PROTOCOL

A Protocol for Systematic Review of Ayurvedic Interventions in Iron-deficiency Anemia

Devi R Nair[1], Pradeep Kumar PP[2], Remya E[3]

Abstract

Background: In India, iron-deficiency anemia (IDA) among women is a problem of major health significance. This study reviews the clinical trials on Ayurvedic management of IDA to generate evidence on their safety and efficacy.

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

Materials and methods: Randomized controlled trials (RCTs), quasi-RCTs (QRCT), controlled clinical trials (CCTs), and multiple-arm clinical trials that are of at least 3 weeks' duration will be included. Studies having patients fulfilling the diagnostic criteria based on the symptomatology of *Pandu* and IDA will be selected. Search strategy (for electronic search) Ayurveda OR Ayurvedic OR Ayurvedic treatment OR *Pandu* OR iron-deficiency anemia AND *Mrit bhakshana janya pandu* as titles, abstracts, or keywords from online databases will be searched. 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 the participants (inclusion criteria). Data extraction forms for individual study shall be prepared.

Dissemination: The results of systematic review will be disseminated manually and electronically in peer-reviewed journals. The present systematic review may help the health authorities in framing health policies more effectively.

Trial registration number: PROSPERO 2019 CDR42019131191 Dated 29/07/2019.

Keywords: Ayurveda, Iron-deficiency anemia, *Pandu*.

Journal of Research in Ayurvedic Sciences (2019): 10.5005/jras-10064-0076

Introduction

Rationale

Iron-deficiency anemia (IDA) is a global public health crisis. As per the World Health Organization's (WHO) report, half of the total anemia is IDA. In children and other groups, 30–50% of anemia is caused by iron deficiency.[1] As such, iron deficiency is the most common cause of anemia worldwide. Iron-deficiency anemia afflicts a subset of the 2 billion people worldwide who are nutritionally iron deficient.[2] Iron-deficiency anemia among women in India is a problem of major health significance. According to WHO guidelines for control of IDA, nutritional anemia is a major health problem in India and is primarily due to iron deficiency. The National Family Health Survey-3 data suggest that the prevalence of anemia in adolescent girls (15–19 years) is 56%.[3] Prevalence is the highest among adolescent girls, pregnant women, and lactating mothers. In pregnancy, IDA is associated with maternal mortality, preterm labor, low birth weight, and infant mortality. This may be due to deficient intake or absorption of iron, increased demand during adolescence, heavy blood loss during menstruation, parasitic infestation, etc.

The features of the disease *Pandu* (anemia) especially, *Mrtibhakshanajanyapandu* (anemia caused by ingestion of mud) mentioned in different Ayurveda texts are similar to that of IDA in modern science. It may be either due to *Alparakta* (less *Rakta Dhathu*) or *Dushtaraktadhathu* (vitiated *Rakta Dhathu*). *Dushti of Raktadhathu* may be attributed to vitiated *Rasa* leading to *Raktadhathudushti* (vitiation of *Rakta Dhathu*) due to *Dhatwagnimandya* (due to less metabolic fire in *Dhathu* level) and *Srotodushti* (vitiation of body channels).

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How to cite this article: Nair DR, Pradeep Kumar PP, Remya E. A Protocol for Systematic Review of Ayurvedic Interventions in Iron-deficiency Anemia. J Res Ayurvedic Sci 2019;3(2):60–63.

Source of support: Central Council for Research in Ayurvedic Sciences, Ministry of Ayush, Government of India

Conflict of interest: None

Treatment Modalities of IDA

The treatment of IDA will depend on its cause and severity. Treatment modalities may include iron supplements, procedures, and dietary changes. Severe deficiency may require intravenous iron therapy or a blood transfusion.[4]

Complications of Iron Supplementation

Patients in whom the gastrointestinal blood loss exceeds the intestinal ability to absorb iron (e.g., intestinal angio dysplasia) may develop IDA refractory to oral iron supplementation. This population of patients proves to be the most challenging to manage.[4]

Ayurvedic Treatment Approach

Treatment modalities followed in Ayurveda is purely based on the type of above-mentioned *Nidaana* (etiological factors).

