INPLASY PROTOCOL

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Corresponding author:
Xun Li

tina000341@163.com

Author Affiliation:
Beijing University of Chinese Medicine.

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Efficacy and safety of Zuogui Wan combined with conventional Western medicine for postmenopausal osteoporosis: A protocol for a systematic review

Wei, YH[1]; Mao, H[2]; Jiang, ZY[3]; Liu, LY[4]; Quan, YQ[5]; Li, X[6].

Review question / Objective: **The proposed systematic review of randomized controlled trials (RCTs) will address the effectiveness and safety of Zuogui Wan combined with conventional Western medicine (CWM) for osteoporosis in postmenopausal women, and provide reference for clinical practice.**

Information sources: **We will use computers to search PubMed, Cochrane Library, Embase, Web of Science, Chinese National Knowledge Infrastructure database (CNKI), WanFang database, Chinese Biomedical Database (CMB), Chinese Science and Technology Periodical database (VIP), China Master's Theses Full-text Database (CMFD), China Proceedings of Conference Full-text Database (CPFD), WHO International Clinical Trials Registry Platform (ICTRP), Chinese Clinical Trials Registry (ChiCTR) and ClinicalTrials.gov, and select all eligible RCTs from inception to October, 2021. Clinicians will also be consulted for additional studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 April 2022 and was last updated on 17 April 2022 (registration number INPLASY202240099).

INTRODUCTION

Review question / Objective: **The proposed systematic review of randomized controlled trials (RCTs) will address the effectiveness and safety of Zuogui Wan combined with conventional Western medicine (CWM) for osteoporosis in postmenopausal women, and provide reference for clinical practice.**

Condition being studied: **Postmenopausal osteoporosis (PMOP), also called type I osteoporosis, is one of the most common diseases among women within five to ten**

years after menopause, characterized by decreased bone strength and increased risk of fracture. According to the first epidemiological survey of osteoporosis in China published by National Health Commission of the People's Republic of China in 2018, the total incidence rate of Chinese population over 50 years old was 19.2%, while that figure of postmenopausal women was even higher, reaching 32.1%. In addition, over one in two Chinese women older than 65 years would experience PMOP, which were far more than those in western countries. What's more, PMOP would make people under the high risk of fragile fractures, which could be costly and result in disability or death, causing a huge burden to the patients' family and the whole society. However, CWM for PMOP could have certain adverse events and drug reactions in clinical practice, such as gastrointestinal reactions, hormone disorders, memory impairment, etc. Therefore, this study will apply Zuogui Wan, a formula of traditional Chinese medicine (TCM), combined with CWM to patients with PMOP, and evaluate the effectiveness and safety of this intervention.

METHODS

Search strategy: Terms: (take PubMed as an example) postmenopausal osteoporosis; osteoporotic fractures in postmenopausal women; Post-Menopausal Osteoporoses; Postmenopausal Bone Losses; Perimenopausal Bone Loss; Post-Menopausal Osteoporosis; Perimenopausal Bone Losses; Postmenopausal Osteoporoses; PMOP; Zuogui Wan; ZGW; zuo gui wan; zuogui pills; ZGP; zuo gui pills; Chinese patent medicine; Chinese preparatory medicine; herbal patent medicine; herbal formula; Chinese patent drugs; Chinese preparatory drugs; herbal patent drugs; Chinese herbal medicine; chinese herbal drugs; materia medica; Chinese medicinal materials; Chinese medical formula; Chinese compound formula; randomized controlled trial; controlled clinical trial; randomized; placebo; randomly; trial; groups; Drug Therapy. We will search the following databases and clinical trials registry platforms: PubMed, Cochrane Library, Embase, Web of Science, Chinese National Knowledge Infrastructure database (CNKI), WanFang database, Chinese Biomedical Database (CMB), Chinese Science and Technology Periodical database (VIP), China Master's Theses Full-text Database (CMFD), China Proceedings of Conference Full-text Database (CPFD), WHO International Clinical Trials Registry Platform (ICTRP), Chinese Clinical Trials Registry (ChiCTR) and ClinicalTrials.gov.

Participant or population: According to any one of the following diagnostic criteria: 1) history of hip or vertebral fragility fracture; 2) T-score measured by dual-energy X-ray absorptiometry (DXA, previously DEXA) is –2.5 or lower; 3) T-score is between –1.0 and –2.5, with proximal humerus, pelvic or distal forearm fragility fracture; 4) lumbar spine bone mineral density (BMD) measured by quantitative computed tomography (QCT) is 80 mg·cm-3 or lower; 5) BMD measured by DXA has reduced by over 25%; 6) BMD measured by DXA is lower than peak bone mass (PBM) M-2SD, we will include postmenopausal women diagnosed as PMOP, regardless of age, race, ethnicity or disease severity. We will exclude studies involving both male and female participants with osteoporosis unless the primary study reported results separately for each gender, or involving patients with PMOP caused by other diseases and drugs.

