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Comparative effectiveness of interventions for improving adherence to ocular hypotensive therapy in patients with glaucoma or ocular hypertension: protocol for network meta-analysis

Mirinae Jang,[1] Sung Ryul Shim ,[2] Ahnul Ha,[3,4] Young Kook Kim [1,5]

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AH and YKK contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Professor Young Kook Kim; md092@naver.com and Professor Ahnul Ha; zzammy486@gmail.com

ABSTRACT

Introduction Poor medication adherence is an important issue in healthcare. Various types of interventions for improved adherence to ocular hypotensive therapy have been proposed, though evidence on the effectiveness of any isolated intervention remains limited. The current protocol is an ongoing network meta-analysis (NMA) design that enables comparative investigation of any and all interventions for which there are available randomised controlled trials (RCTs). Our aim is the systematic comparison of the efficacy of different types of adherence interventions for patients suffering from glaucoma or ocular hypertension (OHT).

Methods and analysis Studies of interest will assess the effects of any interventions on medication adherence in adults (age ≥18 years) with either glaucoma or OHT. Four electronic databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE and Scopus) will be searched for RCTs published in any language, without any time limitation. First, titles and abstracts, and then full-text papers, will be screened by two reviewers, who will extract the useful data. The primary outcome measure is an intervention's impact on adherence. The two reviewers will also assess, using the relevant domain-based risk-of-bias assessment tool, the internal validity of the studies. The overall quality of the evidence will be assessed by the Confidence in Network Meta-Analysis approach, and will be summarised with network diagrams. To allow for assessment of both direct and indirect evidence, a contribution matrix will be used. For visualisation of the effects of all of the included interventions, forest plots will be constructed. Pairwise effect sizes will be calculated according to all of the evidence available in the network.

Ethics and dissemination This work will synthesise evidence from already published studies and, as such, will not require an ethics review or approval. A manuscript 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 use of a network meta-analyses (NMA) design should enable comparative investigation of all available adherence interventions for which randomised controlled trials are available.
- This NMA could potentially allow for generation of a hierarchy of interventions for improving ocular hypotensive therapy adherence that is clinically meaningful.
- This work could not exclude the potential influence of different trial-defined adherence criteria.
- The sample size and the number of included studies may be inadequate, and, as a result, the network of intervention arms may not be formed.

INTRODUCTION

Poor medication adherence most often leads to increased resource utilisation, owing to a reduction in effectiveness and an associated increase in the risk of therapeutic failure.[1] Treatment failure may necessitate waste of unfinished pharmaceutical supplies, increased healthcare expenditure and risk to the patient if subsequent surgical intervention is required. Medication adherence is a significant healthcare issue, particularly for patients with chronic diseases such as glaucoma or ocular hypertension (OHT). The treatment for glaucoma or OHT entails the lowering of intraocular pressure (IOP) to prevent disease progression. Patients with glaucoma or OHT have been deemed to be adherent if they had ≥292 days with an IOP-lowering medication (ie, ocular hypotensive therapy) supply over the 365-day assessment period (equivalent to the proportion of days covered ≥0.80).[2 3] Research from a systematic review indicates that the prevalence of

non-adherence to ocular hypotensive therapy ranges from 23% to 60% over 12 months.[4] Simplifying eye drop regimes, providing adequate information, teaching drop instillation techniques and ongoing support according to patient need have been getting attention for their potential positive effects on improving adherence to ocular hypotensive therapy.

Two systematic reviews already have examined the effectiveness of adherence interventions for patients with glaucoma or OHT.[5 6] They indicate that whereas complex interventions in the form of patient education combined with personalised behavioural change (eg, tailoring of daily routines for promotion of adherence to eye drops) may improve glaucoma medication adherence, overall there is still insufficient evidence for recommendation of any particular intervention. Traditional (meta-analytical) pairwise investigation of those isolated interventions proved impossible, as they varied by study, and randomised controlled trials (RCTs) were insufficient in number to evaluate each of the different intervention types.

