INPLASY PROTOCOL

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None declared.

Efficacy and safety of Zuogui Pill combined with western medicine in the treatment of Osteoporosis A protocol for systematic review and meta-analysis

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Review question / Objective: **Zuogui Pill (ZGP) efficacy and medication safety were investigated in combination with western medicine in osteoporosis treatment.**

Condition being studied: **Osteoporosis (OP) is one of the prevalent orthopedic conditions. It is characterized by low bone mass, microarchitecture degradation, and reduced bone strength. The incidence of OP is highly correlated with age [1]. Recently, as the world population has increased, the primary osteoporosis incidence has increased too significantly [2]. Concurrently, OP patients are very prone to fragility fractures-osteoporotic fractures, which can cause complications such as infection and thrombosis, and even lead to disability and death of patients, seriously affecting the patients' quality of life and bringing huge economic benefits to the society [3, 4]. Disturbances in the homeostasis of bone remodeling are the underlying cause of osteoporosis. Bone remodeling is a physiological process in which osteoblasts form new bone and resorb the original bone matrix, which is a key process in maintaining healthy bone tissue in adults, and multiple factors are involved in regulating this process [5]. Bisphosphonates, estrogens, and raloxifene are commonly used to treat osteoporosis by reducing the number of osteoclasts, inhibiting bone resorption, slowing bone loss, and maintaining bone health [6]. Although these drugs significantly increase bone mass, they have limitations and side effects, such as suboptimal efficacy in a large number of patients, thromboembolism, and gastrointestinal irritation [7-8]. Therefore, it is necessary to identify new drugs to improve osteoporosis while minimizing side effects.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 October 2022 and was last updated on 26 October 2022 (registration number INPLASY2022100090).

INTRODUCTION

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METHODS

Participant or population: For patients with a definite diagnosis of osteoporosis.

Intervention: The treatment group use ZGP or its modified prescription based on the control group treatment.

Comparator: The control group use conventional western medicine.

Study designs to be included: All ZGP randomized controlled trials in combination with the western medicine in OP treatment were collected, whatever their blinding, publishing status, or location, done in Chinese and English only. For patients with a definite diagnosis of osteoporosis, there are no restrictions on the patient's nationality, ethnicity, gender, age, occupation, disease course, and onset time.

Eligibility criteria: To treat OP, the intervention measures did not use Chinese herbal medicine combined with clinical medicine clinical randomized controlled trials, non-randomized controlled trials, relevant animal experiments, reviews, retrospective research literature, conference abstracts, case reports, duplicate publications, literature articles without data information, etc.

Information sources: Chinese literature through China National Knowledge Infrastructure (CNKI), VIP (VIP), Wanfang (Wanfang) and China Biomedical Literature Database (CBM). English literature was searched through PubMed, EMbase, and Cochrane Library.

Main outcome(s): The effective rate of clinical efficacy was the main outcome indicator. The secondary outcome indicators were lumbar spine bone mineral density (BMD), femoral neck BMD, 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3], serum phosphorus (P), alkaline phosphatase (ALP), serum calcium (Ca), and the occurrence of adverse reactions.

Quality assessment / Risk of bias analysis: The literature quality was evaluated regarding the Cochrane 5.0.1 Manual of Systematic Review, from the six aspects of randomization method, allocation concealment, blinding, data results completeness, selective reporting of research results, and other factors that may potentially affect the authenticity. The quality of literature was evaluated at three levels: "high" (high bias) and "unclear" (lack of relevant information or uncertain bias).

Strategy of data synthesis: 1 Traditional Meta-Analysis - Among the evaluation indicators included in this study, the total effective rate was a binary variable, so the odds ratio (OR) was used as the effect analysis statistic. The remaining outcome indicators were continuous variables, and standardized mean difference (SMD) was used as the effect analysis statistic. Concurrently, the effect size and its 95% confidence interval (CI) were calculated. Meta-analysis and literature quality assessment was done by the Review Manager 5.3 software usage. All included literature in this study was compared in pairs without forming a closed loop. The heterogeneity test was mainly judged by I2. If there was no heterogeneity between the results (I2≤50%), a fixed-effect model was used for meta-analysis. If there is heterogeneity among the study results (I2>50%), the heterogeneity source was further analyzed. After excluding the obvious clinical heterogeneity influence, the random-effects model was utilized for meta-analysis.

2 Network Meta-analysis - Network meta-analysis was performed based on Bayesian model, direct and indirect evidence of included studies was merged and compared, followed by using R4.0.2 software and Ge MTC to establish four chains for simulation. The number of iterations was set to 5000 times, and the first 20000 times was used for annealing to remove the effect of the initial value, while the step size was set to 10. Brooks-Gelman Using Rubin diagnostic method to judge the degree of model convergence, the median value of the reduction factor after iteration and 97.5% tended to 1 and reached stability after iterative calculation, indicating that the degree of model convergence was satisfactory. In addition, Stata 16.0 software was used to calculate and draw the area under the cumulative ranking curve (SUCRA) to intuitively reflect the relative pros and cons of efficacy and safety between drugs. The value of SUCRA ranges from 0 to 1, and the higher the value of SUCRA Larger means a better curative effect.

3 Publication bias - Stata 16.0 was utilized to draw comparison-adjusted funnel plots and publication bias analysis was conducted according to whether the funnel plot is symmetrical and the results of Egger and Begg tests. "The funnel plot should be symmetrical along the midline around the regression line, with a P-value >0.05 for Egger, Begg's test.

Subgroup analysis: None reported.

Sensitivity analysis: Sensitivity scores are given to the included indicatorsanalysis, one by one to eliminate a certain RCT, a new meta-analysis, results. None changed, confirming that the meta-analysis results were relatively stable.

Country(ies) involved: China.

Keywords: Zuogui Pill, Osteoporosis, systematic review, complementary and alternative medicine,meta-analysis.

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