Protocol for Systematic Review and Meta-analysis of Ayurvedic Interventions for Essential Hypertension

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ABSTRACT

Introduction: A systematic review (SR) is planned to investigate the safety, efficacy, and effectiveness of Ayurvedic interventions in the management of essential hypertension through analyzing published and unpublished clinical research. 

Materials and methods: A systematic review of published and unpublished clinical researches on Ayurveda interventions in the management of essential hypertension will be conducted. Electronic search will be carried out in PubMed, AYUSH Research Portal, the Cochrane Central Register of Controlled Trials (CENTRAL), and hand search, snowballing of studies will also be performed to fetch complete available literature. Manual search will be carried out for Ayurveda Post Graduate (PG) and Doctor of Philosophy (PhD) dissertations on management of essential hypertension. The selection of the studies, data extraction, and synthesis will be performed independently by researchers, and disagreements will be sought by a third reviewer. Established guidelines for study selection, quality assessment and narrative synthesis will be followed. Risk of bias assessment will be performed with help of Cochrane RoB2 tool for randomized controlled trials (RCTs) and ROBINS-I tool for non-RCTs (NRCTs). Results will be narratively synthesized and will present the same in count, percentage and frequency. As this will be the first SR 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 sought from the institutional ethics committee.

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

Trial registration number: PROSPERO 2019 CRD42019123886.

Keywords: Ayurvedic intervention, Essential hypertension, Meta-analysis, Systematic review.


INTRODUCTION

Essential Hypertension and Ayurveda

Hypertension remains the principal risk factor for cardiovascular diseases associated with significant morbidity and mortality worldwide. Globally, hypertension accounts for 9 million deaths among the 1 billion adults living with the condition. Antihypertensive treatment should, in addition to lowering blood pressure, reduce the incidence of cardiovascular morbidity and mortality and total mortality. So there is need of strong evidence of safe and effective treatment. Many clinical trials have been carried out with Ayurveda intervention.

Having a critical glimpse of previous research works, the symptomatology of hypertension has been correlated with Vyanabalavashayama (vitiation of Vyanabala), Raktgata Vata (Vata provocation in vessels), Dhamanipratchayaya (narrowing of vessel), Raktavata (vitiation of Rakta and Vata), Avrutta-vata (Vata provocation due to obstructive pathology), Shelmanruttata-vata (Vata provocation due to obstruction by Kapha), Raktavarta Vata (Vata provocation due to obstruction by Rakta), Pittavruta Vata (Vata provocation due to obstruction by Pitta), Medavrutta Vata (Vata provocation due to obstruction by Meda), and Mishraavarma (different obstructive pathologies).

Why this Study?

Plenty of studies are found individually proving the efficacy of various Shodhana (bio-purification therapy), Shamana (internal medicine) in subjective and objective improvement of essential hypertension. However, we do not see any SR for Ayurveda interventions for essential hypertension. This study aims at thorough review of published data of Ayurvedic interventions as in the management of essential hypertension. This will provide more precise estimates of effectiveness of Ayurvedic interventions in the management of essential hypertension.

This study will review clinical trials on management of essential hypertension with Ayurveda to generate evidence on 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 SR and meta-analysis protocols, Cochrane Handbook for

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Systematic Reviews of Interventions,3 and Consolidated Standards of Reporting Trials (CONSORT).4

Ethical approval has been sought from the Institutional Ethics Committee of RRAP CARIC (IEC/11/19-20, 27/05/2019). Trial has been registered in PROSPERO (PROSPERO 2019 CRD42019123886).

Inclusion Criteria

Type of Studies
The review will include RCTs, quasi-RCTs, NRCTs, controlled clinical trials (CCTs), parallel-group trial, and multiple-arms clinical trial. We will also include PG and PhD dissertations.

There will not be any restriction of language, if we encounter languages other than English or Hindi, we will either contact the original authors or obtain a translation of the manuscript from professional service. We will rerun the search just before the final analyses and further studies are retrieved for inclusion.

Type of Participants
Studies that have participants diagnosed as cases of essential hypertension of both sexes. Subjects/participants who did not complete the study period (dropouts) will be excluded.

