date or country, will include data on IOP-lowering eyedrops. The planned overall start date for our study is 1 March 2024,

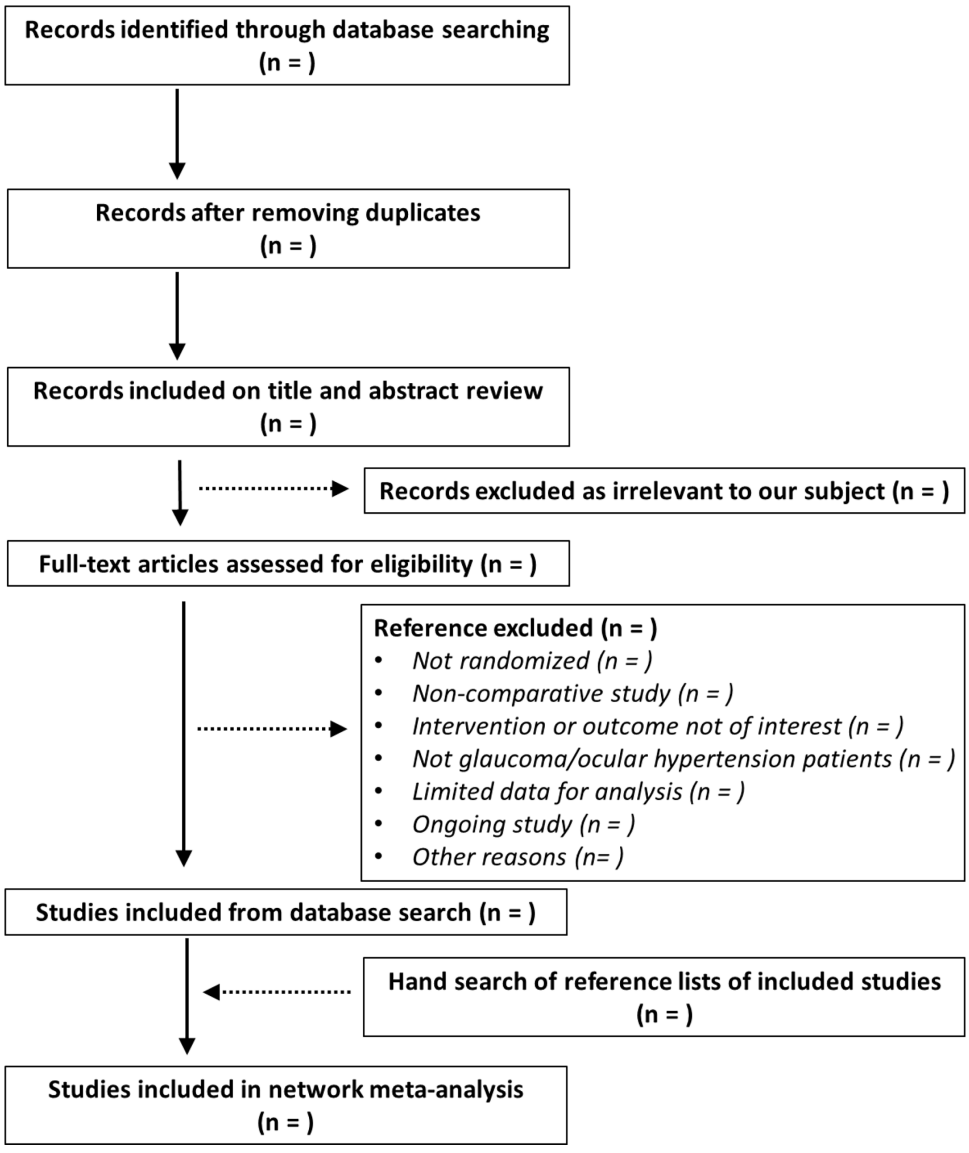

Figure 1 PRISMA flow diagram of study-selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

and the finish date will be within 6 months of the start date.

Selection process

Two reviewers will review independently screen titles and abstracts to identify potentially eligible studies. For each study thus identified, the two reviewers will review its full text, again independently. A third reviewer will resolve any disagreements in either the first or the second stage indicated above. For multiple-paper studies, the paper with the most comprehensive effectiveness analysis will be selected. A PRISMA flowchart will outline the complete stepwise process (figure 1).