Drawing conclusions on the comparative effectiveness of different adherence interventions based on individual RCTs and systematic review is difficult. Traditional meta-analyses, moreover, are limited by the relative unavailability of pairwise comparisons of interventions.[7] It is difficult, therefore, to interpret the entire body of evidence available, many RCTs being available for only some interventions, and the evidence being limited for some others. Furthermore, for many types of adherence interventions, there are no available direct comparisons.

Network meta-analysis (NMA) is a study design that allows for investigation of the efficacy of different interventions.[8 9] Creation of a network of pairwise RCTs enables use of all direct and indirect evidence for determination of such efficacy.[10] NMA makes possible the comparative analysis of all adherence interventions for which there are available RCTs, unlike traditional systematic review and meta-analysis, which can analyse only two. Furthermore, with this design, the efficacies of available interventions can be ranked.

The protocol presented in these pages describes an ongoing NMA design for systematic comparison of the effectiveness of different intervention types for improved adherence to ocular hypotensive therapy among adult patients with glaucoma or OHT. The main research question was: What are the efficacies of different types of interventions for adherence? The above-alluded-to objective—to evaluate the efficacies of different types of interventions—will allow for generation of a hierarchy of interventions that is clinically meaningful.

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for protocols (PRISMA-P) is followed by this protocol.[11] The NMA results will be reported in accordance with the PRISMA statement and the PRISMA extension for NMA (PRISMA-NMA).[12 13] The research has been registered on PROSPERO.

Eligibility criteria

Studies eligible for inclusion in the NMA are those that are RCTs indicating the effects of any interventions on adherence to ocular hypotensive therapy by adults (age ≥18 years) with either glaucoma or OHT. Any intervention, control-treatment or no-treatment group will be included as a comparator. Studies reporting secondary results (eg, intraocular pressure and visual field test results) other than adherence also will be included. Any studies for inclusion need to be available in the full-text format. Studies reporting on subjects younger than 18 years of age or non-human subjects, along with those assessed as high risk of bias, will be excluded.

Categorisation of studies

To improve interpretability and thereby support decision making, we will group the intervention arms using categories. By an iterative process entailing review of relevant RCTs and discussion, 12 categories for the present NMA were identified: (A) standard of care, (B) enhanced standard of care, (C) interacting education, (D) motivational interview and behaviour change counselling, (E) multimedia education, (F) tailored care, (G) physician education, (H) printed material, (I) short message service, (J) provision of the patient's own medical records, (K) incentives and (L) telephone call. The control arm will be the standard of care (ie, if only the instructions by the healthcare provider at treatment initiation regarding how to take ocular hypotensive medication are provided, without any intervention for improving adherence to the medication).

Information sources

Four electronic databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE and Scopus) were searched for RCTs, with no time limitation.

Search strategy

With the assistance of a medical librarian, a six-part search strategy including terms by which to identify studies relevant to (1) glaucoma, (2) OHT, (3) OHT therapy, (4) intervention, (5) adherence and (6) RCTs was developed. The keywords included were *glaucoma, ocular hypertension, medication, adherence and compliance*. The search terms were based on the established terminology, and the extensive Medical Subject Headings (MeSH) and Embase search terms were employed when available. The search strategy was developed for the MEDLINE database and then adjusted to meet the conditions of the other databases. The full search strategies are provided in online supplemental file.

