PROTOCOL

Efficacy and Safety of Ayurveda Interventions for Hypothyroidism in 18–60 Years' Age-group: A Systematic Review Protocol

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Abstract

Introduction: Ayurvedic interventions have been in practice for treatment of thyroid-related disorders alone or in combination with complementary medicine. No systematic review has been conducted for assessing the efficacy and safety of Ayurvedic intervention in hypothyroidism. Present study aimed to provide quality evidence to assess for the efficacy and safety of Ayurveda interventions for hypothyroidism in the 18–60 years' age-group.

Materials and methods: For collection of data, all research article based on randomized controlled trials, multiple-arm clinical trials, nonrandomized clinical trial, quasi-randomized controlled trials having intervention period of at least 12 weeks' duration will be considered and searched from inception to September 2019 in several databases. Primary outcome will include response to treatment (improvement in subjective criteria of assessment, i.e., hypothyroidism-related symptoms), effect on values of laboratory measures related to thyroid gland functioning like tri-iodothyronine (T3), tetra-iodothyronine (T4), and thyroid-stimulating hormone (TSH) and serious adverse events. Secondary outcome will include measurement of health-related quality of life. Data extraction will be done independently by three reviewers in a predefined format. A narrative synthesis will be conducted for all included study. If extracted data will be eligible for meta-analysis, a meta-analysis will be conducted.

Ethics and dissemination: This review does not require formal ethical assessment and approval, as no confidential participant data will be included. Findings will be disseminated widely through publication, conference, and symposia.

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Keywords: Ayurveda, *Galaganda*, Hypothyroid, Protocol, Systematic Review.

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Background

Modern Perspective

"Hypothyroidism is characterized by a broad clinical spectrum ranging from an overt state of myxedema, end organ effects and multisystem failure to an asymptomatic or subclinical condition with normal levels of thyroxine (T4) and tri-iodothyronine (T3) and mildly elevated levels of serum thyrotropin. The prevalence of subclinical hypothyroidism in the developed world is about 4–15%".[1]

Thyroid gland produces two hormones i.e., T3 and T4. For cell differentiation (in developmental phase) and maintenance of homeostasis (metabolic and thermogenic homeostasis), these hormones play a key role. In "Harrison's Principles of Internal Medicine" book, it is mentioned that "autoimmune disorders of the thyroid gland can stimulate the overproduction of thyroid hormones (thyrotoxicosis) or cause glandular destruction and hormone deficiency (hypothyroidism)".[2] Hypothyroidism is defined as reduced production of thyroid hormones. The causes of hypothyroidism are various and are usually divided into two categories: first, the permanent loss or destruction of the thyroid through processes such as autoimmune diseases or irradiation injury is described as primary hypothyroidism, which is the cause of approximately 99% of cases of hypothyroidism; second, insufficient stimulation of the normal thyroid gland as a result of a hypothalamic or pituitary disease or defects in the TSH molecule is called central or secondary hypothyroidism.[3] Hypothyroidism can affect all organ systems and its clinical presentations vary with the severity of thyroid hormone deficiency and the length of time the body has been deprived of the proper amount of the hormones. Signs and symptoms in adults may include fatigue and sluggishness, increased sensitivity to cold, constipation, pale and dry skin, brittle fingernails and hair, a puffy face, hoarse voice, an elevated blood cholesterol level, unexplained weight gain, muscle aches, tenderness, stiffness and weakness, pain, stiffness or swelling in the joints, heavier than normal menstrual periods, and depression. Hypothyroidism in infants and teenagers may result in poor growth and mental development as well as delayed development of permanent teeth and puberty.

An appropriate laboratory evaluation is critical to establish the diagnosis and the cause of hypothyroidism. Per "Harrison's