Data collection and management

For missing data, we will attempt to obtain more information from the original authors. In the absence of a reply, we will try to calculate the data through the available coefficients according to the Cochrane Handbook for Systematic Reviews.[16] Whenever necessary, we will approximate means and measures of dispersion from plots.[17]

For study data extraction and recording, the two reviewers will employ a standardised extraction table to which all of the authors pre-agree (online supplemental appendix 2). Data will be independently extracted by two investigators in a masked manner and entered electronically into Microsoft Access 2016 (Microsoft Corporation). Conflicting data entries will be identified using algorithmic methods and resolved through discussion.

Data items

The extracted data will include the following: (1) study characteristics (author, year, country, etc), (2) participant characteristics (sample size, age, sex, race, etc), (3) glaucoma types (primary open-angle glaucoma, normal-tension glaucoma, ocular hypertension) and (4) glaucoma stage. Means and SDs of the primary outcome

(ie, IOP) measured at the baseline, as well as the time points after, and closest to, the end of the treatment, will be extracted in order to accommodate predicted variation in cross-study treatment duration. Where studies report more than two medications (or control groups), both of which could have been included in the NMA independently, all study-arm data will be extracted. For example, if one RCT has three treatment arms (A, B and C), all three arms' data will be extracted. If feasible, we plan to collect data related to ocular surface status (such as tear breakup time or corneal staining results) and patient adherence.

For primary outcomes for which mean±SE is reported, SDs will be calculated by the formula, $SD=SE\times\sqrt{n}$. Where there are reported medians and IQRs, the methods reported by Wan *et al* will be employed for computation of both means and SDs.[18] Where means and 95% CIs are reported, SDs will be calculated according to the formula, $SD=\sqrt{n}\times$ (upper 95% CI limit−lower 95% CI limit)/t, t being the t-distribution value for the 95% CI of a sample distribution having degree of freedoms equal to the group sample size −1. If a paper does not provide sufficient data, that information will be obtained, where possible, from the author. All of the extracted data will be tabulated.

Outcomes and prioritisation

The primary outcome will be IOP change of the given glaucoma eyedrops from the baseline to the follow-up, as measured in each study. The secondary outcomes will be ocular surface status and patient adherence, as assessed by discrete data.

Risk of bias (ROB) in individual studies

The two independent reviewers will assess the included studies' internal validity (ie, risk of bias (ROB)) using a tool revised for assessment of ROB in randomised trials.[19] A third reviewer will resolve any inter-reviewer inconsistencies. We will conduct a sensitivity analysis by excluding results with a high ROB from the ROB assessment to determine whether consistent results can be obtained for the primary outcome.

Data synthesis

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

Assessment of transitivity and meta-biases

For all medication comparisons 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 evidence types.

To assess the transitivity assumption, we will analyse the distribution of the following potential effect modifiers and evaluate whether subgroup analyses produce differing results: (1) age, (2) baseline IOP, (3) geographical region, (4) type of glaucoma and (5) glaucoma stage. Additionally, potential effect modifiers will be examined using a multivariable meta-regression model,[20 21] where applicable.

Network meta-analysis (NMA)

Frequentist NMA will be conducted assuming cross-study similarity of the effect-modifier distribution. After obtaining all of the network's available evidence, calculation of pairwise effect sizes will be performed.[22] For treatments not already compared in a pairwise RCT, effect measures will be compared indirectly by application of a common comparator.[8 23 24] Given the potential for heterogeneity both within and between studies, the pooled standardised effect sizes will be calculated using a random-effects model. The corrected effect size (Hedges' g) will be employed in order to allow smaller studies to be included.[25] For ranking of mixed (ie, direct and indirect) effect sizes and 95% CIs for all treatment combinations in the network, we will employ network forest plots, interval plots and league tables.

In cases where disconnected networks occur, we will analyse the connected and disconnected networks separately, presenting the results for each subnetwork independently. Additionally, for treatments in the disconnected parts of the network, we will perform standard pairwise meta-analyses using available direct comparison data.