For prospectively identified systematic reviews and meta-analyses, the reference lists of which may include potentially relevant studies, manual searches will be conducted to identify any of those missed by the electronic searches. The studies that are analysed will include data on types of

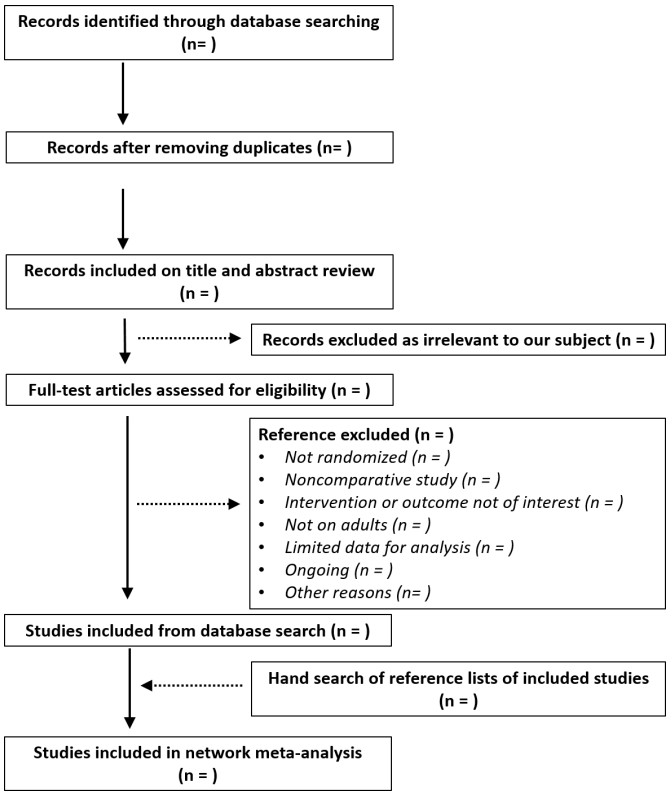

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection process.

intervention and improved adherence to OHT therapy, regardless of the language, publication date, country or study design.

Selection process

Two reviewers will each independently screen titles as well as abstracts so as to identify potentially eligible studies. For each identified study, the two reviewers will then independently review the full-text papers. In either of these two stages, a third reviewer will be brought in to resolve any disagreements. The inter-rater agreements will be reported in terms of Cohen's kappa coefficient (κ). For studies that have been reported in multiple papers, the paper that reports the most complete effectiveness analysis will be selected (ie, reports on either subgroup or secondary analyses will be excluded). The entire stepwise process will be presented using a PRISMA flow chart (figure 1).

Data collection and management

The two reviewers will use a standardised extraction table agreed to by all of the authors to extract and record study data.

Data items

The extracted data will include study characteristics (author, year), participant characteristics (sample sizes, age, sex, type of glaucoma, proportion of open-angle glaucoma), types of intervention on adherence, duration, frequency and intensity and timing of follow-up assessment. Means and SDs of primary outcome measures at baseline, as well as the time points after and closest to the end of the treatment will be extracted, so as to accommodate predicted treatment-duration variation across studies. Although there is no current consensus on the appropriate duration of adherence interventions, it is expected that most interventions will fall somewhere between 4 and 12 weeks. Given the potential differences in the treatment durations, this second time point will allow for an investigation that ensures completion of the treatment regimen and will likely be the point of maximal therapeutic effect.

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

For primary outcomes where mean±SE are reported, SDs will be calculated using the formula: $SD=SE\times\sqrt{n}$. Where medians and IQRs are reported, the methods described by Wan *et al* will be used for computation of means and SDs.[14] Where means and 95% CIs are reported, SDs will be calculated according to the formula: $SD=\sqrt{n}\times(\text{upper 95\% CI limit} - \text{lower 95\% CI limit})/t$, t being the value from a t-distribution for a 95% CI for a sample distribution having df equal to the group sample size −1. If a paper does not provide sufficient data, they will be obtained from the corresponding author if possible. Extracted data will be tabulated.

