A Systematic Review Protocol Evaluating the Efficacy and Safety of Ayurvedic Interventions for Glaucoma

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**ABSTRACT**

Introduction: The features of glaucoma have similarities with those of Adhimantha as mentioned in Ayurveda, where it exhibits features based on the Doshas involved. The aim of this study is to conduct systematic review of published studies in view of safety and efficacy of Ayurvedic interventions in the management of glaucoma and to run meta-analysis of the published clinical data if sufficient homogeneous studies are available.

Materials and methods: This systematic review process would include review of randomized controlled trials (RCTs), quasi-experimental designs, multiple arms clinical trials and observational studies (case series and case control) on the management of glaucoma or Adhimantha through Ayurvedic interventions. Interventions and procedures administered from a minimum of 7 days to maximum of 6 months will be included. Electronic databases search through Ayurvedic research databases and medical journal databases such as MEDLINE, Web of Science, Cochrane register, Scopus, EMBASE, directories of open access journals and hand searching will be done using predefined search terms to identify relevant studies which would include studies done between January 1990 and January 2020. The study selection, data extraction, analysis, and synthesis of results will be done by three researchers. Study selection will follow the symptomatology of Adhimantha/glaucoma as explained in different classical texts of Ayurveda, and the quality of studies will be assessed by the Cochrane risk of bias assessment for RCT and non-RCTs. The heterogeneity of reviewed studies will be evaluated by examining forest plots, and meta-analysis will be planned by using quantitative synthesis if they are sufficiently homogeneous.

Ethics approval: Formal ethical approval is not necessary as the primary data of patients will not be collected. The final results of the review will be disseminated through a peer-reviewed publication.

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Keywords: Adhimanta, Ayurveda, Glaucoma, Intraocular pressure, Systematic review.


**INTRODUCTION**

The term glaucoma does not define a disease entity but embraces composite features of pathological conditions which have the common features of their clinical manifestation that are more or less dominated by the raised intraocular pressure (IOP) and its consequences.¹ It is primarily characterized by optic nerve head cupping and visual-field damage which may lead to irreversible blindness. The prevalence in people aged 40 years or more is about 3–5%, and the progression may be stopped by reducing the IOP by 30–50% from baseline. The global prevalence of primary open-angle glaucoma is about 3.1%, and of primary angle-closure glaucoma is 0.5% which is six times more common than the former. The current treatment of glaucoma is to lower IOP based on topical medications, laser therapies, and finally surgical intervention if other therapeutics fail to prevent its progression.² Hence, it was found that there is a need for a potent alternative treatment protocol that can tackle the condition with minimal or no untoward effects. In Ayurveda, there is a detailed description of the causes, risk factors, pathogenesis, clinical features, and management of glaucoma wherein its features are having similarities with those of Adhimantha, a clinical condition described under Sarvagata Netra Roga according to Acharya Sushruta¹ and Sarvakshi Roga⁴ as mentioned by Acharya Vagbhaṭa. The patients here usually present with excessive churning type of pain in eyes. The pain is so severe that the patient feels as if his or her eye is pulled out from orbit and churned along half of the head. If this condition is neglected or improperly treated, it may lead to loss of vision within certain period based on the Doshas involved.⁵ The scientific world has started to look forward to alternative or traditional system of medicine as an effective adjunctive therapy to minimize the adverse events caused by the therapeutic interventions in glaucoma. Inspite of a plethora of research works on Ayurvedic interventions in glaucoma, an evidence based data generated through extensive systematic review is lacking. Thus, a systematic review protocol has been developed, which follows the preferred reporting items for systematic reviews and meta-analyzes protocols (PRISMA-P)⁶ checklists as guidelines. The reviewers will adhere to this protocol to substantially review and synthesize published studies focusing on

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the safety and effect of Ayurveda interventions for the management of glaucoma.

**Materials and Methods**

This review study followed the PRISMA checklist as guidelines to review and synthesize results.

**Types of Study**

This systematic review will include randomized controlled trials (RCTs), quasi-experimental designs, and multiple arms clinical trials and observational studies (case series and case control).