We will report heterogeneity based on 95% prediction intervals and I^2. Forest plots will be examined visually so as to identify any apparent inconsistency between the effects of direct and indirect treatment (loop consistency); any such inconsistency could be indicative of non-satisfaction of the transitivity assumption. In cases where significant heterogeneity is detected, the node-splitting approach will be used to evaluate inconsistency by comparison.[26] Additionally, we will assess funnel plot asymmetry visually and apply statistical methods, such as Egger's test, to detect small-study effects, which may indicate publication bias.[27 28] If publication bias is suspected, we will clearly state its detection and discuss the potential impact on the results. Sensitivity analyses, such as trim-and-fill analysis, will be performed to estimate the adjusted effect size after accounting for missing studies.[29] We will emphasise that the presence of publication bias limits the reliability and generalisability of the findings.

Confidence in cumulative evidence

The Confidence in Network Meta-Analysis (CINeMA) approach will be used to assess overall evidence quality based on study limitations, imprecision, indirectness, heterogeneity and publication bias. CINeMA is derived from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, but with differences both in conception and in semantics.[30] It accounts for six domains: (1) within-study bias (ie, impact of ROB in included studies); (2) reporting bias (ie, publication and other reporting bias); (3) indirectness; (4) imprecision; (5) heterogeneity and (6) incoherence.[31] For both within-study bias and indirectness, the reviewer's input is required at the study level. To each of these domains, CINeMA renders one of three judgements (no concerns, some concerns, major concerns) based on user-defined rules. Also, summarised cross-domain judgements will indicate one of four confidence levels for each relative treatment effect, which levels will correspond to the standard GRADE assessments (very low, low, moderate, high).

Statistical analyses

In all of the statistical analyses, the statistical package R will be used. To address within-study correlation, we will reweight all comparisons in multi-arm studies by back-calculating variances using the Laplacian matrix and its pseudoinverse. This will be performed using the 'netmeta' function in R.[32] The visual nodes-and-connections network will be created using the netmeta package's forest.netmeta function.

The analysis outcomes will be ranked using P-scores, a commonly used metric analogous to the surface under the cumulative ranking curve.[12 33] The P-score, ranging between 0 and 1, reflects the probability that a given treatment is among the most effective. To support clinical decision-making, we will present the mean reductions in IOP in mm Hg at 1 and 3 months, ordered from the most to least effective treatments based on the P-scores.

Sensitivity analysis

To ensure the robustness of our results, the following sensitivity analyses will be performed: (1) excluding studies with a high ROB, (2) including only studies reporting IOP outcomes after at least 3 months of treatment, (3) excluding studies that include patients with a history of previous laser or surgical interventions and (4) excluding studies with missing data.

Patient and public involvement

No patients or other members of the public will be involved directly in the study; rather, only already-reported data in the literature, with the aforementioned sources, will be used.

DISCUSSION

A systematic review and an NMA comparing the efficacy and safety of BAK-preserved, AP and PF eyedrops in glaucoma treatment will hold significant clinical implications. Glaucoma management relies heavily on topical medications to lower IOP, but the preservatives in these formulations, particularly BAK, have been associated with ocular surface damage, inflammation and reduced patient compliance. Future findings from such a study could provide valuable insights into whether alternative preservation methods or PF formulations offer comparable efficacy with improved safety profiles.

The potential results of this research could assist clinicians in tailoring treatment choices for patients, especially those with ocular surface disorders or those using multiple medications. Furthermore, this study could guide the development of clinical guidelines and support the formulation of PF or AP medications as viable options, ultimately improving patient adherence and quality of life. On a larger scale, these findings could influence the pharmaceutical industry to prioritise safety in glaucoma treatments, fostering advancements in drug development and patient-centred care.

Ethics and dissemination

As this work will only synthesise already-published evidence, no ethics review or approval will be required. Upon write-up of its findings and results, which will be reported based on the PRISMA statement and PRISMA-NMA guidelines, a paper will be submitted to a peer-reviewed journal for publication.

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Contributors MK, SR and AH conceived and wrote the paper. AH and MK developed the search strategy and evaluated the protocol. YKK and SR designed the study and revised the protocol. All of the authors read the protocol and have given their final approval for publication. The guarantor of the study is AH who accepts full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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