Intervention: Zuogui Wan (adjustable, no limitations in preparation forms or dosage) combined with CWM (including Calcium Carbonate-Vitamin D3, Alendronate, Caltrate D, etc. that have been proved to be effective in the treatment of PMOP). The standard formula of Zuogui Wan is composed of eight ingredients: Shu Di, Rhizoma Dioscoreae, Achyranthes bidentata, dogwood meat, dodder, medlar, tortoise shell glue and antler glue. Zuogui Wan focuses on the unusual physiological and pathological characteristics of yin deficiency and blood stasis in postmenopausal women, and regulates the

blood and body fluid in order to treat both the manifestation and root.

Comparator: Placebo formula combined with CWM (including Calcium Carbonate-Vitamin D3, Alendronate, Caltrate D, etc. that have been proved to be effective in the treatment of PMOP) or CWM only.

Study designs to be included: We will include randomized controlled clinical trials.

Eligibility criteria: Excluded from this systematic review are duplicated publications and studies with incomplete data. There is no restriction on language, time frame, country, publication status or setting.

Information sources: We will use computers to search PubMed, Cochrane Library, Embase, Web of Science, Chinese National Knowledge Infrastructure database (CNKI), WanFang database, Chinese Biomedical Database (CMB), Chinese Science and Technology Periodical database (VIP), China Master's Theses Full-text Database (CMFD), China Proceedings of Conference Full-text Database (CPFD), WHO International Clinical Trials Registry Platform (ICTRP), Chinese Clinical Trials Registry (ChiCTR) and ClinicalTrials.gov, and select all eligible RCTs from inception to October, 2021. Clinicians will also be consulted for additional studies.

Main outcome(s): Clinical safety (including safety index and adverse events) and bone mineral density (BMD).

Additional outcome(s): Fragility fractures rate, clinical symptoms improvement (including low back pain Visual Analogue Scale and TCM Syndrome Scale), bone turnover markers (BTM) and quality of life.

Data management: Two reviewers will independently assess the eligibility of the primary studies according to the inclusion and exclusion criteria, and extract data from the included RCTs. Disagreement will be settled by discussions with a third review author. NoteExpress and Excel softwares will be used respectively in the process of eligibility assessment and data extraction.

Quality assessment / Risk of bias analysis: Two reviewers will independently evaluate the quality of the included RCTs in accordance with the criteria from the Cochrane handbook, involving random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each RCT will be classified as "low risk of bias", "high risk of bias" or "uncertain risk of bias" for the above items. Disagreement will be settled by discussing with a third reviewer. If there are more than 10 studies included in one single synthesis, a funnel plot will be used to assess the publication bias.

Strategy of data synthesis: We will use the Cochrane Collaboration's RevMan (v.5.4) software for a quantitative analysis. For dichotomous outcomes, risk ratio (RR) will be used as the effect indicators, with 95% confidence intervals (CIs); and for continuous outcomes, mean difference (MD) or standard mean difference (SMD) will be applied, with 95% CIs. If the clinical heterogeneity (including participant, intervention, comparator and outcome) exists, we will use the random-effect model (REM); otherwise, we will apply I2 statistic to test the statistical heterogeneity. If $I2 > 30\%$, REM will also be performed; if not, we will use the fixed effect model (FEM) for meta-analyses. In addition, if all the studies included in one single meta-analysis are the same in terms of the composition and preparation forms of Zuogui Wan as well as the mechanism of conventional Western medicine, together with $I2 \leq 30\%$, we will also use FEM.

Subgroup analysis: We will carry out the following subgroup analysis if possible: the mechanism of CWM is different; the composition of Zuogui Wan formula is different; or the disease severity of included patients is different.

Sensitivity analysis: If possible, we will perform the sensitivity analysis to explore the effects of risk of bias on main outcomes, by respectively including and excluding low-quality RCTs in the meta-analysis to examine whether the results change. If there are different studies regarding disease status, sample size, intervention, comparator or outcome, we will also do sensitivity analyses to test the robustness of the meta-analysis results.

Language: There is no restriction on language.

Country(ies) involved: China.

Keywords: Zuogui Wan; Zuogui Pills; conventional Western medicine; postmenopausal osteoporosis; primary osteoporosis; randomized controlled trials; systematic review; meta-analysis.

Contributions of each author:

Author 1 - Yuehui Wei - Conceiving the review, managing and analyzing the data, and writing the protocol and review.
Email: wyhh0814@163.com
Author 2 - Hui Mao - Collecting the data.
Author 3 - Ziyun Jiang - Assessing the eligibility of the primary studies.
Author 4 - Luyao Liu - Supervising the review.
Author 5 - Yuqiao Quan - Supervising the review.
Author 6 - Xun Li - Coordinating and supervising the review.
Email: tina000341@163.com