**Types of Participants**

The studies that involve cases fulfilling the diagnostic criteria based on symptomatology of Adhimantha explained in different classical texts of Ayurveda and glaucoma, belonging to either sex and use of Ayurveda interventions, polyherbal, herbomineral, metallic preparations with the intent of cure or as add-on will be included. The studies involving laboratory or nonhuman experiments, healthy volunteer studies of antiglaucoma drugs, studies including cases of glaucomatous blindness, or any complications of glaucoma or cases that require surgical interventions, etc. will be excluded from the review process.

**Types of Interventions**

Ayurvedic interventions with any dose, type, schedule, drug, dosage form, lifestyle modifications, and Pathyapathya (dietary restrictions) and patients receiving additional non-Ayurveda interventions for a duration of at least 7 days and maximum up to 6 months in all groups of study are also included.

**Comparators/control**

- Ayurveda treatment (Shamana or and Shodhana) with different dose, type, schedule, medicine, medicine form as compared to intervention(s)/exposure(s).
- Placebo and/or sham therapy and/or Shamana therapy and/or non-Ayurveda interventions.

**Types of Outcome Measures**

The following outcome measures will be assessed,

**Primary Outcomes**

- Response to treatment (improvement in subjective and/or objective criteria of assessment)
- Serious adverse events (resulting in the loss of vision, disability, or complications led to hospitalization).

**Secondary Outcomes**

- Withdrawals due to adverse events or inconvenience of therapy/treatment.
- Reported improvement in the participants’ health-related quality of life.

**Timing and Effect Measures**

No restrictions will be made in inclusion of study in review on the basis of outcomes mentioned above. Timing and effect measures, administration timings vary from 7 days to 6 months as different categories of medications are included for review.

### Identification of Studies

**Search Methods**

**Electronic search:** The following databases will be searched for analysis such as complementary and alternative medicine (CAM) databases, HerbMed, Cochrane Complementary Medicine trial register, annotated bibliography of Indian medicine (ABIM), Web of Science, MEDLINE via PubMed, PubMed Central, Cochrane Register, National Institute of Science Communication and Information Resources (NISCAIR) and NISCAIR online periodicals repository (NOPR), IndMED, SCOPUS, EMBASE, Directory of Open access journals (DOAJ), Google Scholar, DHARA (digital helpline for ayurveda research abstracts), and AYUSH research portal, clinical trial registry of India-ctrl.nic.in, for dissertations in public domain: http://shodhganga.inflibnet.ac.in/simple-search will be used.

**Hand searching:** Hand searching for studies that are not indexed in any electronic database are also done. In such case, Ayurvedic research database (ARD)-https://www.ayurvedahealthcare.info/content/ayurveda-research-database-ard, and conference proceedings/reports/compendia’s/Grey literatures/Bibliographies/Souvenirs will be searched. If required, the library resources of other universities/institutions will also be utilized after taking due permission from the authorities. There will be no language restrictions. Studies published between January 1990 and January 2020 will be sought.

