PROTOCOL

A Systematic Review Protocol for Assessing Efficacy and Safety of Ayurveda Medicine in Treatment of Allergic Rhinitis

Parth P Dave[1], Azeem Ahmad[2], Manohar S Gundeti[3]

Abstract

Introduction: A systematic review is planned to investigate the safety and efficacy of Ayurveda interventions for allergic rhinitis (AR) through analyzing published and unpublished clinical research.

Materials and methods: A systematic review of published clinical work or Ayurveda interventions for AR will be conducted. PubMed, AYUSH Research Portal, the Cochrane Central Register of Controlled Trials (CENTRAL), hand searches, snowballing of studies will also be performed to fetch complete available literature. Manual search includes Ayurveda postgraduate (PG) and doctor of philosophy (PhD) dissertations on the management of AR. The selection of the studies, data extraction, and synthesis will be performed independently by researchers, and a third reviewer will seek disagreements. Established guidelines for study selection, quality assessment, and narrative synthesis will be followed. Risk of bias assessment will be performed with the help of Cochrane risk-of-bias tool for randomized trials (RoB2) tool for randomized controlled trials (RCTs) and risk of bias tool to assess nonrandomized studies of interventions (ROBINS-I) tool for non-RCTs (NRCTs). Results of the study will be narratively synthesized and presented in count, percentage, and frequency. As this will be the first systematic review on this topic, outlining the protocol ensures transparency for the completed review. Patients will not be involved in any phase of the study; however, ethical approval has been received from the Institutional Ethics Committee (IEC).

Dissemination: The review is ongoing, and after completion, it will be published in a peer-reviewed journal. The study will be updated to inform and guide healthcare practice and policy.

Trial registration number: PROSPERO 2018 CRD42018107035.

Keywords: Allergic rhinitis, Ayurveda, Systematic review protocol.

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Introduction

Allergic rhinitis (AR) (*International Classification of Diseases* 10: J30), also known as hay fever is an immunoglobulin-E-mediated immune response of nasal mucosa to an aero-allergen in genetically predisposed individuals, which is characterized by bouts of sneezing, rhinorrhea, nasal blockage, nasal itching, and ocular symptoms. According to the World Health Organization, the global burden of AR was estimated to be 400 million,[1] and approximately 20 to 30% of the Indian population suffers from AR.[2] However, AR is not a life-threatening condition; it may worsen the quality of life. Conventional medicine consists of various groups of medicines for the management of AR, such as H1 receptor antagonists (antihistamines), mast-cell stabilizers, leukotriene receptor antagonists, and corticosteroids.[3] In real-life, a significant number of patients continue to experience bothersome symptoms despite adequate treatment.[4]

Based on the similarities in causes, signs and symptoms, and treatment, Ayurveda scholars correlate AR with types of disease *Pratishyaya/Pinasa* [National Ayurveda Morbidity Code (NAMC): I-1]. Ayurveda has many treatment modalities, including both *Shodhanakarma* [biocleansing therapy - Standard Ayurveda Terminology (SAT)-I.76] and *Samshamana* (palliative procedure - SAT-I.37) treatments for this ailment according to the condition of the disease and patient.[5] Primary treatment modality for management of diseases of head and neck is *Nasya* (medication through nasal route - SAT-I.156). Most Ayurveda drugs and preparations used for the treatment of AR have proven immunomodulatory, antiallergic, and anti-inflammatory properties.[6] Studies have demonstrated promising results of some Ayurveda interventions in the management of AR. Amid rising concerns about the safety of Ayurveda drugs, it is crucial to establish the safety and efficacy of Ayurveda interventions.

