

INPLASY PROTOCOL

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Conflicts of interest:

None.

Effect of Chinese herbal medicine for patients with benign thyroid nodules in adults

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Review question / Objective: Does Chinese herbal medicine have therapeutic effect on thyroid nodules? Is it safe to treat thyroid nodules with Chinese herbal medicine? This is the problem that this review want to solve in this research.

Condition being studied: A thyroid nodule is a discrete lesion within the thyroid gland that is palpable and ultrasonographically distinct from the surrounding thyroid parenchyma. Thyroid nodule (TN) are divided into cysts, inflammatory nodules and tumoural nodules (benign, malignant) and may present as proliferative nodular goiter. TN, whether solitary or multiple, are a common clinical problem. Epidemiologic studies have shown the prevalence of palpable TN to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world. In contrast, high-resolution ultrasound (US) can detect TN in 19%–68% of randomly selected individuals, with higher frequencies in women and the elderly. The incidence of TN varies among different populations around the world. In iodine-sufficient areas, for instance, palpable TN are found in about 4% to 7% of the population, and they are even more prevalent among individuals living in areas of iodine deficiency. TN are more common as age increases and as iodine intake decreases, and they occur more frequently in women. In all, 3% to 7% of the population with palpable thyroid nodules has been found in China; however, high-resolution ultrasonography can detect thyroid nodules in 20% to 70% of the population. As a result, we are now facing an 'epidemic' of TN.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 December 2020 and was last updated on 18 December 2020 (registration number INPLASY2020120093).

INTRODUCTION

Review question / Objective: Does Chinese herbal medicine have therapeutic effect on

thyroid nodules? Is it safe to treat thyroid nodules with Chinese herbal medicine? This is the problem that this review want to solve in this research.

Rationale: Traditional Chinese Medicine holds that the occurrence of thyroid nodules is related to environment, diet and emotion. The treatment of benign thyroid nodules is based on its etiology, pathogenesis, and treatment rules. Most of the prescriptions are combined with self-made prescriptions, and drugs such as resolving phlegm and softening, soothing the liver and regulating qi, activating blood and removing blood stasis, clearing heat, and tonic drugs are often used. Clinical studies from the Chinese literature show that Chinese herbal preparations might shrink TN without producing significant adverse effects. According to the theory of Chinese medicine, practitioners recognise that TN are caused by blood stasis, Qi stagnation and phlegm coagulation. Several explanations have been offered for the effects of CHM in inhibiting the proliferation of TN cells: (1) decreased sensitivity of thyroid nodule cells to TSH; (2) decreased activity of TSH; (3) induced apoptosis of TN cells; and (4) direct injury of TN cells.[31] Herbal preparations are prescribed by practitioners on the basis of patients' symptoms and observations of the tongue and pulse. This accounts for the great variation seen in the use of herbal preparations.

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even more prevalent among individuals living in areas of iodine deficiency. TN are more common as age increases and as iodine intake decreases, and they occur more frequently in women. In all, 3% to 7% of the population with palpable thyroid nodules has been found in China; however, high-resolution ultrasonography can detect thyroid nodules in 20% to 70% of the population. As a result, we are now facing an 'epidemic' of TN.

METHODS

Search strategy: We will search electronic databases, such as PubMed, Excerpta Medica Database (EMBASE), MEDLINE, Web of Science, Cochrane Library, SpringerLink, WHO International Clinical Trials Registry Platform (ICTRP), Wanfang Database, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and Chinese Scientific Journal Database (VIP). There are no language restrictions for retrieving literatures. Case reports, animal studies, editorials, expert opinions, reviews without original data and studies on pediatric population were excluded. Using keywords included benign thyroid nodules, thyroid benign nodules, thyroid nodules, herbal, drug therapy, herbal treatment and traditional treatment.

Participant or population: Participants must be imaging-confirmed TN, and aged 18 years and older. Participants with malignant thyroid nodules, infection and other pathologic change was not taken in consideration in this study.

Intervention: Experimental interventions use Chinese herbal medicines (CHM) as a separate exercise. CHM included all type of herbal medicine. There is no restriction of dosage, frequency, administration method, or duration of treatment. The usage of western medicine in the control group should be consistent with that in the experimental group.

