Efficacy of Ayurveda Interventions in Parkinson's Disease: A Protocol for Systematic Review

Remya E[1], Akashlal Maneeri[2], Parvathy G Nair[3], KM Pratap Shankar[4]

ABSTRACT

Introduction: Parkinson's disease (PD) is the most common form of a group of progressive neurodegenerative disorders characterized by motor, autonomic, and cognitive disturbances. The prevalence of PD is increasing with age and it affects 1% of the population above 60 years. In light of the demand for alternative measures to control PD, a systematic review is being planned to generate evidence for the efficacy, effectiveness, and safety profile of Ayurvedic interventions in the management of PD.

Objectives: The primary objective of the present study is the systematic review of published clinical data in view of the safety, efficacy, and effectiveness of Ayurvedic interventions in the management of PD.

Materials and methods: Electronic searches from various online databases and clinical trial registries will be done. A manual search for gray literature will also be done from various sources, e.g., printed journals, conference proceedings, colleges, university libraries, etc. Studies published in the English and Hindi language till March 2019 will be sought. Types of study include randomized controlled trials (RCTs), quasi-experimental trials, single group clinical trials, comparative clinical trials (CCTs), pragmatic trials, and review papers on Ayurvedic management of PD or *Kampavata*. Three investigators shall independently screen all citations and abstracts identified by a primary comprehensive search to sort out potentially eligible trials and eligible trials will be independently evaluated for inclusion in the review based on the inclusion criteria. Data extraction forms for individual study including methods, participants, intervention, comparator, and the outcome shall be prepared. Each of the included trials will be assessed for risk of bias. Primary data analysis will be done for both qualitative and quantitative data. Heterogeneity among trials will be assessed by inspecting forest plots. If heterogeneity is detected, and it is still considered clinically meaningful to combine studies, 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.

Dissemination: The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and via print. The review may guide healthcare practices and policy-framing in the treatment of PD with Ayurvedic interventions.

Trial registration number: PROSPERO 2019: CRD42019131920 Dated 20/12/2019.

Keywords: Ayurveda, Ayurveda intervention, *Kampa*, *Kampavata*, Parkinson's disease.

Journal of Research in Ayurvedic Sciences (2020): 10.5005/jras-10064-0114

INTRODUCTION

Parkinson's disease (PD) is the most common form of a group of progressive neurodegenerative disorders characterized by the clinical features of parkinsonism, including bradykinesia, resting tremor, muscular rigidity, shuffling gait, and flexed posture.[1] Although defined clinically as a movement disorder, PD can be accompanied by a variety of non-motor symptoms, including autonomic, sensory, sleep, cognitive, and psychiatric disturbances.[2] Nearly all forms of parkinsonism result from a reduction of dopaminergic transmission within the basal ganglia. Although most patients with PD appear to have no strong genetic determinant, epidemiologic evidence points to a complex interaction between genetic vulnerability and environmental factors. Parkinson's disease affects 1–2 per 1,000 of the population at any time. Parkinson's disease prevalence is increasing with age, with no decrease in extreme ages.[3]

Parkinson's disease affects 1% of the population above 60 years. As a result of advances in experimental therapeutics, many promising therapies for PD are emerging. Levodopa remains the most potent drug for controlling PD symptoms, yet is associated with significant complications such as the "wearing off" effect, levodopa-induced dyskinesias, and other motor complications.[4] This poses a greater challenge in the management of PD. Acharya

[1,3,4]National Ayurveda Research Institute for Panchakarma, Thrissur, Kerala, India

[2]Regional Ayurveda Research Institute, Port Blair, India

Corresponding Author: Remya E, National Ayurveda Research Institute for Panchakarma, Thrissur, Kerala, India, Phone: +91 9447378133, e-mail: drremyaenair@gmail.com

Charaka describes "*Vepathu*" as 1 of the 80 types of vataja Nanatmaja Vyadhi.[5] The term "*Kampavata*" was mentioned for the first time in the text "*Basavarajeeyam*" with most of its clinical features similar to that of PD.[6] The proper combination of two major limbs of treatments of Ayurveda—*Shodhana* and *Shamana* can yield better results in the management of the disease and also in improving the quality of life (QoL) of PD patients. In light of the demand for alternative measures to control PD, we considered it necessary to conduct a systematic review regarding efficacy and safety on the topic of Ayurvedic treatments for PD. To date, there

are no systematic reviews undertaken in this regard. Therefore, we prepared a study protocol to conduct the systematic review questioning the efficacy, safety, and advantages of Ayurvedic treatments for PD compared with any non-Ayurvedic treatment or no treatment.

