PROTOCOL

A Systematic Review Protocol to Assess the Effectiveness of Ayurveda Interventions in Gout

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ABSTRACT

Introduction: Ayurveda offers healthy, harmonious, and long life by its holistic approach. Gout is a form of arthritis caused by excess uric acid in the bloodstream. Gout may be considered as Vatarakta or Vatasonita as per Ayurveda. Even though gout is managed well with conventional medicine, there are a lot of side effects. Ayurvedic treatment is found to be effective in the management of gouty arthritis with very few ill effects. But research works carried out in gout with Ayurvedic medicines are not yet compiled and analyzed. The purpose of this study is to conduct a systematic review of published data and gray literature on Ayurveda management of gout viz-à-viz Vatarakta to establish its safety and clinical effectiveness. Thus, finding more precise estimates of various Ayurveda interventions' effects in the management of gout either as stand-alone or as an add-on to conventional management.

Materials and methods: Source for data analysis involves electronic search done from PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), AYUSH Research Portal (Govt. of India), DHARA, Google Scholar, Ancient Science of Life, Shodhganga@ INFLIBNET, and online clinical trial registers. Manual search in central and departmental libraries of Government Ayurveda College, Trivandrum and IPGT & RA, Gujarat Ayurved University, Jamnagar. There will be no language restrictions. Studies published till date (until March 2019) will be sought. The search will be rerun just before the final analyses, and further studies shall be retrieved for inclusion. Type of studies included randomized controlled trials (RCTs), quasi-experimental trials, single-group clinical trials, comparative clinical trials (CCTs), pragmatic trials, and review papers on Ayurvedic management of Gout, which will all be screened for data analysis. The study selection will follow the preferred reporting items for systematic review and meta-analysis guidelines. Data collection and synthesis: three investigators shall independently screen all citations and abstracts identified by a primary comprehensive search to sort out potentially eligible trials based on inclusion criteria. Data extraction forms for individual study shall be prepared and it may include methods, participant characteristics, intervention, and outcome. When disagreement persists or in case of ambiguity at the time of data extraction, efforts shall be initiated to obtain clarifications directly from authors/coauthors as much as possible. Primary data analysis of both the qualitative and quantitative data will be performed. Heterogeneity among trials will be assessed by inspecting forest plots. If heterogeneity is detected and it is still considered clinically meaningful to combine studies, then a random-effects model (Dersimonian–Laird Model) will be used. 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 methodological appraisal will be done by Cochrane risk-of-bias tool for RCT); others would be presented by narrative synthesis [using Risk of Bias tool in non-randomised clinical trials/non-randomised controlled trials (NRCT)] and shall be represented in tabular and graphical form. The analysis of the systematically collected data shall be analyzed using R software. 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.

Timelines: Data collection and analysis: 06 months (from the date of initiation). Journal selection and publication: 03 months (from the date of study completion).

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 gout with Ayurvedic interventions.

Trial registration number: PROSPERO 2019: CRD42019131198.

Keywords: Ayurveda interventions, Gout, Systematic review, Vatarakta.


INTRODUCTION

Ayurveda is an ancient indigenous medical system. Ayurveda offers the way of having a healthy, harmonious, and long life by its holistic approach.¹ ² Gout is a form of arthritis caused by excess uric acid in the bloodstream. It is a systemic disease that occurs due to the accumulation of monosodium urate crystals in tissues. Hyperuricemia is the main pathogenic cause for gout, but many people with hyperuricemia do not develop gout. Genetic predisposition also plays a major role in the pathogenesis of gout.³ ⁴ ⁵ It is a metabolic disorder causing inflammatory arthritis. The accumulation of tiny needle-like uric acid crystals triggers the inflammation.⁶

The globally reported prevalence of gout ranges approximately from 0.1% to 10% and the incidence of gout cases are 0.3–6 cases per 1,000 population.⁷ Although the prevalence of gout is less, most cases of gout are at increased

