Systematic Review and Meta-Analysis

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Clinical efficacy of zoledronic acid combined with percutaneous kyphoplasty in the prevention and treatment of osteoporotic vertebral compression fracture

A systematic review and meta-analysis

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Abstract

Objective: The aim of this study is to investigate the clinical efficacy of zoledronic acid (ZOL) in the treatment and prevention of osteoporotic vertebral compression fractures (OVCF) after percutaneous kyphoplasty (PKP) for elderly patients.

Methods: The PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, VIP, and Embase were investigated through June 2020. All randomized controlled trials (RCT) involving ZOL injections for OVCF were enrolled. Outcome indicators included the bone mineral density (BMD), Visual Analog Scale (VAS), recompression vertebral fracture (RVF), Oswestry Disability Index (ODI), and bone metabolism (Procollagen type I N-terminal propeptide [PINP] and βcross-linked C-telopeptide of type I collagen [β-CTX]), bone cement leakage. Review Manager 5.3 was used to analyze these indicators.

Results: In this study,

(1) Eight studies had met the eligibility criteria, a total of 578 participants were involved (285 and 293 in the experimental (ZOL) group and control [no ZOL] group, respectively).

(2) The BMD scores of patients with OVCF in the experimental group were significantly higher than that in the control group ($P < .05$).

The VAS scores were significantly different between the 2 groups at the 6, 12 months follow-up ($P < .05$). After PKP operation, ZOL injections reduced the rate of RVF ($P < .05$). In the comparison of ODI scores, the experimental group improved compared with the control group ($P < .05$). Respectively, the bone metabolism of patients with OVCF after ZOL was better than that of patients in control group ($P < .05$).

Conclusion: Zoledronic acid had a significant effect on the treatment and prevention of OVCF in elderly osteoporotic patients after PKP. Due to the limited quality and data, more high-quality studies are needed to confirm the results of this meta-analysis.

Abbreviations: β-CTX = βcross-linked C-telopeptide of type I collagen; AEs = adverse events; BMD = bone mineral density; CI = confidence interval; CNKI = China National Knowledge Infrastructure; MD = mean difference; NC = not clear; ODI = Oswestry Disability Index; OVCF = osteoporotic vertebral compression fractures; PINP = Procollagen type I N-terminal propeptide; PKP = percutaneous kyphoplasty; PRISMA = preferred reporting items for systematic reviews and meta analyses; RCT = randomized

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Ethical Review Committee Statement was not necessary because this study is a meta-analysis of previous RCTs, the need for consent to participate is not applicable.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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control trial; RR = relative risk; RVF = recompression vertebral fracture; SMD = standardized mean difference; VAS = Visual Analog Scale; ZOL = zoledronic acid.

Keywords: meta-analysis, osteoporotic vertebral compression fracture, OVCF, percutaneous kyphoplasty, systematic review, zoledronic acid

1. Introduction

Osteoporosis is a very common public health problem among the elderly, especially for postmenopausal women, which may be related to the change of estrogen level. Nearly 7% of the total population in China suffers from osteoporosis.[1] As a chronic progressive disease, bone mineral density (BMD) decreases and bone structure changes to a certain extent, resulting in fractures, especially osteoporotic vertebral compression fractures (OVCF).[2] Studies have shown that OVCF had become the most severe complication of osteoporosis, accounting for almost 50% of the osteoporotic fractures.[3] Many patients with OVCF are characterized by low back disability pain, kyphosis, mental disorders, and functional limitations, this has severely reduced the quality of life for the elderly.[4] There are lots of conservative therapy for OVCF, including oral calcium tablets, sun-bathe, functional exercise, etc, which can relieve pain symptoms and have a positive effects.[5] However, it may lead to more complications including decubitus ulcers, pneumonia, and venous thromboembolism.[6] Therefore, there is an urgent need to find a solution to the problem.

In recent years, the advantages and efficacy of percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP) have become more and more obvious, and gradually become the most commonly used treatment methods for OVCF, especially PKP, which can quickly relieve pain and stabilize spinal structure.[7] As a new treatment, PKP can effectively increase the height of vertebral, significantly improve the kyphosis angle and reduce the risk of cement leakage.[8] Several literatures reported that PKP has become a " gold standard" in the treatment of OVCF.[9] However, there are considerable controversies in the application of PKP. Yi et al's[10] study showed that PKP still could not inhibit the aggravation of osteoporosis in patients, which showed some limitations in the treatment of OVCF. Rho et al[11] considered that osteoporosis was the main risk factor of recompression vertebral fracture after PKP. We should pay attention to the treatment of osteoporosis to ensure the curative effect of operation.