OBJECTIVES

Primary Objective

Systematic review of the published clinical data and *gray* literature in view of safety, efficacy, and effectiveness of Ayurvedic interventions in the management of PD.

Secondary Objective

Meta-analysis of the published clinical data and *gray* literature in view of safety and effectiveness of Ayurvedic interventions in the management of PD.

Review Question

The review question includes what is the efficacy and safety of Ayurveda interventions in the management of PD.

MATERIALS AND METHODS

The study type is a systematic review, meta-analysis. The purpose of the study is evidence generation for the safety and efficacy of Ayurveda interventions for PD. A protocol is prepared based on Prisma-P guidelines for systematic review protocol.[7]

Source for Data Analysis

- Published data available on search engines namely PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials), AYUSH Research Portal (Govt of India), DHARA, Google Scholar, and Online clinical trial registries.
- Gray literature available from Govt Ayurveda Colleges at Trivandrum. Tripunithura, Kannur, VPSV Ayurveda College, Kottakkal (Manual Search), IPGT and RA, Gujarat Ayurved University, Jamnagar, Shodhganga@INFLIBNET.

Timelines

- Data collection and analysis: 06 months.
- Journal selection and publication: 03 months.

Criteria for Selection of Study

Types of Study to be Included

Randomized controlled trials (RCTs), quasi-experimental trials, single group clinical trials, comparative clinical trials (CCTs), pragmatic trials, case reports, case series, and review papers on Ayurvedic management of PD or *Kampavata* will be screened for data analysis. Cross-over trials and multicentric studies may also be included if available.

Types of Participants

The trials with patients fulfilling the diagnostic criteria based on the symptomatology of *Kampavata* explained in Ayurvedic classics and diagnostic criteria of PD with or without other comorbidities irrespective of age and sex will be included. A sample size of individual studies is not specifically mentioned; it may start from 1 as inclusion criteria comprise case reports also.

Types of Interventions

Ayurvedic treatment protocol (*Shamana* or/and *Shodhana*) with different dosage forms, type, schedule, drug, treatment procedures, with or without *Pathayapathya* (lifestyle modifications and or specific diet charts) as the intervention group in PD shall be screened for data analysis. Patients may receive additional non-Ayurveda intervention in all groups of study.

Comparator(s)/control

Ayurvedic treatment protocol (*Shamana* or/and *Shodhana*) with different dosage forms, type, schedule, drug, treatment procedures, with or without *Pathayapathya* (lifestyle modifications and or specific diet charts) as the comparative group to intervention(s)/exposure(s) in PD shall be screened, and/or *Shamana* therapy and/or non-Ayurveda interventions in PD too shall be screened. Placebo and/or sham therapy may be preferably avoided.

Outcome

Primary Outcomes

The primary outcome will be a response to treatment (improvement in subjective and/or objective criteria of assessment), serious adverse events (resulting in death, disability or incapacity, life-threatening complications, prolonged hospitalization). Response to the treatment is not further specified as it is expected that the test-batteries will be heterogeneous. Different measures will be included if they are quantitative and have been clearly defined.

Timing and effect measures: During the study period or up to 1 month after completion of the study.

Secondary Outcomes

Secondary outcomes include assessment of cognitive function, health-related QoL, withdrawals due to adverse events or lack of efficacy or inconvenience of therapy/treatment. The number of patients with specific adverse events will also be treated as a secondary outcome.

Timing and effect measures: During the study period or up to 1 month after completion of the study.

Search Methods for Identification of Studies

- Electronic Database search—PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials), AYUSH Research Portal (Govt. of India), DHARA, Google Scholar, Shodhganga@INFLIBNET, and Online clinical trial registries.
- Manual search in Central and departmental libraries of Govt Ayurveda Colleges at Trivandrum, Tripunithura, Kannur, VPSV Ayurveda College, Kottakkal (Manual Search), IPGT and RA, GAU, Jamnagar with due permissions and Ayurveda Research Databases from authorities.

Studies published in the English language till March 2019 will be sought. The searches will be re-run just before the final analyses and further studies retrieved for inclusion.

Keywords for Electronic Search/Search Strategy

Ayurveda or Ayurvedic or Ayurvedic treatment or PD or *Kampavata* or *Kampa* as title, abstract, or keyword.