Type of Interventions
Ayurveda treatment (Shamana or/and Shodhana) with any dose, type, schedule, drug, dosage form, and advised Pathayapathy (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 (Shamana or/and Shodhana) with a different dose, type, schedule, medicine, medicine than intervention(s).

Types of Outcome

Primary outcome:
• Response to treatment, i.e., improvement in subjective and/or objective criteria of assessment.

Secondary outcome:
• Safety of Ayurveda treatment in essential hypertension by assessment for occurrence of any adverse events

Type of Studies
The review will include RCTs, quasi-RCTs, NRCTs, CCTs, parallel-group trials, and multiple-arms clinical trials.

Data Sources
Search will be performed following electronic databases—PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), and AYUSH Research Portal (Govt. of India). Manual search in central and departmental libraries of IPGT and RA, GAU, Jamnagar and Ayurveda Research Database by MS Baghel (https://www.researches-in-ayurveda.co.in/). References from the studies collected from electronic search and snowballing of the studies will be performed to fetch all possible available data. The search will be rerun before the final analyses and further studies retrieved for inclusion.

Search Strategy
Search strategy combining MeSH terms and free-text words using the Boolean operators “AND” and “OR,” such as (Ayurved* OR Ayurved+ Treatment) AND (essential hypertension OR primary hypertension OR benign essential hypertension OR Raktaviratta Vata OR Raktapitta OR Raktagata Vata was used. To isolate the clinical trials, we applied appropriate filters. Different search strategies were used for different databases.

Study Selection
Two independent investigators (SD, PM) 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 re-evaluated and, if the disagreement persisted, a third reviewer (MSG) would make a final decision. Same independent investigators will conduct full-paper screening.

Data Extraction
We will prepare a pro forma following current guidelines to extract data from the included studies for assessment of study quality and data analysis. Data will be extracted independently by two review authors SD and PM. Any disagreement will be consulted and settled through discussions with a third author MSG where necessary. If necessary, additional/missing information will be obtained from the corresponding author of the study through e-mail or telephone more than twice in an interval of 1 month.

Quality Assessment
Two independent reviewers (SD, PM) will evaluate the methodological quality of eligible trials, and any disagreement will be resolved by a third reviewer (MSG).

The risk of bias for each outcome across studies will be summarized as a narrative statement and supported by a risk of bias table. We will assess methodological quality of the RCTs by following the CONSORT 2010 statement,4 and this assessment will be done under three categories, “Yes” reporting, “No” reporting, and “Incomplete” reporting. Two points will be given for each item if it is reported completely, 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.5.1.0,5 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. We will assess NRCT 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.6

Details of number of studies identified, screened, and assessed for eligibility for inclusion in qualitative synthesis will be given in PRRISMA flowchart (Flowchart 1).
Data Synthesis
Two investigators including consultant (statistics) will analyze data by using appropriate software. Dichotomous data will be presented and combined using relative risks and standard deviations, data will be combined by using weighted mean differences; both will be accompanied by 95% confidence intervals. Medians and ranges will be reported in tables. Arithmetic means and standard deviations will be used to summarize continuous data, when the data are assumed to be normally distributed. Separate summary effect estimates will also be generated for studies that meet and do not meet the individual quality criterion. Heterogeneity among trials will be assessed by inspecting forest plots, to look for overlapping confidence intervals, applying the Chi-square test, with a $p$ value of 0.05, indicating statistical significance, and using the $I^2$ test with a value of 50%, used to denote moderate levels of heterogeneity. If heterogeneity is detected and it is still considered clinically meaningful to combine studies, then a random-effects model will be used. A sensitivity analysis, to investigate the robustness of the results to the quality components will be done provided there are sufficient trials. A funnel plot will be utilized to indicate publication bias, heterogeneity of results, or differences in the methodological quality.

Additionally, the complete data extraction and synthesis process will be meticulously detailed, and objective third-party review (MSG) will be utilized.