Several studies[12,13] have shown that zoledronic acid (ZOL) had anti-osteoporosis activity and might be beneficial to osteoporosis, which indicates that zoledronic acid has new targeted and specific effects in improving bone quality. ZOL is a bisphosphonate, which is often used in the treatment of various bone diseases and calcium metabolic diseases. It can promote osteoclast apoptosis and restrain osteoclast formation, facilitate calcium absorption, reduce bone loss, increase bone mass, and reduce the risk of new fracture and recompression vertebral fracture. It has become the first choice of drugs to prevent and treat osteoporosis. However, these drugs have also shown some side-effects and controversies, especially the efficacy of PKP combined with ZOL in the treatment of OVCF.[14] The purpose of this study is to evaluate the clinical efficacy of ZOL in the treatment and prevention of OVCF after PKP for elderly patients, and to compare the scores of BMD, Visual Analog Scale (VAS), recompression vertebral fracture (RVF), Oswestry Disability Index (ODI), Procollagen type I N-terminal propeptide (PINP), and βcross-linked C-telopeptide of type I collagen (β-CTX) during the follow-up period, so as to provide reference for the treatment of OVCF.

2. Methods

According to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) Statement criteria, we performed strictly a prospective protocol to ensure a more precise conclusion, which can be taken and accepted as means to guide decisions. This review is registered in PROSPERO: CRD42020197834.

2.1. Search strategy

A systematically search was performed of the PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, VIP, and Embase for all articles published through June 2020. All randomized controlled trials involving ZOL injections for OVCF were enrolled. The keywords included "zoledronic acid" or "ZOL" and "percutaneous kyphoplasty" or "PKP" and "osteoporotic vertebral compression fractures" or "OVCF." No country and language were excluded. Two reviewers independently assessed the identified articles according to the Cochrane Collaboration guidelines.

2.2. Inclusion and exclusion criteria

Inclusion criteria were:

1) participants diagnosed with the site of compressed vertebrae with low back pain and PKP performed,
2) randomized clinical study,
3) the efficacy of zoledronic acid for the treatment of osteoporosis,
4) osteoporosis indicated by pathological examination,
5) at least one of the following outcome indicators: BMD, VAS, RVF, ODI, etc and at least 6 months follow-up.

Exclusion criteria were:

1) retrospective studies,
2) patients with leukemia, hemophilia, immune disease, and idiopathic thrombocytopenia,
3) patients complicated with vertebral tumors,
4) patients with nerve root dysfunction,
5) a history of allergies to zoledronic acid,
6) incomplete clinical data.

2.3. Outcome measures

Primary outcomes: BMD, VAS, RVF, ODI.

Secondary outcomes: PINP, β-CTX, bone cement leakage.

Our study includes some primary outcomes. BMD is an important indicator of bone quality, reflecting the degree of

osteoporosis and predicting the risk of fracture. It can also be used for clinical efficacy observation and epidemiological investigation. VAS designed by the National Institutes of Health's Clinical Research Center, was used to observe the pain scores. RVF can also reflect the degree of osteoporosis and clinical efficacy. ODI can reflect the status of patients with low back function. All of them are important and significant in reflecting the clinical efficacy of zoledronic acid combined with percutaneous kyphoplasty in the prevention and treatment of osteoporotic vertebral compression fracture.

2.4. Quality assessment

Study methodological quality employed the following 8 items: adequate sequence generation, allocation concealment, blinding of participants, blinding of investigators, blinding of assessors, incomplete outcome data inexistent or addressed, free of selective reporting, and free of other bias according to the Cochrane Collaboration "Risk of bias." The 2 reviewers independently estimated each study to determine whether there was a high, low, or uncertain risk of bias. A third reviewer resolved any disagreements when discrepancies.[1,5]

2.5. Data extraction

The general data extracted from this study included first author, years, country, sample size, groups, intervention, age of participants, ethic, and follow-up periods, and measured outcomes of BMD, VAS, RVF, ODI, PINP, β-CTX, and bone cement leakage. In case of missing or unavailable data, we will contact the corresponding authors.