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risk of comorbidities and thus are at increased risk of death.\textsuperscript{8} It may also worsen the quality of life (QOL).\textsuperscript{9} A retrospective study across clinics in India shows an increased prevalence of hyperuricemia with increased association of type II diabetes mellitus and hypertension.\textsuperscript{10} Even though gout is managed well with conventional medicine, there are a lot of side effects. Colchicine is the preferred medicine for gout flare management but care should be given while administering in patients with kidney disease, hepatic dysfunction, and other comorbidities.\textsuperscript{11} The incidence of gout in India is not very clear. The prevalence is 0.12\% per the International League of Nations Against Rheumatism, Community Oriented Program for Control of Rheumatic Diseases study in Bhigwan village of India.\textsuperscript{12} Gout is the most common form of inflammatory arthritis in men (5 to 27 per 1,000 men). Most of the cases are characterized by the sudden onset of severe acute monoarthritis in a peripheral joint, mostly in the lower limb, exquisite pain, and warm pink shiny swelling usually at the base of a great toe (podagra). Arthritis remits completely within few days with or without therapy and then recurs in the coming days with increasing frequency. After approximately 10 years of recurrent gout arthritis, the patient develops into chronic gout with the appearance of tophi.\textsuperscript{13,14}

Gout may be considered as \textit{Vatarakta} or \textit{Vatasonita} per Ayurveda. \textit{Vatarakta} comes under one of the major diseases that affect the joints. \textit{Vatoraka} occurs due to the aggravation of \textit{Vata} and \textit{Rakta}. The vitiated \textit{Rakta} obstructs the pathways of \textit{Vata}, and \textit{Vata} aggravates by this obstruction and causes \textit{Vataraka}. The main feature of \textit{Vataraka} is \textit{Sandhi Soola} (joint pain). The onset is at \textit{Hasta} or \textit{PadoMoolam} (small joints of hands and foot) and spreads to other parts like \textit{AakhuVisha} (rat poison). It produces various symptoms like \textit{Ruk} (excruciating pain), \textit{Swayathu} (swelling), \textit{Daha} (burning sensation), \textit{Stabdha Sandhi} (joint stiffness), \textit{Shyaya RaktaVarnata} (blackish-red color), and \textit{Sparasahatwa} (severe tenderness and hyperesthesia).\textsuperscript{15,16}

Ayurvedic treatment is found to be effective in the management of gouty arthritis with very few ill effects. But research works carried out in gout with Ayurvedic medicines are not yet compiled and analyzed. Hence, it is essential to conduct a systemic review on Ayurveda interventions in this regard. This study will review published data and gray literature on Ayurveda management of gout \textit{viz-à-viz Vatarakta} to establish its safety and clinical effectiveness. This study shall provide more precise estimates of various Ayurveda intervention’s effects in the management of gout either as stand-alone or as an add-on to conventional management.

\textbf{OBJECTIVES}

\textbf{Primary Objectives}

- Systematic review of the literature to produce a database of outcome measures used in gout \textit{viz-à-viz Vatarakta}

\textbf{Secondary Objectives}

- A qualitative review of clinical and methodological characteristics of individual studies and patterns across the study in gout \textit{viz-à-viz Vatarakta}
- Documentation of strength and limitations of individual studies and patterns across the study in gout \textit{viz-à-viz Vatarakta}

\textbf{MATERIALS AND METHODS}

\textbf{Study Type}

Systematic review and meta-analysis.

\textbf{Purpose}

- Evidence generation for safety and effectiveness of Ayurveda treatment protocols in gout \textit{viz-à-viz Vatarakta}.
- Documentation of different treatment protocols and their comparisons.
- To document the relevance, strength, and weaknesses of individual studies (Ayurvedic treatment protocols) in gout and also to study the pattern across the study.

\textbf{Source for Data Analysis}

- Published data available on search engines, namely, PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), AYUSH Research Portal (Govt. of India), DHARA, Google Scholar, Ancient Science of Life, and Online clinical trials registers
- Gray literature available from Government Ayurveda College, Trivandrum (Manual Search); IPGT & RA, Gujrat Ayurveda University, Jamnagar; Shodhganga@INFLIBNET.

\textbf{TIMELINES}

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

\textbf{Criteria for Selection of Study}

\textbf{Type of Study}

The randomized controlled trials (RCTs), quasi-experimental trials, single-group clinical trials, comparative clinical trials (CCTs), pragmatic trials, and review papers on Ayurvedic management of Gout, which will all be screened for data analysis.

\textbf{Types of Interventions}

Ayurvedic treatment protocol (\textit{Shamana} or/and \textit{Shodhana}) with different dosage forms, type, schedule, drug, treatment procedures, with or without \textit{Pathayapathy} (lifestyle modifications and or specific diet charts) as the intervention group in gout shall be screened for data analysis.