Data Collection/Synthesis—Data Extraction/Management

Three investigators shall independently screen all citations and abstracts identified by a primary comprehensive search to sort out potentially eligible trials. Full articles of potentially eligible trials shall be obtained and independently evaluated for inclusion in the review based on types of participants (inclusion criteria). Data extraction forms for individual study shall be prepared. This shall include (1) Methods used in the study (randomization/allocation concealment/blinding/sampling and sample size calculation/length of follow-up); (2) Participant characteristics of individual studies (along with disease characteristics/number of participants randomized/number of participants completing follow-up/reasons for withdrawal from the study); (3) Interventions (treatment protocol administered/formulations used/standard operating procedures (SOPs) administered/adverse events developed during the intervention); (4) Outcomes (in terms of safety/effectiveness/efficacy/improvement in QoL). For each outcome measured from individual studies, efforts shall be taken to discuss the risk of bias, consistency, precision, and reporting bias.

When disagreement persists or in case of ambiguity while data extraction, efforts shall be initiated to obtain clarifications directly from authors/co-authors as much as possible.

Data Analysis

Both qualitative and quantitative data as collected from various sources shall be considered for primary data analysis. In cases where pooled estimates can be obtained, the systematic review will be followed by a meta-analysis (based on the homogeneity of the RCT); others would be eligible for qualitative synthesis and shall be represented in suitable tabular and graphical form. The analysis of the systematically collected data shall be conducted by appropriate software. Dichotomous data will be presented and combined using relative risks/risk ratio/odds ratio, etc., while continuous data if assumed to be normally distributed will be summarized by arithmetic means 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. 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-squared 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.[8]

Ethical Considerations

Before the commencement of the trial, written approval of the Institutional Ethics Committee (IEC) shall be obtained. A voluntary signed witnessed informed consent shall be obtained from the institutes/practitioners for sharing the unpublished data.

Coordination of Study

Coordinating Centers: National Ayurveda Research Institute for Panchakarma, Cheruthuruthy, Thrissur, Kerala (CCRAS), CCRAS Headquarters.

Systematic Review Registration

The study has been registered in Prospero with registration number CRD42019131920.

Study Monitoring

This study will be monitored periodically with the approval of the authority of CCRAS. The investigator will allocate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and has adequate space to conduct the monitoring visit. Particularly as an investigator in this study implies acceptance of potential inspection by CCRAS and other external experts.

Acknowledgments

References

1. Mahlon R, Delong, Juncos JL. Parkinson's disease and other extra-pyramidal movement disorders. Harrison's Principles of Internal Medicine, vol. 2, ch. 366 17th ed., The McGraw-Hill Companies, p. 2549.
2. National Collaborating Centre for Chronic Conditions (UK). Parkinson's Disease: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care. London: Royal College of Physicians (UK); 2006. (NICE Clinical Guidelines, No. 35.) 9, Non-motor features of Parkinson's disease. Available from: https://www.ncbi.nlm.nih.gov/books/NBK48501.
3. de Rijk MC, Tzourio C, Breteler MM, et al. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON collaborative study. European community concerted action on the epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;62(1):10–15. DOI: 10.1136/jnnp.62.1.10.
4. Jankovic J, Stacy M. Medical management of levodopa-associated motor complications in patients with Parkinson's disease. CNS Drugs 2007;21(8):677–692. DOI: 10.2165/00023210-200721080-00005.
5. Shastri R, ed. Samhita C. Vidyotini Hindi Commentary Part I Sutrasthana, chapter 20/11 Reprinted ed., Varanasi: Pub: Bharathi Academy; 2001. p. 399.
6. Basavarajeeyam Prof, Krishnamurthy MS. Aeitology - symptomatology and treatment of vatic disorders. Chaukhamba Orientalia. 1st ed., 2014. p. 149.
7. PRISMA-P Guidelines for Systematic Review Protocols. https://www.prisma-statement.org/Extensions/Protocols.aspx.
8. Nair DR, Pradeep Kumar PP, Remya E. A protocol for systematic review on Ayurvedic interventions in iron deficiency anemia. J Res Ayurvedic Sci 2019;3(2):60–63. DOI: 10.5005/jras-10064-0076.