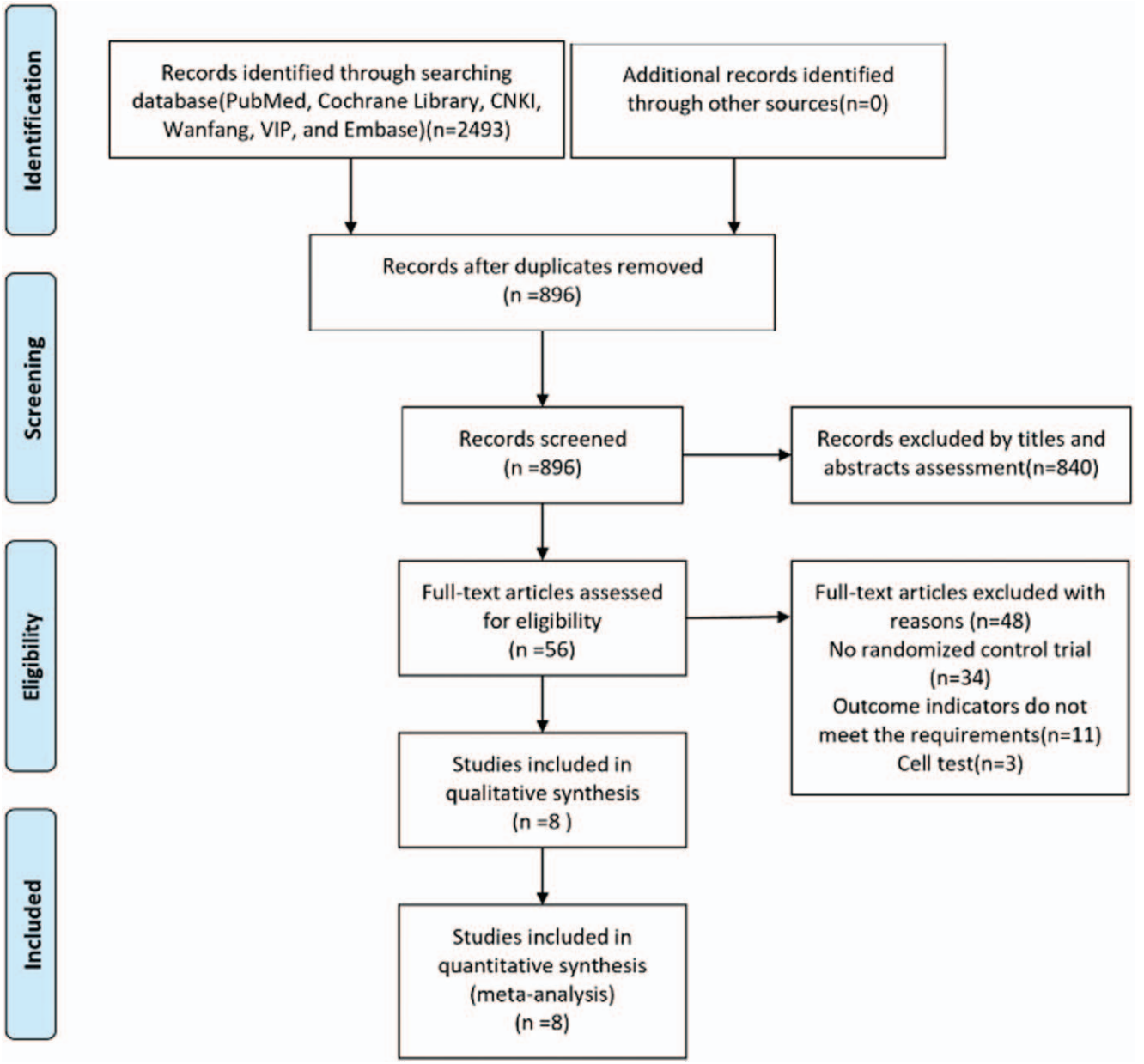

Figure 1. Flow diagram of study selection.