Two main types of treatment modalities in Ayurveda are *Shodhana* (purification) and *Samana* (pacification). *Shodhana* (purification) therapy is advised whenever there is a *Dhatwagni Mandya* (low metabolic fire) and *Pravara Rogibala* (high patient strength). According to Ayurvedic concepts, the *Nidana* (etiology) factors cause *Pitta Pradhana Srotorodha* (obstruction of body channels with increase in *Pitta Dosha* symptoms), which will affect *Anuloma Gati* (movement in right direction) of *Vayu*, will ultimately lead formation of *Ama* (cellular undigested material). Treatment modality of *Pandu* should aim at clearing the *Srotorodha* (obstruction of body channels) and making *Anuloma Gati* (movement in right direction) of *Vayu*. For this purpose, *Teekshna Shodhana* (strong purification) should be done. After clearing *Srotorodha*, to enable the *Dhatu* to regain its *Bala* (strength), *Sarpipana* (administration of Ghee)[5] is indicated as *Samana* modalities (pacification therapy). But, in cases of *Avara Shareera Bala* (less physical strength), *Shamana Chikitsa* (pacification therapy) has to be done directly.

Many *Shamana* (pacification) drugs are mentioned in Ayurveda text but very few of them have been tested clinically in the present era. Along with efficacy, safety and quality of these modalities and trials should also be analyzed and critically evaluated and highlighted in public domain.

Objectives

Primary objective of the present study includes systematic review of selected studies and systematic review of the published clinical data in view of safety and efficacy of Ayurvedic interventions in the management of IDA. Secondary objective of the present study includes meta-analysis of the published clinical data in view of safety and efficacy and effectiveness in the management of IDA.

Review Question

The review question includes what is the efficacy and safety of Ayurveda interventions for the management of IDA and what is the relative efficacy and safety of *Shodhana* (purification) and *Shamana* (pacification) Ayurveda treatment modalities for IDA management.

Materials and Methods

Study type is systematic review, meta-analysis.

The purpose of the present study was evidence generation for the safety and efficacy of Ayurveda interventions for IDA. Search strategy includes published data available on search engines like PubMed and gray literature and published data available at Institute for Post Graduate Teaching and Research in Ayurveda, Gujarat Ayurved University, Jamnagar, Govt. Ayurveda Medical Colleges at Kannur, Kottakkal, Trivandrum, Trippunithura, and VPSV Ayurveda College, Kottakkal on Ayurveda interventions in IDA.

Timelines of the Present Study

The timeline of the present study is 6 months for data collection and analysis and 3 months for journal selection and publication.

Criteria for Selection of Study

Types of study include randomized controlled trials (RCTs), quasi-randomized controlled trials (QRCTs), controlled clinical trials (CCTs), and multiple-arm clinical trials. Studies having patients fulfilling the diagnostic criteria based on symptomatology of *Pandu* and IDA explained in classic Ayurveda texts and medical literature of age ranging from 10 to 70 and of either sex will be selected. Inclusion criteria will be low hemoglobin (<7.7 mmol/L in men and 7.4 mmol/L in women), a low serum iron (<7.1 μg/L), a low serum ferritin (storage form of iron) (<30 ng/L), a low transferrin saturation (<15%), and a high total iron-binding capacity (>13.1 μmol/L).[6]

Types of Interventions

It includes Ayurveda treatment (*Shamana* or/and *Shodhana*) with any dose, type, schedule, drug, dosage form, and advised *Pathyapathya* (lifestyle modifications). (Patients may receive additional non-Ayurveda intervention in all groups of study.) Comparators/control in present study are Ayurveda treatment (*Shamana* or/and *Shodhana*) with different dose, type, schedule, medicine, and medicine form as compared to intervention(s)/exposure(s), placebo and/or sham therapy and/or *Shamana* therapy and/or non-Ayurveda interventions.