\textbf{Comparators/Control}

- Ayurvedic treatment protocol (\textit{Shamana} or/and \textit{Shodhana}) with different dosage forms, type, schedule, drug, treatment procedures, with or without \textit{Pathayapathy} (lifestyle modifications and or specific diet charts) as the comparative group to intervention(s)/exposure(s) in gout shall be screened
- Placebo and/or sham therapy and/or \textit{Shamana} therapy and/or non-Ayurveda interventions in gout too shall be screened.

\textbf{Types of Participants}

\textit{Inclusion Criteria}

Cases diagnosed with gout by blood tests or symptom wise who underwent Ayurvedic treatment protocol (administered from 7 days to 60 days)}/cases diagnosed with \textit{Vatarakta} (symptom wise)
who underwent Ayurvedic treatment protocol (administered from 7 days to 60 days).

Exclusion Criteria
Cases with systemic illnesses other than the musculoskeletal system or any major comorbidities who underwent Ayurvedic treatment protocol for gout/Vatarakta.

Types of Outcome Measures
Effectiveness/efficacy parameters
• Response to treatment (improvement in subjective and/or objective criteria of assessments)
• Improvement in QOL

Timing and effect measures of effectiveness parameters
Administration timings vary from 7 days to 60 days as different categories of medications are included for review.

Safety/Morbidity Parameters
• Serious adverse events resulting in death, disability, or incapacity or complications, which were life-threatening, led to hospitalization or prolonged hospitalization.
• Withdrawals due to adverse events or lack of efficacy or inconvenience of therapy/treatment.
• The number of patients with a specific adverse event.

Timing and Effect Measures of Safety Parameters
During the study period or up to 1 month after completion of the study. No restrictions will be made in the inclusion of study in the review process based on the outcomes mentioned above.

Search Methods for Identification of Studies
The electronic databases are PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), Google Scholar, AYUSH Research Portal (Govt. of India), DHARA, Ancient Science of Life, Shodhganga@INFLIBNET, online clinical trial registers.

Manual search in central and departmental libraries of Government Ayurveda College, Trivandrum; IPGT & RA, GAU, Jamnagar with due permissions and Ayurveda Research Database from authorities.

There will be no language restrictions. Studies published till date (until March 2019) will be sought. The search will be rerun just before the final analyses and further studies shall be retrieved for inclusion.

Search Strategy (Keywords)
Ayurveda OR Ayurvedic OR Ayurvedic treatment OR Ayurvedic treatment protocol OR Gout OR Goutyarthitis OR Vatarakta OR Vatashonita OR Vatasonita 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 procedure (SOPs) administered/adverse events while the review protocol), and (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 at the time of data extraction, efforts shall be initiated to obtain clarifications directly from authors/coauthors as much as possible.

Data Analysis
Three investigators shall independently screen all studies identified by a primary comprehensive search to sort out potentially eligible trials. Full articles of potentially eligible trials shall be obtained. Data extraction forms for individual study shall be prepared. When disagreement persists or in case of ambiguity at the time of data extraction, efforts shall be initiated to obtain clarifications directly from authors/coauthors as much as possible. 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 presented by narrative synthesis and shall be represented in tabular and graphical form. The analysis of the systematically collected data shall be analyzed using R software. Dichotomous data will be presented and combined using relative risks, and continuous data will be summarized by arithmetic means and standard deviation 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. Heterogeneity among trials will be assessed by inspecting forest plots, to look for overlapping confidence intervals, applying the chi² 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 (Dersimonian–Laird 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.

Ethical Considerations
Written approval of 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.

Coordinating of Study
Coordinating centers: National Ayurveda Research Institute for Panchakarma, Cheruthuruthy, Thrissur, Kerala (CCCRAS), CCRAS Headquarters.

Study Monitoring
As per the approval of the authority of CCRAS, the investigators shall communicate the 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. Particular as an investigator in this study implies acceptance of potential inspection by CCRAS and other external experts.

