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None declared.

Chinese herbal medicine for children with idiopathic short stature (ISS): a meta-analysis

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Review question / Objective: **Idiopathic short stature (ISS) describes a heterogeneous group of children with many unidentified causes of short stature presently. Chinese herbal medicine (CHM) is an alternative and complementary treatment for children with ISS and has been widely used for ISS. However, the effectiveness of CHM remains unclear and lacks evidence-based medicine support. To systematically evaluate the effect of CHM in the treatment of ISS, we conducted this meta-analysis. Method: Databases including PubMed, Embase, Web of science, Sino-Med, Cochrane, CNKI, VIP, Wangfang Data were electronically searched to collect randomized controlled trials (RCTs) of CHM treatment of ISS from inception to May 2021. Two reviewers independently screened literature, extracted data, and assessed the risk of bias of included studies. Meta-analysis was then performed by using RevMan 5.3. Result: 7 articles were included. There were 569 children with ISS, including 297 in the experimental group and 271 in the control group. The Meta-analysis indicated that herbal medicine was associated with increased height (MD 2.16 points; 95%CI, 0.22 to 4.10; P=0.03), growth velocity (MD 1.47 points; 95%CI, 0.28 to 2.67; P=0.02), IGF-1 level (MD 28.13 points; 95%CI, 22.80 to 33.46; P<0.00001) and growth hormone stimulation test peak (GHP) (MD 3.29 points; 95%CI, 1.54 to 5.04; P=0.0002). Conclusion: Current evidence shows that CHM is effective for children with ISS. Due to the limited quality and quantity of the included studies, more high-quality studies are needed to verify the above conclusions.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 January 2022 and was last updated on 08 January 2022 (registration number INPLASY202210034).

INTRODUCTION

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systematically evaluate the effect of CHM in the treatment of ISS, we conducted this meta-analysis. Method: Databases including PubMed, Embase, Web of science, Sino-Med, Cochrane, CNKI, VIP, Wangfang Data were electronically searched to collect randomized controlled trials (RCTs) of CHM treatment of ISS from inception to May 2021. Two reviewers independently screened literature, extracted data, and assessed the risk of bias of included studies. Meta-analysis was then performed by using RevMan 5.3. Result: 7 articles were included. There were 569 children with ISS, including 297 in the experimental group and 271 in the control group. The Meta-analysis indicated that herbal medicine was associated with increased height (MD 2.16 points; 95%CI, 0.22 to 4.10; P=0.03), growth velocity (MD 1.47 points; 95%CI, 0.28 to 2.67; P=0.02), IGF-1 level (MD 28.13 points; 95%CI, 22.80 to 33.46; P<0.00001) and growth hormone stimulation test peak (GHP) (MD 3.29 points; 95%CI, 1.54 to 5.04; P=0.0002). Conclusion: Current evidence shows that CHM is effective for children with ISS. Due to the limited quality and quantity of the included studies, more high-quality studies are needed to verify the above conclusions.

Condition being studied: Chinese herbal medicine for children with idiopathic short stature (ISS).

METHODS

Participant or population: Children with ISS have clear diagnostic criteria and basis.

Intervention: Chinese herbal medicine, Chinese herbal medicine plus rhGH, Chinese herbal medicine plus lifestyle interventions.

Comparator: rhGH, lifestyle interventions, nutrient supplement.

Study designs to be included: RCTs.

Eligibility criteria: Trials were selected based on the following inclusion criteria:1. Design: Randomized controlled trials (RCTs). 2. Population: Children with ISS have clear diagnostic criteria and basis.3. Treatment duration: At least six months.4. Intervention and control: (a) CHM compared with rhGH; (b) CHM plus rhGH compared with rhGH; (c) CHM plus lifestyle intervention compared with lifestyle intervention; (d) CHM compared with nutrient supplement; (e) CHM plus nutrient supplement compared with nutrient supplement. 5. Outcomes: The primary outcomes are height, bone age, growth velocity, IGF-1 level after treatment. The secondary outcomes are osteocalcin, height standard deviations score (HtSDS), predicting adult height (PAH), change in HtSDS (changes in HtSDS before and after treatment, HtSDS), growth hormone peak (GHP). 6. Languages: Chinese and English.