2.6. Statistic analysis

All included data were analyzed using the Review Manager 5.3 software, with risk ratios and 95% confidence intervals (CIs) being determined for binary variables. The relative risk (RR) was used to evaluate the effects of binary variables, the effect size was calculated with mean difference (MD) when the same outcome was measured by the same scale at the end of intervention. Meanwhile, standardized mean difference (SMD) was chosen if the clinical outcome was the same but was measured using different methods, evaluation criterion or the baselines of the studies were inconsistent in the different trials. In addition, for homogeneous data sets, $I^2 < 50\%$ were used as the test standards. When the above statistical conditions were achieved, a fixed-effects model was used for the meta-analysis because the pooled effect sizes were relatively homogenous. If the above standards did not conform, the homogeneity of the pooled effect size was not ideal, then a random effects model was applied. $P < .05$ would be considered statistically significant.[15]

2.7. Reporting bias analysis

When there were more than 10 qualified studies included in our study, funnel plots and Egger regression analysis would be carried out to assess the publication bias.

3. Results

3.1. Literature search and study characteristics

A total of 2493 studies were obtained at first search strategy. The titles of 896 studies were investigated, and 840 studies were not related to this topic and were excluded. Of these, 56 studies were included according to the eligibility criteria and 8 studies[16–23] were eventually selected for assessment. The studies of screening process and results are shown in Figure 1. All studies included, that one trial[16] was published in English, the others[17–23] in Chinese. Eight studies were RCTs and included in this meta-analysis. Five hundred seventy eight patients were included in the experimental (ZOL) group and the control (no ZOL) group. All studies had been conducted from 2015 through 2019, and the age range was mainly concentrated from the 60 to 80 years. The trial sample size was ranged from 52 to 92 participants. The follow-up period was 6 to 12 months. In the 8 studies, baseline materials of sex, age, BMD, and sample size of the patients were comparable, both $P > .05$ (Table 1).

3.2. Quality assessment

According to the Cochrane Collaboration "Risk of bias,"[15] 5 trials showed methods of randomization using a random number table,[17,19] Doll's clinical random table method,[18,23] or simple randomization.[21] The remaining 3 trials[16,20,22] indicated " randomly allocating," the detailed method used to generate the randomization sequence was not revealed. The incomplete outcome data was reported in all the studies resulting in a low risk bias. In general, all the 8 trials included were of good quality, the outcome measurement process was mainly unclear risk and low risk, and no high risk was found in the trials, and the results of methodological processes are shown in Figures 2 and 3.

Table 1

Characteristics of the included studies.

Author (yr)	Country	Study	Sex (M/F)	Age, yr, Mean (SD) Experiment/control	Groups Experiment/control	Simple size Experiment/control	BMD (g/cm^2) Experiment/control	Ethical approval	Clinical indicators	Intervention (ZOL)	Follow-up period
Daijun Li 2018	China	RCT	31/61	62.31 (4.72); 62.50 (4.76)	ZOL + oral calcium + PKP; PKP + oral calcium	46/46	0.81 (0.13); 0.82 (0.14)	Yes	VAS, ODI, BMD, PINP, BCP, AEs, RVF	1 time, 4 mg: 100 ml, ivd	3, 6 mo
Zifeng Huang 2019	China	RCT	17/43	76.11 (8.30) 74.36 (9.08)	ZOL + oral calcium + PKP; oral calcium + PKP	30/30	−3.14 (0.38); −3.15 (0.41)	Yes	BMD, VAS, AEs, RVF	1 time, 5 mg: 100 ml, ivd	1, 6, 12 mo
Ji Li 2019	China	RCT	14/56	80.5 (3.6); 79.7 (3.8)	PRP + ZOL; PKP	35/35	−3.51 (0.11); −3.48 (0.12)	Yes	VAS, ODI, BMD, PINP, β-CTX, PTH, AEs, RVF	1 time, 4 mg: 100 ml, ivd	1, 12 mo
Xianchun Liu 2019	China	RCT	27/33	68.27 (4.08); 69.09 (4.31)	PRP + ZOL; PKP	30/30	NC	Yes	VAS, BCP, ALP, AEs, RVF	1 time, 100 ml, ivd	6, 12 mo
Wenhu Xuan 2017	China	RCT	32/48	70.5 (4.9); 72.3 (4.6)	PRP + ZOL; PKP	40/40	0.65 (0.24); 0.66 (0.21)	Yes	VAS, BMD, AEs, RVF	1 time, 5 mg: 100 ml, ivd	12 mo
Daolu Zhan 2017	China	RCT	37/47	65.3 (5.6); 64.8 (5.4)	ZOL + oral calcium + PKP; PKP + oral calcium + SC	42/42	0.41 (0.05); 0.41 (0.05)	Yes	VAS, BMD, PINP, β-CTX	1 time, 5 mg: 100 ml, ivd	6, 12 mo
Tao Zhang 2015	China	RCT	33/47	67.2 (6.8); 68.3 (5.7)	PRP + ZOL; PKP	40/40	NC	Yes	VAS, ODI, RVF	1 time, 5 mg: 100 ml, ivd	1, 12 mo
Mingming Liu 2015	China	RCT	10/42	74.13 (5.09); 74.25 (5.20)	PRP + ZOL; PKP	24/28	−2.77 (0.44); −2.80 (0.54)	NC	VAS, ODI, BMD, RVF	1 time, 5 mg: 100 ml, ivd	12 mo