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

Discussion
Systematic review (SR) generates the data, which is a reproducible and transparent procedure. In this protocol, we clearly describe the participants, interventions, comparators, outcomes, and types of studies that will be included, as well as the data sources, search strategy, data extraction methods (including quality assessment), and methods of combining data. By publishing the research protocol, we reinforce the clarity of the strategy and minimize the risk of bias. Results of the review may help future research, clinicians, and policy makers. The study will review published or unpublished studies on management of essential hypertension with Ayurveda.

Major limitation of the study is heterogeneity and less number of studies with good methodological quality that will not allow quantitative analysis.

Amendments
Any modifications to this protocol will be documented with reference to saved search and analysis methods, which will be recorded in Excel templates for data collection and synthesis.

Author Contributions
Saylee Deshmukh and Pallavi S Mundada prepared the protocol; Manohar S Gundeti inspired the idea of this study.

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References


नींदी सारांश
एसेंशियल हायपरप्रेशन के लिए आयुर्वेदिक चिकित्सा के सिस्टेमेटिक रिव्यू और मेटा-एनालिसिस के लिए प्रोटोकॉल

सावली देशमुख, पल्लवी एस. मुंड़ा, साकेत राम दी., मनोहर एस. गुंडेडी

परिचय: प्रकाशित और अप्रकाशित चिकित्सीय अनुसंधान के विश्लेषण के माध्यम से एसेंशियल हायपरप्रेशन के प्रबंधन में आयुर्वेदिक चिकित्सा की सुरक्षा, प्रभावकारिता और प्रभावशीलता की जांच के लिए सिस्टेमेटिक रिव्यू की योजना बनाई गई है।

प्रणाली और विश्लेषण: हम एसेंशियल हायपरप्रेशन के प्रबंधन में प्रकाशित और अप्रकाशित चिकित्सीय अनुसंधान पर आयुर्वेद चिकित्सा की सिस्टेमेटिक रिव्यू करेंगे। PubMed, AYUSH Research Portal, Cochrane Central Register of Controlled Trials (CENTRAL) जैसे इलेक्ट्रॉनिक भाषाओं में खोजकी जाएगी; संपूर्ण उपलब्ध साहित्य को लाने के लिए अध्ययनों की स्थूल-वैज्ञानिक, स्थूल-वैज्ञानिक का भी प्रदर्शन किया जाएगा। हम एसेंशियल हायपरप्रेशन के प्रबंधन पर आयुर्वेद पीठी और पीएचडी लेख प्रबंधकों को मैन्युअल रूप से पढ़ जाएगे। अध्ययन का चयन, डेटा संकलन और संगठन सहयोगी द्वारा स्वतंत्र रूप से किया जाएगा और असहमति के मामलों में, तीव्र सहयोगी की राय मानी जाएगी। हम अध्ययन का चयन, गुणवत्ता मूल्यांकन और विवरणात्मक संगठन के लिए स्थायित्व दिशानिर्देश का पालन करेंगे। RCT के लिए Cochrane RoB2 एवं NRCT के लिए ROBINS-I उपकरण की मदद से रिस्क ऑफ बायस का मूल्यांकन किया जाएगा। हम परिणामों को संशोधित करेंगे और निर्देश, प्रतिबन्ध और आवृत्ति में परिणाम प्रस्तुत करेंगे। चूँकि यह इस विषय पर पहला सिस्टेमेटिक रिव्यू होगा, इसलिए प्रोटोकॉल की स्पष्टता पूर्ण समीक्षा के लिए पारंपरिक सुनिश्चित करती है। मरीजों के अध्ययन के किसी भी घरण में शामिल नहीं किया जाएगा, हालांकि वर्तमान अध्ययन को संस्थागत अध्ययन कमिटी द्वारा अनुमोदित किया गया है।

परिणाम: समीक्षा जारी है और पूरा होने के बाद, समीक्षा पीयर रिव्यू जरूरत में प्रकाशित की जाएगी। स्वास्थ्य सेवा अभ्यास और नीति को सुधारित करने और मार्गदर्शन करने के लिए समीक्षा को अद्यतन किया जाएगा।