Information sources: Evidence was gathered by searching electronic English and Chinese language databases, and the methods followed the Cochrane Handbook of Systematic Reviews. English language databases included PubMed、Embase、Web of science、Sino-Med、Cochrane. Chinese language databases included CNKI、VIP、Wangfang Data. Databases were searched from their inception to May 2021 with language limited to Chinese and English. We use subject words and keywords including pediatric, short stature, and CHM to be our search strategy. We also scanned reference lists of the included studies to find additional studies.

Main outcome(s): In the present meta-analysis, we investigated the effects of CHM in children with ISS. The main results of the meta-analysis showed that CHM had an excellent efficiency in increasing the height, growth velocity, IGF-1 level, and GHP. In the comparison between CHM and other essential treatments that are widely used in the clinic, e.g., rhGH, nutrient supplements, and lifestyle intervention including aerobic exercise, dietary structure adjustment, and ensuring adequate sleep, we found that CHM exhibited a similar effect to other treatments in the comprehensive clinical effect such as height, growth velocity, and PAH. Compared with this alone, a

significant impact favored CHM plus rhGH in increasing growth velocity and IGF-1. Compared with lifestyle intervention alone, a significant effect favored CHM plus lifestyle intervention in increasing growth velocity, IGF-1, HtSDS, and PAH. It indicated that a combination with CHM was a more efficacious treatment in ISS than rhGH and lifestyle intervention alone.The primary outcomes are height, bone age, growth velocity, IGF-1 level after treatment. The secondary outcomes are osteocalcin, height standard deviations score (HtSDS), predicting adult height (PAH), change in HtSDS (changes in HtSDS before and after treatment, HtSDS), growth hormone peak (GHP).

Quality assessment / Risk of bias analysis: All studies specified that "randomization" was used to allocate participants to the herbal medicine intervention or the control groups. However, 42.8% of studies(n=3) did not specify the method of random sequence generation [19-21]. Four studies used the random number table method and were at low risk of bias. [15-18] All documents lacked information about allocation concealment, blinding, selective reporting, and other bias and were assessed as unclear risk. The majority (85.7%) were at low risk because there was no missing data. Only one study [16] was at high risk for six missing outcome data.

Strategy of data synthesis: Two researchers (CXY and LYY) independently searched for, selected, and extracted data from the literature. Inconsistent data were discussed by the two investigators to reach a consensus or evaluated by a third senior investigator. The extracted data mainly includes: 1. general characteristics of the included literature (first author's name, publication year, country of study); 2. patient characteristics (age, gender composition, sample size, diagnostic criteria); 3. study design (randomized or non-randomized controlled clinical trial); 4. intervention and control groups (study drug, treatment dose, treatment duration); 5. study outcomes (height, bone age, growth velocity, IGF-1 level, osteocalcin, HtSDS, PAH, HtSDS, GHP); 6. side effects.

Subgroup analysis: The high heterogeneity was detected in height (I2=95%), bone age (I2=72%), growth velocity (I2=100%), IGF-1 level (I2=64%), HtSDS (I2=98%), HtSDS (I2=98%), PAH (I2=92%), osteocalcin (I2=73%) among control groups versus experimental groups. However, due to the small sample size that only seven trials were included in the meta-analysis, it was hard to find the exact resource of heterogeneity. Thus, we further performed subgroup analysis in height, growth velocity, IGF-1 level, HtSDS, osteocalcin, PAH according to the kinds of comparisons (CHM plus rhGH vs. rhGH, CHM plus nutrient supplement vs. nutrient supplement, CHM plus lifestyle intervention vs. lifestyle interventions, CHM plus other intervention vs. other intervention, CHM vs. rhGH, CHM vs. nutrient supplement), duration of treatment (6 months vs. 12 months), which indicated that the comparisons and treatment duration were not the main resources of high heterogeneity. Additionally, the different formulas of CHM used in each study can also affect the pooled results; however, six studies reported six prescriptions of CHM used in the seven studies. Therefore, we failed to perform a subgroup analysis based on the prescriptions of CHM.

Sensitivity analysis: The meta-analysis only included seven studies, so we did not investigate the publication bias using a funnel plot.

Country(ies) involved: China.

Keywords: Chinese herbal medicine; Idiopathic short stature; IGF-1 level; System review; Meta-analysis

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