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Principles of Internal Medicine" (chapter: Disorders of thyroid gland) TSH assay should always be used as the primary test to establish the diagnosis of primary hypothyroidism; free thyroxine or total thyroxine are more valuable measures than TSH for the diagnosis of secondary hypothyroidism. Additional tests may include thyroid peroxidase antibodies (TPOAbs), thyroglobulin antibodies, thyroid scans, and ultrasonography. Normal TSH level excludes a primary abnormality of thyroid function. The finding of an abnormal TSH level must be followed by measurements of circulating thyroid hormone levels to confirm the diagnosis of hyperthyroidism (suppressed TSH) or hypothyroidism (elevated TSH). Autoimmune thyroid disease is detected most easily by measuring circulating antibodies against TPO iodine deficiency remains a common cause of hypothyroidism worldwide. Autoimmune process gradually reduces the thyroid function, and there is a phase of compensation when the normal thyroid hormone levels are maintained by a rise in TSH. Some patients may have minor symptoms, and it is referred to as subclinical hypothyroidism. By definition, subclinical hypothyroidism refers to biochemical evidence of thyroid hormone deficiency in patients who have fewer no apparent clinical features of hypothyroidism. Later, unbound T4 levels fall and TSH levels rise further; symptoms become more readily apparent at this stage (usually TSH >10 mIU/L), which is referred to as clinical hypothyroidism or overt hypothyroidism. Once clinical or subclinical hypothyroidism is confirmed, the etiology is usually easily established by demonstrating the presence of TPOAbs, which are present in >90% of patients with autoimmune hypothyroidism.[2]

Ayurveda Perspective

Even though there are no direct references in Ayurvedic classical texts in terms of hyper- or hypoproduction of the hormone by the thyroid gland (*Avatu Granthi* in Sanskrit), but according to principles of Ayurvedic pathogenesis, the main factor responsible is hypofunctioning of *Agni* (*Agnimandya*). *Dhatvagnimandhya* also occurs in pathogenesis of the disease and all these features are similar to the modern concept of metabolism, i.e., decreased basal metabolic rate.

Apart from this, there is a disease by the name *Galaganda* and *Gandmala*, which are characterized by neck swelling, which are known to be diseases of the thyroid gland. *Galaganda* is due to vitiation of the *Kapha dosha* mainly along with *Vata* and *Medas*.

Description of the Intervention

Modern Perspective

Conventional treatment for hypothyroidism is laevo-thyroxine. Dose of laevo-thyroxine must be adjusted according to age and weight, considering the duration and progress of the disease.

Ayurvedic Perspective

Dipana, *Pachana* drugs may be used to treat *Agnimandata*. For *Samprapti Vighatana, Medohara, Karshana,* and *Lekhana dravya* may be used. *Rasayan* therapy (*Naimittika Rasayana*) may be beneficial for long-term use.

The therapies like *Vamana, Virechana, Nasya, Swedana, Dhoomapana, Siravyadha, Agnikarma, Ksharayogas, Pralepa, Langhana*, and *Purana ghritapana.*

In *Kaphaja Galaganda*, *Upanahasweda* is advised. The *Chikitsa* includes *Nidana Parivarjana*, *Samshodana Chikitsa*, *Samshamana Chikitsa*, and *Rasayana.*

Rationale of the Study

Ayurvedic interventions have been in practice for treatment of thyroid-related disorders alone or in combination with complementary medicine. No systematic review has been conducted for assessing the efficacy and safety of Ayurvedic intervention in hypothyroidism. This systematic review will provide evidence for the inclusion of Ayurvedic interventions in the treatment protocol of hypothyroidism.

Objectives

Primary

Systematic review of the published data in view of the safety and efficacy of Ayurvedic interventions in the management of hypothyroidism.

Secondary

A meta-analysis of the published clinical data in view of the safety and efficacy of Ayurvedic interventions in the management of hypothyroidism.

Materials and Methods

Eligibility Criteria

Study Characteristic: Inclusion Criteria

Population

- Individual having hypothyroidism (age-group 18–60 years) irrespective of the cause.
- Studies with diagnostic and classification criteria that are consistent with the accepted diagnostic criteria will be taken, considering valid criteria at the time of initiation of the trial.
- If it is necessary to take the study, then the diagnostic criteria used by the author may be considered.

Intervention

- Ayurvedic intervention: oral formulations or any *panchakarma* therapy or herbs (single/multiherbal) following the principles of Ayurvedic treatment for hypothyroidism/*Galaganda* including lifestyle modifications, i.e., diet/lifestyle/Yoga (*Pathayapathya*)
- Ayurvedic intervention with/without any pharmacological intervention of hypothyroidism (including thyroid hormone therapy)

Comparisons or control groups

- No treatment
- Placebo
- Any pharmacological intervention of hypothyroidism (including thyroid hormone therapy)
- Nonpharmacological intervention, i.e., diet/lifestyle/Yoga

Outcomes: primary outcome

- Response to treatment, i.e., improvement in subjective (hypothyroid-related symptoms) and/or objective (hypothyroid-related laboratory parameters) criteria of assessment.
- Improvement in objective parameters (hypothyroid-related laboratory measures, i.e., T3, T4, and TSH).
- Any adverse events leading to hospitalization, disability, and death.

