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Meta-Analysis of Chinese Patent Medicine Combined with Zoledronic Acid in the Treatment of Primary Osteoporosis

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Abstract: Objective: To systematically evaluate the safety and efficacy of Chinese patent medicine combined with zoledronic acid in the treatment of primary osteoporosis. Methods: CnKI, VIP, Wanfang Database, Chinese Biomedical literature database, PubMed, Web of Science, The Cochrane Library, Embase and CnKI were searched by computer RCTs of clinical randomized controlled trials of Chinese patent medicine combined with zoledronic acid in the treatment of primary osteoporosis in Embase database were retrieved from the database construction to April 1, 2022, and meta-analysis was performed using RevMan 5. 3 software. Results: A total of 14 RCTs were included, and the results of meta-analysis showed that:Compared with the control group, Chinese patent medicine combined with zoledronic acid had significant effects on the improvement of total clinical response rate, VAS score, MDL score, lumbar vertebra bone mineral density, femoral neck bone mineral density, Ward's triangle bone mineral density, osteocalcin and ALP, and significantly reduced alkaline phosphatase, with statistically significant differences. It had no significant effect on serum phosphorus, calcium and adverse reactions (P >0. 05). Conclusion: The safety and efficacy of Chinese patent medicine combined with zoledronic acid in the treatment of POP are clear, but the quality of the included studies is limited, and more high-quality studies are needed to enhance the evaluation evidence.

Keywords: Chinese Patent Medicine; Zoledronic Acid; System Evaluation; Primary Osteoporosis; Randomized Controlled Trial

Introduction

Osteoporosis(OP) is a systemic progressive bone metabolic disease with reduced bone mass, damaged bone microstructure and increased bone fragility[1]. OP can be divided into three types according to etiology: primary, secondary and idiopathic. Primaryosteoporosis (POP) is a physiological degenerative disease that inevitably occurs with age [2]. Zoledronic acid, as a third-generation bisphosphonate drug, is the first-line drug in the clinical treatment of POP and is widely used in clinic [3].

1. Data and methods

1.1 Retrieval strategy

Computer retrieval of CNKI, VIP, Wanfang Database, Chinese Biomedical literature database,PubMed、 Web of science、 The Cochrane Library、 EmbaseThe retrieval period is from database construction to April 10, 2022. Retrieval method is given priority to with "subject + keywords", Chinese retrieval subject includes: "osteoporosis", "primary osteoporosis in postmenopausal osteoporosis"", "Chinese medicine", "proprietary Chinese medicine", "Chinese herbal medicine", "azole phosphonic acid", "capsule", "pill", "mixture", "fluid", "loose" and "a randomized controlled trial". English keywords included: "osteoporosis", "OP", "Chinese patent drug", "traditional Chinese medicine", "Azole Phosphonic acid", "RCT".

1.2 Inclusion and exclusion criteria

(1)Study type: Randomized controlled clinical trials (RCTS) published in Chinese and English about Chinese patent medicine combined with zoledronic acid in the treatment of primary osteoporosis; (2) Subjects: Patients with primary osteoporosis, gender and source of cases were not limited; (3) Intervention measures: the experimental group was treated with oral marketed Chinese patent medicine combined with zoledronic acid, and the control group was treated with zoledronic acid. Calcium, vitamin D and other basic treatments could be used in both groups.

1.3 Data extraction and quality evaluation

1.3.1 Data extraction

Two researchers independently screened the literature by title and abstract, and made judgment by reading the full text if they could not make judgment. Disagreement is resolved through discussion or by a third researcher. Two researchers independently extracted data, including basic information, intervention measures, sample size and outcome indicators of the included study.

1.3.2 Use of all data for quality

All data are managed by Revman5. 3 management software. The "Riskofbias" evaluation tool in the Cochrane manual was used to evaluate the methodological quality of the included literature[5], and judgments of lowrisk, highrisk, and unclearrisk were made for the final included literature.

1.4 Statistical methods

Meta-analysis was performed using RevMan5. 3 software provided by the Cochrane collaboration. The relative risk (RR) and 95%CI were used for categorical variables, and the mean difference (MD) and 95%CI were used for continuous variables. I2 test was used for heterogeneity of literature, and when I2 < 50%, fixed effect model was used for Meta analysis. If I2 > 50%, the source of heterogeneity was analyzed and sensitivity analysis or random effect model was used. Funnel plots were used to analyze publication bias when ≥10 articles were included in an outcome index.

2. Results

2.1 Literature screening process and results

A total of 68 related literatures were obtained by systematic retrieval of relevant databases, and the remaining 28 literatures were removed after the removal of duplicate literatures. After reading the title and abstract information, 20 literatures were initially selected for full-text reading and screening, and 14 literatures were finally included for data.

2.2 Basic Features of included Studies

A total of 14 RCTS were included in this study, including 1559 patients with primary osteoporosis. It involved 6 kinds of oral Proprietary Chinese medicine, including 5 studies on Jintiange capsule, 5 studies on Xianling Gubao capsule, 1 study on Hugu capsule, Gusongbao granule, Gambohuang Jiangu capsule and Guyuling capsule respectively.

2.2.1 Literature quality evaluation

Among the 14 original literatures, 5 [10, 12-15] used the random number table method for grouping, the rest only mentioned "randomness", and 14 literatures did not describe the allocation hiding. Considering the intervention measures of the study, blind method could not be implemented for the subjects and interveners, which was evaluated as high risk of bias.