Outcome

Primary Outcome

Primary outcome will be response to treatment (improvement in subjective and/or objective criteria of assessment), serious adverse events (resulting in death, disability or incapacity, complications, life-threatening, or hospitalization or prolonged hospitalization).

Timing and Effect Measures

No restrictions will be made in inclusion of study in review on the basis of outcomes mentioned above. Administration timings vary from 7 to 60 days as different categories of medications are included for review.

Secondary Outcome

Withdrawals due to adverse events or lack of efficacy or inconvenience of therapy/treatment, number of patients with specific adverse event will be treated as secondary outcome.

Timing and Effect Measures

During the study period or up to 1 month after the completion of study.

Search Methods for Identification of Studies

Following electronic databases will be searched—PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), AYUSH Research Portal (Govt. of India), etc.

There will be no language restrictions. Studies published between January 1990 and upto March 2019 will be sought. The search will be rerun just before the final analyzes and further studies will be retrieved for inclusion.

Search Strategy (for Electronic Search)

Ayurveda OR Ayurvedic OR Ayurvedic treatment OR Pandu OR iron deficiency anemia and Mrtbhakshanajanyapandu as titles, abstracts, or keywords. Online database searched include PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials), AYUSH Research Portal (Govt of India), DHARA, Google Scholar, and online clinical trials registers.

Data Analysis[7]

Two investigators including a consultant (statistics) will analyze data by using appropriate software. Dichotomous data will be presented and combined using relative risks, continuous data will be summarized by arithmetic means and standard deviations, and data will be combined by using weighted mean differences. 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 the 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 Operative Procedures (SOPs) administered/adverse events during the protocol), and (4) outcomes (in terms of safety/effectiveness/efficacy/improvement in quality of life).

Risk of Bias Assessment

For each outcome measured from individual studies, efforts shall be taken to discuss the risk of bias, consistency, precision, and reporting bias. Cochrane risk of bias tool may be used for RCTs and risk of bias in nonrandomized studies of interventions for nonrandomized controlled trials for risk of bias assessment.

When disagreement persists or in case of ambiguity at the time of data extraction, efforts shall be initiated to obtain as much clarifications as possible directly from authors/coauthors.

Strategy of Data Synthesis

Both qualitative and/or quantitative data as collected from various sources shall be considered for primary data analysis. If it is a narrative review, the different treatment modalities and different presentation of the disease condition shall be discussed. The narrative pooled data in the form of descriptive and summary measures shall be represented in tabular and graphical form.

In cases where pooled estimates can be obtained, the systematic review will be followed by a meta-analysis; others would just be presented as a narrative review. The analysis of the systematically collected data shall be analyzed using R/Rev Man software. Dichotomous data will be presented and combined using relative risks, continuous data will be summarized by arithmetic means and standard deviations, and 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 χ^2 test, with a p value of 0.05, indicating statistical significance, and using the I^2 test with a value of 50% 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 Consideration

Written approval of Institutional Ethics Committee will be obtained. A voluntary, signed, witnessed informed consent will be obtained from the institutes/practitioners for sharing the unpublished data.

Coordination of Study

Coordinating Center

National Ayurveda Research Institute for Panchakarma, Cheruthuruthy, Thrissur, Kerala, India.

Study Monitoring

This study will be monitored periodically with approval of authority of Central Council for Research in Ayurvedic Sciences. 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.

Acknowledgments

Author acknowledged Director General, Central Council for Research in Ayurvedic Sciences for his continuous support.