हिन्दी सारांश

पार्किंसंस रोग में आयुर्वेद के हस्तक्षेप की प्रभावकारिता – व्यवस्थित समीक्षा के लिए एक प्रोटोकॉल

सार परिचय: पार्किंसंस रोग प्रगतिशील तंत्रिका अपक्षयी विकारों के एक समूह का सबसे आम रूप है जिसकी विशेषताएँ मोटर, स्वायत्त और संज्ञानात्मक बाधाएँ हैं। पार्किंसंस रोग की व्यापकता उम्र के साथ बढ़ रही है और यह 60 साल से ऊपर की जनसंख्या के 1% को प्रभावित करता है। पार्किंसंस रोग को नियंत्रित करने के लिए वैकल्पिक उपायों की मांग के मद्देनजर, पार्किंसंस रोग के प्रबंधन में आयुर्वेदिक हस्तक्षेपों की प्रभावकारिता, प्रभावशीलता और सेफ़्टी प्रोफ़ाइल के लिए प्रमाण उत्पन्न करने के संबंध में एक व्यवस्थित समीक्षा की योजना बनाई जा रही है।

उद्देश्य: वर्तमान अध्ययन का प्राथमिक उद्देश्य पार्किंसंस रोग के प्रबंधन में आयुर्वेदिक हस्तक्षेपों की सुरक्षा, प्रभावशीलता और प्रभावशीलता को देखते हुए प्रकाशित नैदानिक आंकड़ों की व्यवस्थित समीक्षा है।

सामग्री और तरीके: विभिन्न ऑनलाइन डेटाबेस और नैदानिक परीक्षण रजिस्ट्रियों से इलेक्ट्रॉनिक खोज की जाएगी। ग्रे साहित्य के लिए मैनुअल खोज विभिन्न कॉलेजों और विश्वविद्यालयों से की जाएगी। मार्च 2019 तक अंग्रेजी भाषा में प्रकाशित अध्ययन की मांग की जाएगी। अध्ययन के प्रकार में यादृच्छिक नियंत्रित परीक्षण (आरसीटी), अर्ध-प्रायोगिक परीक्षण, एकल समूह नैदानिक परीक्षण, तुलनात्मक नैदानिक परीक्षण (सीसीटी), पार्किंसंस रोग या कंपवात के आयुर्वेदिक प्रबंधन पर व्यावहारिक परीक्षण और समीक्षा पत्र शामिल हैं। तीन जांचकर्ता स्वतंत्र रूप से संभावित योग्य परीक्षणों को हल करने के लिए प्राथमिक व्यापक खोज द्वारा पहचाने गए सभी उद्धरणों और सार को स्क्रीन करेंगे और प्रतिभागियों के प्रकार (समावेशन मानदंड) के आधार पर समीक्षा में शामिल करने के लिए पात्र परीक्षणों का स्वतंत्र रूप से मूल्यांकन किया जाएगा विधियों, प्रतिभागी, हस्तक्षेप, तुलना और परिणाम सहित व्यक्तिगत अध्ययन के लिए डेटा निष्कर्षण प्रपत्र तैयार किए जाएंगे। प्रत्येक शामिल परीक्षणों को पूर्वग्रह के खतरों के लिए मूल्यांकन किया जाएगा। प्राथमिक डेटा विश्लेषण गुणात्मक और मात्रात्मक डेटा दोनों के लिए किया जाएगा। वन भूखंडों का निरीक्षण करके परीक्षणों के बीच विषमता का मूल्यांकन किया जाएगा। यदि विषमता का पता लगाया जाता है, और यह अभी भी अध्ययन को संयोजित करने के लिए नैदानिक रूप से सार्थक माना जाता है, तो एक यादृच्छिक-प्रभाव मॉडल का उपयोग किया जाएगा। गुणवत्ता घटकों को परिणामों की मजबूती की जांच करने के लिए एक संवेदनशीलता विश्लेषण किया जाएगा, बशर्ते कि पर्याप्त परीक्षण हों। एक फ़नल प्लॉट का उपयोग प्रकाशन पूर्वाग्रह, परिणामों की विविधता या पद्धतिगत गुणवत्ता में अंतर को इंगित करने के लिए किया जाएगा।

प्रसार: यह व्यवस्थित समीक्षा एक विषय विशेषज्ञ द्वारा समीक्षा की पत्रिका में प्रकाशित किया जाएगा। इसे इलेक्ट्रॉनिक और प्रिंट में भी प्रसारित किया जाएगा। यह समीक्षा आयुर्वेदिक हस्तक्षेपों के साथ पार्किंसंस रोग के उपचार में स्वास्थ्य देखभाल प्रथाओं और नीति निर्धारण को निर्देशित कर सकती है।

परीक्षण पंजीकरण संख्या: PROSPERO 2019: CRD42019131920 दिनांकित 20/12/2019

मुख्य शब्द: आयुर्वेद, आयुर्वेदिक हस्तक्षेप, पार्किंसंस रोग, कंपवात, कंपा।