2.3 Meta-analysis results

2.3.1 Effective clinical efficacy

A total of 7 studies were used to compare the effectiveness of clinical efficacy, and the effectiveness of each study was transformed by dichotomy. A total of 735 patients were enrolled.

2.3.2 BONE mineral density

Thirteen studies compared lumbar bone mineral density in 1399 patients. The heterogeneity test of mate analysis showed that P < 0. 00001, I2=77%, indicating large heterogeneity, so the random effect model was adopted and the effect size was combined [MD=0. 07,95%CI(0. 05,0. 09)]. The test of combined effect size Z=7. 11,P<0. 00001. Conclusion Compared with zoledronic acid alone, Chinese patent medicine combined with zoledronic acid can effectively improve the bone density of lumbar vertebra in the treatment of primary osteoporosis.

2.3.3 Serum alkaline phosphatase (ALP)

ALP was compared in six studies totaling 685 patients. The heterogeneity test of mate analysis showed that P=0. 52, I2=24%, and mate analysis adopted the fixed effect model. The results suggested that:Chinese patent medicine combined with zoledronic acid significantly reduced ALP level compared with zoledronic acid group, the difference was statistically significant [MD=-4. 55, 95%CI(-5. 18, -3. 92), P=0. 03), P < 0. 00001].

2.3.4 Osteocalcin

Osteocalcin was compared in seven studies involving a total of 698 patients. The heterogeneity test of mate analysis showed that P=0. 90, I2=0%, and mate analysis adopted the fixed effect model. The results suggested that:Chinese patent medicine combined with zoledronic acid significantly improved osteocalcin level compared with zoledronic acid group, the difference was statistically significant [MD=1. 85, 95%CI(1. 66, 2. 05), P < 0. 00001)].

2.3.5 Serum calcium

Serum calcium was compared in seven studies involving a total of 1032 patients. The heterogeneity test of mate analysis showed that P=0. 49, I2=0%, and mate analysis adopted the fixed effect model. The results suggested that:Analysis results showed that there was no statistically significant difference between the two groups [MD=0. 01, 95%CI(-0. 03-0. 05), P=0. 78], indicating that there was no statistically significant difference in serum calcium level between zoledronic acid combined with Proprietary Chinese medicine and zoledronic acid alone in this study, that is, proprietary Chinese medicine combined with zoledronic acid had no significant effect on serum calcium.

2.3.6 Serum phosphorus

Serum phosphorus was compared in seven studies involving a total of 748 patients. The heterogeneity test of mate analysis showed that P=0. 47, I2=0%, and mate analysis adopted the fixed effect model. The results suggested that:Analysis results showed that there was no statistically significant difference between the two groups [MD=0. 02, 95%CI(-0. 01-0. 06), P=0. 21], indicating that there was no statistically significant difference in serum phosphorus level between zoledronic acid combined with Chinese patent medicine and zoledronic acid alone in this study, that is, Chinese patent medicine combined with zoledronic acid had no significant effect on serum phosphorus.

2.3.7 Visual analogue scale of pain(VAS)

VAS scores were compared in 11 studies, with a total of 1178 patients. The heterogeneity test of mate analysis showed that P < 0. 00001, I2=85%, indicating great heterogeneity, so the random effect model was adopted, and the results suggested that:VAS score of Chinese patent medicine combined with zoledronic acid was significantly better than that of zoledronic acid alone, the difference was statistically significant [MD=-0. 72, 95%CI(-0. 82, -0. 62), P < 0. 00001)].

2.3.8 Daily living ability score(ADL)

ADL scores were compared in five studies [6, 19, 7, 12, 18] with a total of 398 patients. The heterogeneity test of mate analysis showed that P < 0. 00001, I2=40%, the heterogeneity was small, so the fixed effect model was adopted, and the results suggested that:VAS score of Chinese patent medicine combined with zoledronic acid was significantly better than that of zoledronic acid alone, the difference was statistically significant [MD=12. 30, 95%CI(10. 52, 14. 08), P < 0. 00001)].

2.3.9 Adverse reactions

A total of 7 studies reported adverse reactions, and a total of 792 patients were included to translate the effective rate of each study using dichotomies. The heterogeneity test of Mate analysis showed that P=0. 98, I2=0%, and the fixed effect model was adopted for Mate analysis. The analysis results show that:A total of 39 cases (9. 89%) of adverse reactions occurred in the integrated Chinese and Western medicine group, and 41 cases (10. 40%) in the alendronate group. Meta-analysis showed that there was no statistically significant difference in the incidence of adverse reactions between the two groups [OR=0. 96, 95%CI(0. 60-1. 53),P = 0. 86).

2.4 Publication bias

Bias analysis was conducted for lumbar bone mineral density and VAS score with more than 10 study samples among the outcome indicators. As can be seen from the funnel plot, there is asymmetry on both sides of the graph, suggesting a certain publication bias.

3. Discussion

This study found that the overall experimental design quality of the included literatures was not high, and the reliability of the conclusions needed further verification with potential publication bias. The randomization method of the included studies was not clear. Although random number table method was mentioned in some studies, the sequence generation process was not described. None of the 14 included studies mentioned or described the allocation hiding mechanism and whether blind method was used, which may lead to multiple risks of bias.

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Topic:

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