Comparator: Control interventions include placebo, blank control, and conventional medicine (such as levothyroxine).

Study designs to be included: RCTs will be included in our study.

Eligibility criteria: We will put all RCTs related to Chinese herbal medicine for thyroid nodules into the study. There are no language restrictions for retrieving literatures. Case reports, animal studies, editorials, expert opinions, reviews without original data and studies on pediatric population were excluded.

Information sources: We will screen the comprehensive literature from relevant electronic databases, including 7 English databases, consisting of PubMed, Excerpta Medica Database (EMBASE), MEDLINE, Web of Science, Cochrane Library, SpringerLink, and WHO International Clinical Trials Registry Platform (ICTRP), and 4 Chinese databases, namely Wanfang Database, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and Chinese Scientific Journal Database (VIP). All the RCTs will be collected from the database establishment to November 2020. The search strategy for selecting the fields of topic, title, or abstract was unique referring to the characteristics of databases.

Main outcome(s): The primary outcomes include nodule volume reduction $\geq 50\%$ (evaluated by ultrasonography measurements), pressure symptoms, cosmetic complaints or both, and adverse events.

Additional outcome(s): The additional outcomes include quality of life (measured by a validated instrument), cancer occurrence and changes in number and size of thyroid nodules.

Data management: We will organize a session for all reviewers to learn relative information of the study for insight on the purpose and process of the study, and the relevant teacher has been trained and gained certifications in Chinese Cochrane Centre. Two reviewers (Peng Yu and Jing He) independently investigate all relevant literatures and screen from title to abstracts respectively to extract eligible

articles, then exclude repeated. Subsequently, reviewing the full-text and comprehensively considering to identify eligible studies. The all studies that reviewers chosen will be discussed in the group until the final team consensus reached. Disagreements between the reviewers will be settled after group discussion with a third reviewer or expert. If the information is insufficient or unclear, we will contact the corresponding author to ask for more information or clarification via email or phone. Data extraction items included: the first and corresponding author, year of publication, clinical diagnostic information, course of disease, sample size, age of participants, intervention details, control and outcome, treatment time, duration of follow-up, and adverse events. Disagreements will be settled after group discussion and if necessary, consulting experts and arbiter.

Quality assessment / Risk of bias analysis: The assessment of potential bias risk and quality will be executed with two reviewers (Han Li and Haiyang Cai) by the Cochrane Handbook 5.1.0 bias risk assessment tool, including random sequence generation, allocation concealment, the blinding method of participants, researchers, outcome assessment, incomplete result data, selective outcome reporting, and other issues. This the bias risk will take L (low risk), U (unclear risk), and H (high risk) to represent the assessment results.

Strategy of data synthesis: The differences between the intervention group and the control group will be evaluated. The continuous data, we will adopt the mean difference (MD) with 95% confidence intervals (CIs) to analysis the therapeutic efficacy. The other forms of data will be converted into MDS. The standard MD of 95% CIs will be used for the outcome variables of different scales. The other binary data will be converted into relative risk (RR) values. With respect to binary data, we will adopt the RRs with 95% CIs to analysis the processing effect. The meta-analysis studied in this review will be performed using the Cochrane

Collaboration's software program Review Manager v.5.3.5 for Windows. For research with insufficient or missing data, the 2 reviewers (Han Li and Jing Wu) will contact corresponding authors via email or phone to integrate and verify data as far as possible.

Subgroup analysis: If there are a plenty of subgroup studies, subgroup analysis will be conducted to detect the heterogeneity among groups. We will take treatment time or dose of CHM, different forms of herbal medicine, duration or severity of TN, syndrome differentiation, formulations, sex and age of patients into account.

Sensibility analysis: Sensitivity analysis will be conducted to identify the robustness of the conclusions. The main decision nodes include methodologically quality, sample size, missing data. Studies that are not randomly generated to improve conclusions will be excluded.

Language: Chinese and English.

Country(ies) involved: China.

Keywords: Chinese herbal medicine, thyroid nodules, protocol, systematic review.

Dissemination plans: The results of our research will be published at a peer reviewed journal.

Contributions of each author:

Author 1 - Shuang Ouyang - The author designed the experiment and drafted the manuscript.

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