Timing and effect measures: No restrictions will be made in the inclusion of the study in review on the basis of the outcomes mentioned above.

Secondary outcome:

- Assessment of health-related quality of life.
- Assessment of number of withdrawal cases.

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

Study Design

For collection of data, all research articles based on randomized controlled trials, multiple arm clinical trials, nonrandomized clinical trial, quasi-randomized controlled trials having intervention period of at least 12 weeks' duration will be considered and searched from inception to September 2019 in several databases. Studies on impact of Ayurvedic intervention having information on thyroid-related laboratory measures and their concentration at baseline and at the end of treatment or studies that report comparative data on at least one of the outcome measures of the effectiveness of the interventions.

Study Characteristic: Exclusion Criteria

Studies on animal trials, observational studies (case–control, cross-sectional, cohort studies), editorials, dissertation, meetings, abstracts, having insufficient information on thyroid-related subjective/objective parameters.

Report Characteristic

Search Dates: Since inception to September 2019

Language: English/Indian Language

Publication Status: Findings will be disseminated widely through publication.

Information Sources (Search Methods)

A predefined search strategy will be used to search for studies in the following manner:

- Search Dates: Since inception to September 2019
- Language: English/Indian Language
- Electronic databases:
  - The Cochrane Library
  - MEDLINE
  - EMBASE
  - Open-access institutional repositories
  - Digital Helpline for Ayurveda Research Abstracts
  - AYUSH Research Portal (maintained by the Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Government of India)
  - For dissertations in public domain: http://shodhganga.inflibnet.ac.in/simple-search
  - Ayurveda research database
  - Ayurveda journals published from India.
  - Clinicaltrials.gov, current controlled trials meta register, the World Health Organization International Clinical Trials Registry Platform.

Search Strategy

A comprehensive, systematic search for information will be conducted in several databases based on the following the main search string:

TSH OR thyrotropin OR triiodothyronine OR thyroxine OR "Iodide peroxidase" OR "TPO protein" OR"TPO proteins" OR thyroid OR T4 OR T3 OR hypothyroid* OR levothyroxine AND Ayurveda OR Ayurvedic OR Ayurvedic treatment AND Galaganda OR Gandmala OR Dhatvagnimandhya

- All terms will be searched in MeSH/ subject headings, abstract, article title.
- Limitation will not be applied for obtaining the best possible results.

Method of Review

- Details of methods: Review will be done by three reviewers and the fourth reviewer will resolve any dispute.
- Quality assessment: Specific tools will be used for the assessment of quality of selected papers.
- Extraction of Data: For studies fulfilling the inclusion criteria, data extraction will be done independently by four authors [Neha Dubey (ND), Girindra Kumar Bora (GKB), Ekta (E), and Jeuti Rani Das (JRD)]. Any dispute will be solved through discussion. If necessary, the author ND will again do the review for resolving the disagreement based on author name, publication year, study design, no of participants in each group, intervention type, duration of treatment, data related to subjective/objective parameters.
- Narrative synthesis: Narrative synthesis will be done on the mechanism of action of intervention, for any correlations between the studies and for assessing robustness of the study.
- Meta-analysis: If extracted data is eligible for meta-analysis, it will be conducted.

Presentation of Results

Presentation of result will include data extraction form, tables, flowchart, and forest plots of the reviewed studies.

Data Analysis

Data analysis will be done by appropriate software. Relative risk assessment will be done for dichotomous data, mean and standard deviation will be used for assessing continuous data keeping 95% confidence interval, assuming that the data are normally distributed. Median and range will be presented in tabular form. For individual studies meeting/not meeting quality criterion, separate summary effect estimates will be generated. Chi-square test (p value < 0.05) will be used for assessing qualitative data and for overlapping confidence intervals (by observing forest plots). If heterogenicity is observed between the studies, then analysis will be done by random-effect model. Robustness of result will be assessed by sensitivity analysis (if there are sufficient trials).