Outcomes and prioritisation

The primary outcome is degree of adherence to ocular hypotensive therapy, measured as defined in each study, including but not limited to patient interviews, questionnaires, patient diaries or electronic monitoring devices. This includes dichotomous (success/failure), nominal (reasons for non/poor adherence) and discrete data (proportions of missed doses over a specific time period). The secondary outcome measure is the persistence with therapy as measured by repeat prescriptions (prescription refill) or dispensing counts, or both. This includes dichotomous (success/failure) and discrete data (proportions of uncollected prescriptions over a specific time period).

Risk of bias in individual studies

The two reviewers will assess the internal validity (ie, risk of bias) of the included studies according to the relevant domain-based risk-of-bias assessment tool, and the results will be presented in a graphical format further to the The Cochrane Handbook recommendation. A third reviewer will be brought in to resolve any disagreements. The inter-rater agreement will be reported based on Cohen's kappa coefficient (κ).

Data synthesis

The included trials' characteristics (ie, type of glaucoma, details of intervention on adherence, outcomes) will be both summarised and tabulated. The summarisation will entail the use of a network diagram, each node in which will represent an intervention class (as categorised in the inclusion criteria), the node size being proportional to the number of patients who are receiving the treatment. The effects of the pairwise comparisons of the two interventions will be shown as edges that interconnect the nodes, the thickness of the edge lines representing the pairwise comparison weight. A contribution matrix will be included to indicate the influence of the individual comparisons as well as the influence of the direct and indirect evidence on the overall effects summary. If quantitative synthesis is not appropriate, we will conduct a narrative synthesis.

Assessment of transitivity and meta-biases

It is expected that all of the interventions on adherence that are identified in the preliminary search will be in-principle jointly randomisable, which attribute will meet the transitivity assumption. For all of the comparisons between interventions in the network, the inferences will be based on direct evidence (pairwise RCTs), indirect evidence (effect B–C derived from A–B and A–C comparisons) or a mixture of both direct and indirect evidence. And, to meet the transitivity assumption, measures that potentially could modify effects such as sex, age, glaucoma type and the distributions of these variables will be inspected.

Network meta-analysis

Assuming that the distribution of the effect modifiers is similar across studies, a frequentist NMA will be performed (see the proposed closed network geometry in figure 2). Pairwise effect sizes will be calculated after including all of the evidence available in the network.[15] If outcome data on the different intervention durations and frequencies are available, their effectiveness for adherence will be investigated. Effect measures for treatments not already compared in a pairwise RCT can be indirectly compared by using a common comparator to contrast the comparisons' effect sizes.[7 16 17] Considering that interventions may vary for certain characteristics, the sample used in each study might slightly differ; thus, a random effects model will be employed to generate pooled standardised effect sizes. Corrected effect size (Hedges' g) will be used in order to allow for inclusion of smaller studies.[18] Network forest plots, interval plots and league tables will be used to rank the mixed (direct and indirect) effect sizes and 95% CIs for all treatment combinations in the network.

Detection of heterogeneity and assessment of inconsistency

Heterogeneity will be reported using 95% prediction intervals and I^2. Forest plots will be visually examined so as to identify any obvious inconsistency existing between direct and indirect treatment effects (loop consistency); any observed inconsistency might indicate non-satisfaction of the transitivity assumption. In cases where significant heterogeneity is detected, inconsistency will be evaluated one comparison at a time using the node-splitting approach.[19] Also, comparison-adjusted funnel plots will be employed for visual inspection and assessment of small-study effects as well as assessment of potential publication bias.[20]