**Search Strategy (for Electronic Search)**

Initially, the search will be verified in database using MeSH terms and key words. Population, intervention, control/comparison, outcome and study design (PICOS) strategy will be used for searching the database as it helps us to narrow the search items which include terms such as (Ayurveda OR Ayurvedic therapy OR Ayurvedic treatment OR Herbal Ayurveda OR Ayurvedic Interventions OR Polyherbal OR Kiya kalpas OR Tarpana OR Putapaka OR Seka OR Ashchyotana OR Bidalaka OR Pindi OR Anjana OR Panchakarma OR Rasaudshadhi OR Rasakalpa OR Herbo-mineral OR Metallic OR Mercurial OR Plants OR Herbs OR Madhu OR Traditional Medicine OR Alternative Medicine OR Complementary Medicine OR Massage OR Shirodhara OR Leech OR Basti OR Vamana OR Virechana OR Nasya OR Sirayadhana OR Jalaibaka OR Lepa OR Vati OR Gutri OR Kwatha) OR AND (Glaucoma OR Vataja, Pittaja, Kaphaja, Raktaja Adhimantha OR Hathadhimantha OR Sarvakshi Roga OR SarvagataNetra Roga OR Siravyadhana OR Jalauka OR Lepa OR Vasaka OR Vatika OR Shirodhatu OR Vata OR Pitta OR Kapha OR Raktavaha) OR AND (Glaucoma OR Vataja, Pittaja, Kaphaja, Raktaja Adhimantha OR Hathadhimantha OR Sarvakshi Roga OR SarvagataNetra Roga OR Best corrected visual acuity (BCVA) OR Tonometry OR Intra Ocular Pressure (IOP) OR Perimetry OR OCT OR Quality of life) AND (Clinical Trial OR Clinical Studies) as title, abstract, or key word will be used. In order to relocate the studies and further enhance the systematic search of available literatures, a filter will further be added after the PICOS search strategy that included the terms such as AND (randomized controlled trial OR clinical trial OR nonrandomized controlled trial or case series or case studies). There will be no restrictions in language.

**Data Collection and Analysis**

Inclusion of selected studies will be done independently by two reviewers initially by assessing the abstracts, and if found eligible, as per the inclusion and exclusion criteria the full article will be included for review process. Trial reports will be examined for multiple publications and the excluded studies will be documented with reason for their exclusion.
Quality Assessment
Jadad score will be used for all selected articles to monitor their quality based on evaluation of allocation concealment and data analysis along with Jadad score.\(^7\) The bias will be minimized by individual assessment by all the three reviewers.

Data Extraction and Management
The data extraction form prepared by Cochrane will be extracted independently by two of the authors (BMB and MNS) and resolve disagreements before analysis through discussion. The unclear or inadequate reported data will be clarified by two of the authors (BMB and MNS) by contacting the corresponding authors through e-mail or telephone. Two reviewers (BMB and MNS) will summarize the data from the included studies. Any disagreements in this will be fixed by a third investigator (RN).

Assessment of Risk of Bias
Risk of bias will be assessed based on Cochrane risk of bias tool, which includes domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting and other sources of bias.\(^8\) Based on this, the quality of the study will be termed as low, unclear, or high risk of bias.

Data Analysis
The data will be analyzed using appropriate software by the investigators and statistician. Relative risks, arithmetic means, and standard deviations will be used for dichotomous data and continuous data, respectively, and the summarized data will be combined by using weighted mean differences with 95% confidence intervals. Forest plot will be used to assess heterogeneity among trials and using the \(I^2\) test with a value of 50% will be used to identify the levels of heterogeneity. Random effect model will be used if meaningful to combine studies. The heterogeneity of results, quality of methodologies used, and publication bias will be done using funnel plot.\(^9\)

Data Synthesis
Methodological heterogeneity between studies will be explored, and meta-analysis will be planned if sufficient studies are identified and included.

Ethics Approval
Ethical approval is not required as patients are not involved in this study. The results of the review study will be published through a peer-reviewed publication.

Discussion
Although numerous works are done on this area, there is lack of review studies that systematically investigate the available works that can help in generalizing the findings despite acknowledgment that they are in a distinct attempt on conceptualizing the facts of etiology, pathogenesis, and literature review, rather than management aspect as a whole.\(^10\)-\(^14\) Hence, it was very much necessary to refine the existing studies and update its findings. Owing to the complexity of definitions of glaucoma mentioned in Ayurveda, and interventions involved, paucity of results obtained, and the difficulty in identifying high-quality studies, there were numerous key challenges experienced while formulating this protocol. Hence, a flexible approach together with careful consideration was necessary in terms of search strategies and key words to ensure that good number of studies can be located with available best evidences. Further, a key strength of this review protocol is the use of standardized guidelines after appropriate trainings by incorporating different fundamentals, with a concrete framework and composition. Thus, this protocol will add on to our field where the research question can be answered appropriately. Nevertheless, this review will make sure in maintaining the transparency of the procedure by disseminating its protocol which has been proposed in evaluating the safety and efficacy of Ayurveda interventions for glaucoma.