References

1. World Health Organization. Conclusions and recommendations of the WHO Consultation on prevention and control of iron deficiency in infants and young children in malaria-endemic areas. Food Nutr Bull 2007;28(4 Suppl):S621–S627. DOI: 10.1177/15648265070284s414.
2. Viteri FE. A new concept in the control of iron deficiency: community-based preventive supplementation of at-risk groups by the weekly intake of iron supplements. Biomed Environ Sci 1998;11(1):46–60.
3. Kumari R, Bharti RK, Singh K, et al. Prevalence of iron deficiency and iron deficiency anemia in adolescent girls in a teritiary care hospital. J Clin Diagn Res 2017;11(8):BC04–BC06. DOI: 10.7860/JCDR/2017/26163.10325.
4. Johnson-Wimbley TD, Graham DY. Diagnosis and management of iron deficiency anemia in the 21st century. Therap Adv Gastroenterol 2011;4(3):177–184. DOI: 10.1177/1756283X11398736.
5. Taradatt Pandit Panta Shaastri, editor. Caraka Samhita of Agnivesa, Chikitsa Sthana, ch. 16, Ver. 117–118, 2nd ed. Varanasi: Choukhamba Orientalia; 2005.
6. Jacob TJ, Perakath B, Keighley MR. Surgical intervention for anorectal fistula. Cochrane Database Syst Rev 2010;5:CD006319. DOI: 10.1002/14651858.CD006319.pub2.
7. Bermejo F, García-López S. A guide to diagnosis of iron deficiency and iron deficiency anemia in digestive diseases. World J Gastroenterol 2009;15(37):4638–4643. DOI: 10.3748/wjg.15.4638.

हिन्दी सारांश

आयरन डेफ़िशियनसी एनीमिया के प्रबंधन में आयुर्वेदिक चिकित्सा- सिस्टेमेटिक रिव्यू के लिए प्रोटोकॉल

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परिचय: भारत में महिलाओं में आयरन की कमी से होने वाली रक्ताल्पता या एनीमिया (आईडीए) एक प्रमुख स्वास्थ्यकी समस्या है। यह अध्ययन आईडीए के प्रबंधन मे आयुर्वेदिक चिकित्सा की सुरक्षितता और प्रभावकारिता पर साक्ष्य उत्पन्न करने की समीक्षा करता है।

उद्देश्य: वर्तमान सिस्टेमेटिक रिव्यू का प्राथमिक उद्देश्य चयनित अध्ययनों की व्यवस्थित समीक्षा, आयर्न की कमी से होने वाली एनीमिया के प्रबंधन में आयुर्वेदिक चिकित्सा की सुरक्षितता और प्रभावकारिता को देखते हुए प्रकाशित नैदानिक आंकड़ों की व्यवस्थित समीक्षा करना है।

विधी और विश्लेषण: रेंडमाइज्ड कंट्रोल ट्रायल, क्वासी रेंडमाइज्ड कंट्रोल ट्रायल, रेंडमाइज्ड कंट्रोलड् क्लीनिकल ट्रायल, मल्टीपल आर्म क्लीनिकल ट्रायल जो कम से कम 3 सप्ताह की अवधि के हैं, ऐसे अध्ययन इस सिस्टेमेटिक रिव्यू में शामिल किए जाएंगे। 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। संभावित पात्र परीक्षणों के पूर्ण लेख प्राप्त किए जाएंगे और स्वतंत्र रूप से प्रतिभागियों के प्रकार (समावेशन मानदंड) के आधार पर समीक्षा में शामिल किए जाने के लिए मूल्यांकन किया जाएगा।

प्रसार : सिस्टेमेटिक रिव्यू के परिणामों को हस्तचालित रूप से और इलेक्ट्रॉनिक रूप से पियर रिव्यूड् जर्नल्स में प्रकाशित कर प्रसारित किया जाएगा। यह अध्ययन स्वास्थ्य नीतियों को अधिक प्रभावी ढंग से तैयार करने में मददगार रहेगा।

परीक्षण पंजीकरण संख्या PROSPERO :2019 No. :CDR42019131191; दिनांक :29-/07/2019