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**References**

A Systematic Review Protocol for Ayurveda Interventions in Gout

नलिनपुरिकुलने धीर्घन अवस्था, प्रतिमा पी. नायर, गिरीजानन्द एन. श्रीदेवी, गड़बुम कुमार स्वामी

परियोजना: आयुर्वेद अपने समय हिन्दुस्तान में स्वस्थ, समाजसेवी पूर्ण एवं दीर्घजीवन प्रदान करता है। गूंट, गठिया का एक रूप है जो रक्तस्राव में अतिरिक्त पीएम के कारण होता है। आयुर्वेद के अनुसार गूंट को वातस्राव या वातशोषित माना जा सकता है। हालांकि, गूंट का पांडरिक विकिर्त्सा के साथ अर्थात तरह से प्राप्तिकर्ता जाता है लेकिन इसके बहुत सारे दुष्प्रभाव है। आमुर्वेद उपचार, गूंट का रूपमें बहुत कम दुष्प्रभाव के साथ भागी यात्रा जाता है लेकिन आयुर्वेदिक दवाओं के साथ गूंट में किया गया शोध कार्य अभी तक संकल्पित और विश्लेषित नहीं किए गए हैं। इस अध्ययन का उद्देश्य अपनी सुधार और नीति योजना प्रभावशीलता को स्पष्ट करने के लिए नतीजात के संबंध में गूंट के आयुर्वेदिक प्रबंध स्पष्ट करने और धृत-साहित्य का एक तत्काल करना है।

विधियों और विश्लेषण: डेटा विश्लेषण के लिए स्रोत: PUBMED, कोनेक्ट पुस्तकालय (नियोजित पश्चिमाना को कोनेक्ट केन्द्रीय रिजर्वार्ड देखें), अरुण अंशुदास पोटेटर (राजस्थान सरकार), DHARA, गुणकाळक, विद्याभूति नेतृत्विया परीक्षण रिजर्वार्ड, सरकार के केन्द्रीय और विभागीय पुस्तकालयों के लिए जी-जी, आयुर्वेद कॉलेज, विद्याभूति, आईपीजीजी और आयुर्वेद गूंट विश्लेषण, जासोस से इलेक्ट्रॉनिक जॉर्ड की जाएगी। यह भी स्पष्ट किया जाएगा कि अगर तक प्रकाशित अध्ययनों (मार्च 2019 तक) की जांच की जाएगी। अधिक विश्लेषण के ठीक पहले चौकियों को पुनर्तात्क चर्चा करें और आगे के अध्ययन को शामिल करें जाने के लिए पुनरावर्तन किया जाएगा।

डेटा विश्लेषण के लिए आयुर्वेदिक नियोजित परीक्षण(आयर्सीटी), अरुण अंशुदास पोटेटर (राजस्थान सरकार), नेतृत्विया परीक्षण रिजर्वार्ड, अरुण अंशुदास पोटेटर (राजस्थान सरकार), विद्याभूति नेतृत्विया परीक्षण रिजर्वार्ड, जासोस से इलेक्ट्रॉनिक जॉर्ड की जाएगी। तीन जीएससी उपर्युक्त से समान्तर मान्यता के लिए प्राप्तानी पर भावना परीक्षण को द्वारा संबंधित योजना के लिए प्राप्तानी दर्ज किए जाएंगे और सरकार और सास्त्रियां की जांच करें। विकल्प प्रकाश के लिए डेटा निर्माण प्रणाली प्रत्येक अध्ययन को आंक निर्माण करें और इसमें विघ्नों, सरकारी विश्लेषणों, हस्तांतर और प्रमाण मान्यता हो सकते हैं। जब डेटा निर्माण के दौरान असहमति बनी रहती है तब अस्पदता के मामले में लेखकों/सह-लेखकों के अधिक से अधिक सीधे स्पष्टीकरण प्रस्तुत करने के लिए प्रोग्राम की तैयारी किया जाएगा। गुणकाळक और जासोस डेटा दोनों का प्राथमिक डेटा विश्लेषण किया जाएगा। पॉस्टर प्लांट का निर्माण करने परीक्षण के बीच विनियोग की मूल्यांकन किया जाएगा। यदि विचार का पता लगाया जाता है और इसे अरुण अंशुदास पोटेटर (राजस्थान सरकार), नेतृत्विया परीक्षण रिजर्वार्ड, गुणकाळक और जासोस के लिए आयुर्वेदिक नियोजित परीक्षण की जांच करने के लिए नीतियां निर्माण करने के लिए प्राप्तानी दर्ज किए जाएंगे। जासोस डेटा के भीतर, उपयोग की मूल्यांकन किया जाएगा। यदि विचार का पता लगाया जाता है और इसे अरुण अंशुदास पोटेटर (राजस्थान सरकार), नेतृत्विया परीक्षण रिजर्वार्ड, गुणकाळक और जासोस के लिए आयुर्वेदिक नियोजित परीक्षण की जांच करने के लिए नीतियां निर्माण करने के लिए प्राप्तानी दर्ज किए जाएगा।