Risk of Bias Assessment

Assessment of risk of bias will be done on the basis of allocation sequence, allocation concealment, blinding, addressing of outcome data inadequately, reporting of selective outcome, and any other problems that may increase the risk of bias.

Strategy of Data Synthesis

Analysis of subgroup/subsets: When sufficient data are available, subgroup analyzes will be used to explore whether the pooled effect sizes differ on the following variables:

- Different Ayurvedic interventions
- Duration of intervention
- Variation due to geographical variability.

Assessment of meta-bias: Publication bias and selective reporting of outcomes within the included studies will also be assessed.

Confidence of Cumulative Evidence

For grading quality of evidence, the grading of recommendations assessment development and evaluation approach will be used. The assessment will include all the studies included in the review.

Ethics and Dissemination

This review does not require formal ethical assessment and approval, as no confidential participant data will be included.

Study Registration

The International Prospective Register of Systematic Reviews (PROSPERO 2019 CRD42019144799).

Acknowledgment

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हिन्दी सारांश

18-60 आयु वर्ग के हाइपोथायरायडिज्म रोगियों में आयुर्वेदीय चिकित्सा विधियों के प्रभाव का मूल्यांकन: एक सिस्टेमेटिक रिव्यू प्रोटोकॉल

नेहा दुबे, एकता, ज्योतिराणी दास, गिरीन्द्र कुमार बोरा, भोगवल्ली चन्द्रशेखर राव, नारायणम् श्रीकान्त

परिचय: आयुर्वेदीय चिकित्सा विधियों का अकेले या थायराइड हार्मोन थेरेपी के साथ संयोजन में कई वर्षों तक हाइपोथायरायडिज्म के उपचार में उपयोग किया गया है। हालांकि, हाइपोथायरायडिज्म में आयुर्वेदिक हस्तक्षेप की प्रभावकारिता का मूल्यांकन करने के लिए कोई सिस्टेमेटिक रिव्यू नहीं किया गया है। प्रस्तुत अध्ययन का उद्देश्य 18-60 आयु वर्ग के हाइपोथायरायडिज्म रोगियों में आयुर्वेदीय चिकित्सा विधियों के सुरक्षितता एवं प्रभावकारिता के मूल्यांकन द्वारा गुणात्मक साक्ष्य देना हैं।

विधियाँ: यह एक सिस्टेमेटिक रिव्यू है अतः इसमें आरंभ से सितंबर 2019 तक, 12 सप्ताह की अवधि के रेंडमाइज्ड कंट्रोल ट्रायल (आरसीटी), नॉन रेंडमाइज्ड कंट्रोल ट्रायल (एनआरसीटी), क्वासी रेंडमाइज्ड कंट्रोल ट्रायल (क्यूआरसीटी), कंट्रोल क्लिनिकल ट्रायल (सीसीटी), मल्टिपल आर्म्स क्लिनिकल ट्रायल से संबन्धित अनुसंधान लेखों को सम्मिलित किया जाएगा। प्राथमिक परिणामों में उपचार का प्रभाव (गुणात्मक/ संख्यात्मक सुधार अर्थात् हाइपोथायरायडिज्म से संबंधित लक्षण), हाइपोथायरायडिज्म से संबंधित प्रयोगशाला परीक्षण पर प्रभाव [जैसे कि थायरोक्सिन (टी4), ट्राईआयोडोथायरोनिन (टी3) और थायराइड-उत्तेजक हार्मोन (टीएसएच)] इत्यादि का अध्ययन किया जाएगा यदि पर्याप्त डेटा उपलब्ध होगा तब एक मेटा अनालिसिस किया जा सकता है।

एथिक्स एवं प्रसार: इस समीक्षा में औपचारिक एथिकल मूल्यांकन और अनुमोदन की आवश्यकता नहीं है, क्योंकि कोई भी गोपनीय प्रतिभागी डेटा शामिल नहीं किया जाएगा। प्रकाशन, सम्मेलन और संगोष्ठी के माध्यम से निष्कर्षों का व्यापक रूप से प्रसार किया जाएगा।

अध्ययन पंजीकरण संख्या: PROSPERO 2019 CRD42019144799

शब्द कुंजी : हाइपोथायरायड, आयुर्वेद चिकित्सा, सिस्टेमेटिक रिव्यू