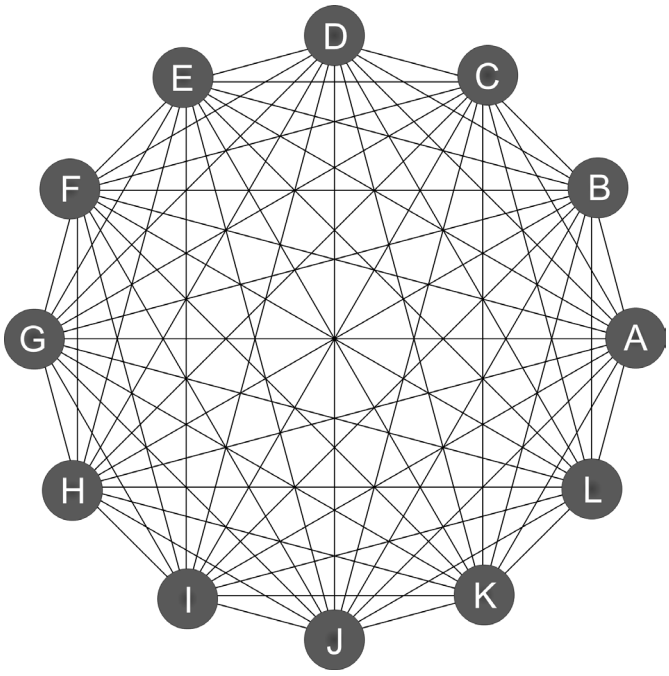

Figure 2 All possible network connections (pairwise comparisons, lines) with 12 nodes (interventions, A–L: (A) standard of care, (B) enhanced standard of care, (C) interacting education, (D) motivational interview and behaviour change counselling, (E) multimedia education, (F) tailored care, (G) physician education, (H) printed material, (I) short message service, (J) provision of the patient's own medical records, (K) incentives and (L) telephone call).

Confidence in cumulative evidence

Based on study limitations, imprecision, heterogeneity, indirectness, and publication bias,[21] the overall quality of evidence will be assessed by the Confidence in Network Meta-Analysis (CINeMA) approach, which is broadly based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, but with a number of conceptual and semantic differences.[21] It covers six domains: (1) within-study bias (impact of risk of bias in included studies), (2) reporting bias (publication and other reporting bias), (3) indirectness, (4) imprecision, (5) heterogeneity and (6) incoherence.[22] The reviewer's input is required at the study level for within-study bias and indirectness. Then, by applying user-defined rules, CINeMA assigns, to each domain, judgements at three levels (no concerns, some concerns, major concerns). Such judgements across domains are summarised in order to obtain four levels of confidence for each relative treatment effect, which levels will

correspond to the standard GRADE assessments (very low, low, moderate, high).

Statistical analyses

Statistical package R will be used in all of the statistical analyses.[23] The netmeta R package will be used to perform and report the NMA. P-scores will enable the treatment efficacy ranking. The netmeta package function forest. netmeta will be employed to create the visual network of nodes and connections.

Patient and public involvement

No patients and members of the public will be directly involved. Only data already existent in the literature and the aforementioned sources will be used for this study.

ETHICS AND DISSEMINATION

This work will synthesise evidence from already published studies, and as such, will not require an ethics review or approval. A manuscript presenting the findings will be submitted to a peer-reviewed scientific journal for publication; the results will be reported in accordance with the PRIMSA statement and the PRISMA-NMA guidelines. We will update this protocol required in the future and the date of amendments and description of changes will be presented as a supplement. Also, important protocol amendments will be documented and updated on PROSPERO.

Author affiliations
[1]Department of Ophthalmology, Seoul National University Hospital, Seoul, South Korea
[2]Department of Preventive Medicine, Korea University College of Medicine, Seoul, South Korea
[3]Department of Ophthalmology, Jeju National University Hospital, Jeju-si, South Korea
[4]Department of Ophthalmology, Jeju National University School of Medicine, Jeju-si, South Korea
[5]Department of Ophthalmology, Seoul National University College of Medicine, Seoul, South Korea

Contributors MJ conceived the content and wrote the paper. SRS and AH developed the search strategy and evaluated the protocol. YKK designed the study and revised the protocol. All the authors read the protocol and have given the final approval for publication.

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ORCID iDs
Sung Ryul Shim http://orcid.org/0000-0003-4143-7383
Young Kook Kim http://orcid.org/0000-0002-6037-8449

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