References
हिन्दी सारांश
अधिमन्थ में आयुर्वेद औषधियों के प्रभावों और सुरक्षा का मूल्यांकन करने वाला एक सिस्टेमेटिक रिव्यू प्रोटोकॉल

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प्रस्तावना: ग्लूकोमा की विशेषताओं में अधिमन्थ के साथ समानताएं हैं जैसा कि आयुर्वेद में उल्लेख किया गया है जहां इसमें शामिल दोषों के आधार पर विशेष लक्षण प्रदर्शित होते हैं। इस अध्ययन में हमारा उद्देश्य आयुर्विदिक औषधियों के माध्यम से ग्लूकोमा के प्रभाव के लिए गुणवत्ता प्रमाणण उपलब्ध कराना है।

पद्धति और विश्लेषण: हम सभी रेंडमाइज़्ड किलिनिकल ट्रायल (आर्सीटी), ट्रायल डब्ल्यूरेंडमाइज़्ड किलिनिकल ट्रायल (सीटीटी), तीन रेंडमाइज़्ड किलिनिकल ट्रायल, मॅल्टीप्ल और सिंगल किलिनिकल ट्रायल की एक व्यवस्थित समीक्षा और औषधि लेने काल, प्रकार, अनुसूची, औषधि, शीषी, परिवर्तन और अत्यधिक अवधि पद्धति के माध्यम से ग्लूकोमा या अधिमन्थ के प्रभाव के लिए सिस्टेमेटिक रिव्यू (केस भंडारण और केस निवंत्रण) कर रहे हैं। औषधि लेने काल 7 दिन से 6 महीने या उससे अधिक तक होती है क्योंकि समीक्षा के लिए विश्लेषण क्षेत्र की औषधियों के समीक्षित हैं। इलेक्ट्रॉनिक डेटाबेस जैसे कि आयुर्विदिक रिसर्च डेटाबेस, मेडिकल, EMBASE, वेब ऑफ साइंस, कोन्नेक्टेड लाइब्रेरी, स्क्रीप्स, PsychiINFO, CINAHL, LILACS आदि की झोंक की जाएगी। अध्ययन का चयन, हेडा सारांश और सत्यापन तीन शोधकर्ताओं द्वारा स्वतंत्र रूप से किया जाएगा। अध्ययन के चयन हेतु आयुर्वेद के विश्लेषण शास्त्रीय ग्रंथों में वर्णित अधिमन्थ के लक्षण विज्ञान का अनुसरण किया जाएगा और अध्ययन की गुणवत्ता का मूल्यांकन पूर्ववर्ती (पूर्ववर्ती) के विषय में उदाहरण किया जाएगा। फॉर्स्ट प्लांट का निर्देश देता है इस की परीक्षण के बीच विषमता का मूल्यांकन किया जाएगा, जब सन्दर्भ यहाँ की पहचान की गई है और उन्हें शामिल किया गया है, तो अध्ययन की पद्धतिगत गुणवत्ता के आधार पर एक मेटा-विश्लेषण संबंध है। व्यक्तिगत परीक्षणों के लिए, जहां भी संभव हो, औसत अंतर (95% कॉन्फिडेंस इनटरवल) को सुनिश्चित किया जाएगा। यह अध्ययन में पर्याप्त सजीवता रहे हो तो मात्रात्मक संलेखण का उपयोग किया जाएगा।

नैतिकता और प्रसार: औषधि क्राउल या मैक्रुल अनुमोदन की आवश्यकता नहीं है क्योंकि प्राकृतिक डेटा एक मामला नहीं किया जाएगा। अध्ययन के परिणामों को पियर रिव्यू जर्नल में प्रकाशित कर प्रसारित किया जाएगा।

परीक्षण परिपथ पंजीकरण संख्या: PROSPERO 2019: CRD42019133911

कृप्या ध्यान दें: अधिमन्थ, आयुर्वेद, ग्लूकोमा, हेडा ओक्स्फोर्ड प्रेसर, व्यवस्थित समीक्षा