β-CTX = βcross-linked C-telopeptide of type I collagen, AEs = adverse events, BMD = bone mineral density, CI = confidence interval, MD = mean difference, NC = not clear, ODI = Oswestry Disability Index, OVCF = osteoporotic vertebral compression fractures, PINP = Procollagen type I N-terminal propeptide, PKP = percutaneous kyphoplasty, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCT = randomized control trial, RR = relative risk, RVF = recompression vertebral fracture, SC = salmon calcitonin, SMD = standardized mean difference, VAS = Visual Analog Scale, ZOL = zoledronic acid.

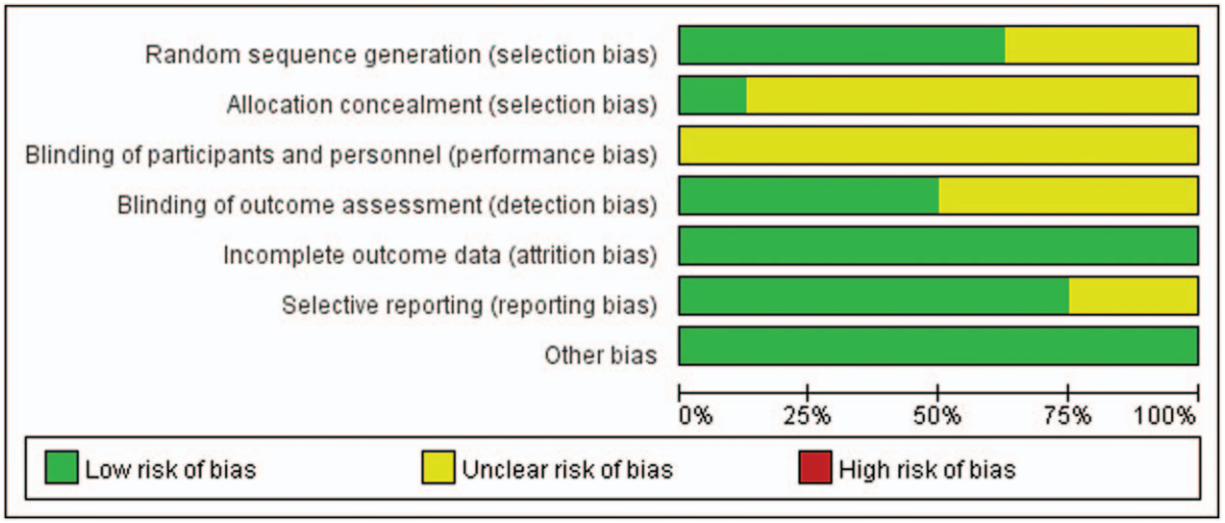

Figure 2. Risk of bias assessment.

