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

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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 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.


Keywords: Ayurveda, Ayurveda intervention, Kampavata, Parkinson’s disease.

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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 dyskineties, and other motor complications.4 This poses a greater challenge in the management of PD. Acharya

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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 Ayurvedic interventions for PD. A protocol is prepared based on Prisma-P guidelines for systematic review protocol.

**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 Pathayapatya (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 Pathayapatya (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-Ayurvedic 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/effectiveness/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 I² 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.

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References

हिंदी सारांश

पार्किंसन रोग में आयुर्वेद द्वारा उपचार की प्रभावकारिता – व्यवस्थित समीक्षा के लिए एक प्रोटोकॉल

सार परिचय: पार्किंसन रोग प्रतिक्षित तत्वीय अपशम्य विकारों के एक समूह का सबसे आम रूप है जिसकी विशेषताएं मोटर, स्वायत्त और संधारणात्मक बाधाएं हैं। पार्किंसन रोग की व्यापकता उम्र के साथ बढ़ रही है और यह 60 साल से ऊपर की जनसंख्या के 1% की प्रभावित करता है। पार्किंसन रोग को नियंत्रित करने के लिए वैकल्पिक उपायों की मांग के मद्देनजर, पार्किंसन रोग के प्रबंधन में आयुर्वेदिक हस्तक्षेपों की प्रभावकारिता, प्रभावशीलता और सेप्टिक प्रोफाइल के लिए प्रमाण उत्पन्न करने के संबंध में एक व्यवस्थित समीक्षा की योजना बनाई जा रही है।

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

सामग्री और तरीक़े: विभिन्न ऑनलाइन डेटाबेस और नैदानिक परीक्षण रिपोर्ट सो से इलेक्ट्रॉनिक खोज की जाएगी। त्यो सामग्री के लिए मेनुअल खोज विभिन्न कॉलेज 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), अर्थ-प्रायोगिक परीक्षण, एकल समूह नैदानिक परीक्षण, तुलनात्मक नैदानिक परीक्षण (सीटी), पार्किंसन रोग या कंप्यूटर के आयुर्वेदिक प्रबंधन पर व्यावहारिक परीक्षण और समीक्षा पत्र शामिल हैं। तीन जांचकर्ताओं के बीच रूप से विभाजित दस्तावेज परीक्षणों को छोड़ करने के लिए प्राथमिक व्यापक खोज द्वारा पहचाने गए सभी उद्देश्यों और सार को स्कीन करते और प्रतिभागियों के प्रकार (समावेश मानदंड) के आधार पर समीक्षा में शामिल करने के लिए पात्र परीक्षणों का स्वतंत्र रूप से मूल्यांकन किया जाएगा। विषयों, प्रतिभागी, हस्तक्षेप, तुलना और परीक्षण सहित व्यक्तिगत अध्ययन के लिए ढेटा निर्वाचन द्वारा तैयार किए जाएंगे। प्रत्येक शामिल परीक्षणों को पूर्वप्रह के बहरे के लिए मूल्यांकन किया जाएगा। प्राथमिक ढेटा विश्लेषण गुणात्मक और मात्रात्मक ढेटा दोनों के लिए किया जाएगा। तब भूमिका का निर्माण करने वाले परीक्षणों के बीच विषय का मूल्यांकन किया जाएगा। यदि विषय का पता लगाया जाता है, और यह अभी भी अध्ययन को संपोषित करने के लिए नैदानिक रूप से सार्थक माना जाता है, तो एक यादृच्छिक-प्रभाव मॉडल का उपयोग किया जाएगा। गुणवत्ता पदार्थों की परिणामों की मजबूती की जांच करने के लिए एक संचालनशीलता विश्लेषण किया जाएगा, बशर्त है कि परीक्षण परीक्षण हो। एक फलन प्लाउट का उपयोग प्राकृतिक पूर्वप्रह, परिणामों की विविधता या पद्धति गुणवत्ता में अंतर की इंगित करने के लिए किया जाएगा।

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

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

मुख्य शब्द: आयुर्वेद, आयुर्वेदिक हस्तक्षेप, पार्किंसन रोग, कंप्यूटर, कंप्यूटर