A few numbers of systematic reviews on Ayurveda management have been registered, and fewer have been published, for example, Ayurveda and plant-based medicines for cancer.[7] Till date, no review on the same topic has been published or registered. One of the reviewers had published a systematic review on the management of AR with herbal medicines; studies included in the report were on

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herbal drug extract or a single formulation only.[8] The present study is not the same as Ayurveda is based on its unique principles and differs from herbal medicine. Another registered review (PROSPERO 2018 CRD42018093586) is on the same subject; however, present review has different inclusion criteria for study designs and focuses on both safety and efficacy.

Materials and Methods

This review protocol followed the preferred reporting items for systematic review and meta-analysis protocols guidelines, comprising 17 items intended to ease the preparation and reporting of systematic review and meta-analysis protocols.[9] The Cochrane Handbook for Systematic Reviews of Interventions,[10] Consolidated Standards of Reporting Trials (CONSORT),[11] and Guidance on the Conduct of Narrative Synthesis in Systematic Reviews[12] as applicable are followed.

Patients will not be involved in any phase of the study. Ethical approval has been obtained from the IEC of RRAP CARIC (IEC/11/19-20, 27/05/2019).

Inclusion Criteria

Type of Studies

The review will include randomized controlled trials (RCTs), quasi-randomized controlled trials, non-randomized controlled trials (NRCTs), controlled clinical trials (CCTs), parallel-group trial, multiple-arms clinical trial. Both postgraduate (PG) and doctor of philosophy (PhD) dissertations will also be included.

The studies without any restriction of language will be included, if languages other than English or Hindi will be encountered, authors will either contact the original authors or obtain a translation of the manuscript from professional service. Search will be rerun just before the final analyzes and further studies retrieved for inclusion.

Type of Participants

Studies with participants aged between 10 years and 70 years with symptoms of *Pratishyaya*/*Pinasa*, as explained in classical Ayurveda texts, and AR.

Above mentioned specific criteria for participant age was adopted which excluded few studies, as Ayurveda has defined different treatment protocols according to age.

Type of Interventions

Ayurveda treatment (*Samshamana* and/or *Shodhanakarma*) with any dose, type, schedule, drug, dosage form, and advised *Pathayapathya* (lifestyle modifications), and patients may receive additional non-Ayurveda intervention in all groups of study.

For this study, Ayurveda treatment has been defined as any internal or external herbal/polyherbal/herbomineral/mineral drug described in classical Ayurveda texts or a new drug containing ingredients described in Ayurveda texts.

Type of Comparators

- Placebo/sham therapy/both
- Any non-Ayurveda interventions.
- Ayurveda Treatment (*Samshamana* or/and *Shodhanakarma*) with a different dose, type, schedule, medicine, medicine than intervention(s)

This review aims to compare the effectiveness of various Ayurveda interventions; therefore, trials comparing two Ayurveda interventions will be included along with the controlled trials.

Types of Outcomes

Primary Outcomes

- Response to treatment, i.e., improvement in subjective and/or objective criteria of assessment
- Serious adverse events (resulting in death, disability or incapacity, complications, were life-threatening, led to hospitalization, or prolongation of hospitalization.).

Secondary Outcomes

- Withdrawals due to adverse events or lack of efficacy or inconvenience of therapy/treatment.
- The number of patients with a specific adverse event as secondary criteria.

No restrictions will be made in the inclusion of the study in review based on the outcomes mentioned above.

Type of Studies

The review will include RCTs, quasi-randomized controlled trials, NRCTs, CCTs, parallel-group trials, and multiple-arms clinical trials.

Data Sources

Following electronic databases will be searched: PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), AYUSH Research Portal (Government of India). Manual search in central and departmental libraries of IPGT and RA, GAU, Jamnagar, and Ayurveda Research Database by Prof MS Baghel. There will be no language restrictions. References from the manuscripts collected from electronic search and snowballing of the studies will be performed to fetch all possible data. Author/s will rerun the search before the final analyzes and further studies retrieved for inclusion.

Search Strategy

Search strategy combining MeSH terms and free-text words using the Boolean operators "AND" and "'OR" was used such as (AYURVED* OR AYURVED* TREATMENT OR NASYA OR HARIDRA KHAND*) AND (ALLERGIC RHINITIS OR HAY FEVER OR PRATISHYAY* OR VATA* PRATISHYAY* OR SANNIPAT* PRATISHYAY*). To isolate the clinical trials, we applied appropriate filters. Different search strategies were used for different databases.

Study Selection

Two independent investigators (Parth P Dave and Azeem Ahmad) will carry out the initial screening of studies, based on the information contained in their titles and abstracts when the reviewers disagree; the article will be reevaluated and, if the disagreement persisted, a third reviewer (Manohar S Gundeti) would make a final decision. The same investigators will conduct full-paper screening.

Data Extraction

A proforma following current guidelines will be prepared to extract data from the included studies for assessment of study quality and data analysis. Two review authors Parth P Dave and Azeem

Ahmad will independently extract the data. Any disagreement will be consulted and settled through discussions with a third author (Manohar S Gundeti) where necessary. If necessary, additional/missing information from the corresponding author of the study will be obtained through e-mail or telephone more than twice in an interval of 1 month.

Quality Assessment

Two independent reviewers (Parth P Dave and Azeem Ahmad) will evaluate the methodological quality of eligible trials, and any disagreement will be resolved by a third reviewer (Manohar S Gundeti).

The risk of bias for each outcome across studies will be summarized as a narrative statement and supported by a risk of bias table. The methodological quality of the RCTs will be assessed by following the CONSORT 2010 statement,[11] this assessment will be done under three categories, "yes" reporting, "no" reporting, and "incomplete" reporting. Two points will be given for each item for complete reporting, in case of incomplete reporting only one point will be given to that item, and no score for no reporting. Results will be interpreted in terms of percentage (%) of the mean of each reporting item.

The internal validity and risk of bias for RCTs will be assessed with the appraisal tool from the Cochrane Handbook for Systematic Reviews of Interventions (V.5.1.0),[10] which evaluates five domains, viz., randomization sequence allocation; allocation concealment; blinding; completeness of outcome data, selective outcome reporting; and categorizes studies into low, high, or unclear risk of bias. The NRCTs will be assessed with ROBINS-I; this tool has seven bias domains arranged chronologically, and the interpretations of domain level and the overall risk of bias judgment are classified in low, moderate, serious, or critical risk of bias.[13]

Data Synthesis

Primary purpose of this study is to review and synthesize published and unpublished studies, focusing on the effectiveness and safety of Ayurveda treatment in the management of AR, all data extracted from the articles will be presented narratively in text and summary tables, as narrative synthesis provides a broad overview of relevant information through a textual approach and is appropriate when studies are too heterogeneous to allow a quantitative summary.[12] To ensure the quality, the Guidance on the Conduct of Narrative Synthesis will be followed in systematic reviews as appropriate to report the review search results and analysis summary accurately.[12] The complete data extraction and synthesis process will be meticulously detailed, and objective third-party review (Manohar S Gundeti) will be utilized.

Assessment of Heterogeneity

If a meta-analysis is possible, we will use the I^2 statistic to assess heterogeneity among the included studies. An I^2 value of >50% will be considered indicative of substantial heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis and sensitivity analysis to explore its possible causes.[14]

Assessment of Reporting Biases

If sufficient studies are available, the reporting biases will be assessed with funnel plots. However, funnel plot asymmetry is not the same as publication bias; therefore, to distinguish the different possible reasons will be attempted for the asymmetry, such as small-study effects, poor methodological quality, and the true heterogeneity of the included studies.[15,16]

Measures of the Treatment Effect

Mean difference (MD) will be used to measure the treatment effect at a 95% confidence interval (CI). In the case of outcome variables with different scales, the standard MD with a 95% CI will be used. For dichotomous data, treatment effects will be presented as relative risk or risk difference with 95% CIs.

Results

The review is ongoing and will be published in a peer-reviewed journal.

Discussion

Applying a reproducible and transparent procedure is one of the strengths of the study. In this protocol, the participants, interventions, comparators, outcomes, and types of studies, as well as the data sources, search strategy, data extraction methods (including quality assessment) and methods of combining data will be described clearly. By publishing the research protocol, the clarity of the procedure will be reinforced and the risk of bias will be minimized. This protocol illustrates how elements from several guidelines were incorporated to answer the research question.

Results of the review may help future researchers, clinicians, and policy makers. The study will review published or unpublished studies on the management of AR with Ayurveda and might act as a whistleblower for the need of developing reporting guidelines of Ayurveda clinical trials.

A significant limitation of the study is heterogeneity and fewer studies with good methodological quality that may not allow quantitative analysis.

Amendments

We will document modifications to this protocol regarding saved searches and analysis methods, in Excel templates for data collection and synthesis.

Author Contribution

Manohar S Gundeti inspired the study and monitored the research entirely; Parth P Dave and Azeem Ahmad prepared the protocol. Parth P Dave prepared the draft document, and Azeem Ahmad and Manohar S Gundeti have finalized the manuscript.

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हिन्दी सारांश

एलर्जिक राइनाइटिस के आयुर्वेद उपचार की प्रभावकारिता एवं सुरक्षितता पर सिस्टेमेटिक रिव्यू का प्रोटोकोल

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परिचय: प्रकाशित और अप्रकाशित नैदानिक शोधों का विश्लेषण करके एलर्जिक राइनाइटिस के लिए आयुर्वेद चिकित्सा की सुरक्षा और प्रभावकारिता की जांच के लिए एक सिस्टेमेटिक रिव्यु किया जायेगा।

सामग्री एवं विधि: पब-मेड, आयुष रिसर्च पोर्टल, कोक्रेन सेंट्रल रजिस्टर ऑफ कंट्रोल्ड ट्रायल (CENTRAL), में सर्च के उपरांत, हेंड-सर्च, स्नो-बॉलिंग ऑफ स्टडीज का प्रयोग किया जाएगा। इस में एलर्जिक राइनाइटिस के प्रबंधन पर हुए स्नातकोत्तर और पीएचडी शोध प्रबंधों को भी शामिल किया जायेगा। अध्ययन, डेटा निष्कर्षण और संश्लेषण का चयन शोधकर्ताओं द्वारा स्वतंत्र रूप से किया जाएगा, और तीसरा समीक्षक असहमति का निवारण करेगा। अध्ययन के चयन, गुणवत्ता मूल्यांकन और संश्लेषण के लिए स्थापित दिशानिर्देशों का पालन किया जाएगा। रिस्क ओफ बायस का मूल्याङ्कन, ROBINS-I और Cochrane RoB2 की मदद से किया जाएगा। परिणामों को संश्लिष्ट रूप से वर्णित किया जाएगा और गिनती, प्रतिशत और आवृत्ति में प्रस्तुत किया जाएगा। चूंकि यह इस विषय पर पहला सिस्मेटेमेटिक रिव्यू है, इसलिए प्रोटोकॉल की रूपरेखा पूर्ण समीक्षा के लिए पारदर्शिता सुनिश्चित करती है। मरीजों को अध्ययन के किसी भी चरण में शामिल नहीं किया जाएगा; हालाँकि, संस्थागत आचार समिति से नैतिक अनुमोदन प्राप्त किया गया है।

प्रसार: समीक्षा जारी है, और पूरा होने के बाद, संशोधन को पीयर-रिव्यू जर्नल में प्रकाशित किया जाएगा। स्वास्थ्य सेवा अभ्यास और नीति को सूचित करने और मार्गदर्शन करने के लिए अध्ययन को अद्यतन किया जाएगा।

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शब्द कुँजी:आयुर्वेद,एलर्जिक राइनाइटिस, प्रोटोकोल, सिस्टेमेटिक रिव्यू