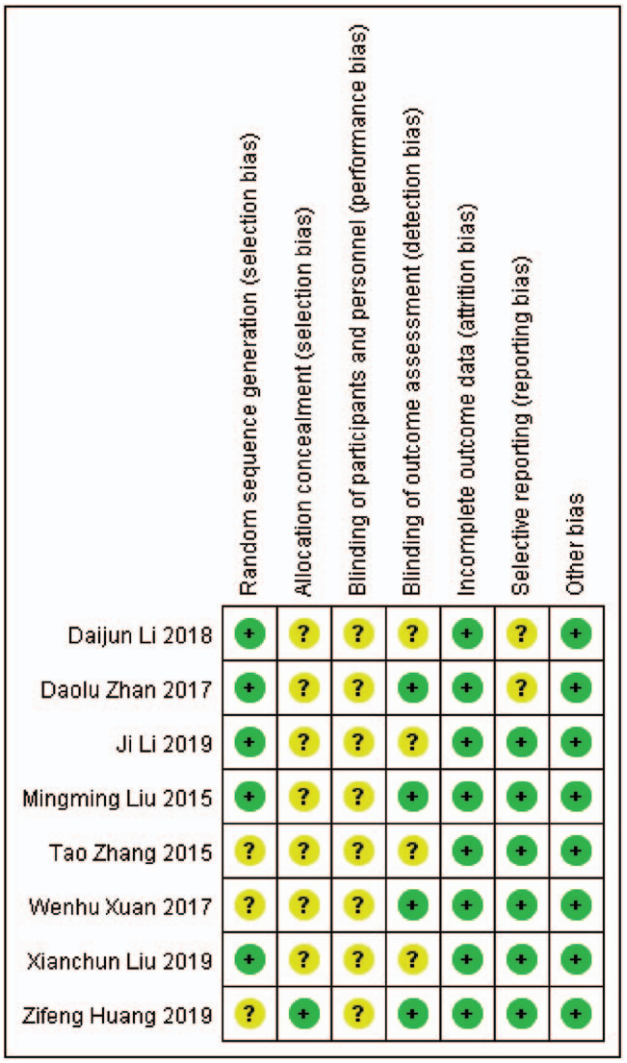

Figure 3. Risk of bias summary.

3.3. Outcomes of the meta-analysis

3.3.1. BMD. A total of 3 studies[16,17,21] reported BMD scores at 6 months after treatment. The heterogeneity test indicated a low degree of homogeneity ($I^2 = 0\%$, SMD: 0.40, 95% confidence interval [CI]: 0.14–0.66). The results showed that ZOL combined with PKP was significantly different from PKP alone ($P = .002 < .05$) (Fig. 4).

Five studies[16,18,20,21,23] respectively reported BMD scores at 12 months after treatment. The heterogeneity test indicated that heterogeneity was high ($I^2 = 95\%$, SMD: 1.88, 95% CI: 0.67–3.09), and a random-effects model was used for meta-analysis. The results showed that there were significant differences in improving BMD in favor of the ZOL combined with PKP ($P = .002 < .05$) (Fig. 4).

3.3.2. VAS. A total of 3 studies[16,18,22] reported comparisons of the VAS scores at 1 month after treatment. The heterogeneity test was high ($I^2 > 50\%$, SMD: 0.70, 95% CI: −0.16 to 1.56), and a random-effects model was used for meta-analysis. The subgroup analysis results indicated that patients in the experimental group were not significantly different from the control group ($P > .05$) (Fig. 5).

Four studies[16,17,19,21] reported the VAS scores at 6 months after treatment. The heterogeneity test suggested a high degree of homogeneity ($I^2 > 50\%$, SMD: 0.99, 95% CI: 0.09–1.89), and a random-effects model was used for meta-analysis. The results showed that PKP combined with ZOL were significantly different from PKP alone ($P = .03 < .05$) (Fig. 5).

A total of 7 studies[16,18–23] reported comparisons of the VAS scores at 12 months after treatment. The heterogeneity test exhibited significant heterogeneity ($I^2 > 50\%$, SMD: 0.97, 95% CI: 0.45–1.49), and a random-effects model was used for meta-analysis. The subgroup analysis results indicated that patients in the experimental group were significantly better than the control group ($P < .05$) (Fig. 5).

3.3.3. RVF. Eight studies[16–23] reported the rate of RVF after follow-up period. The heterogeneity test suggested a low degree of homogeneity ($I^2 < 50\%$, RR = 0.20; 95% CI: 0.10–0.41), and a fixed-effects model was used for meta-analysis. We found that

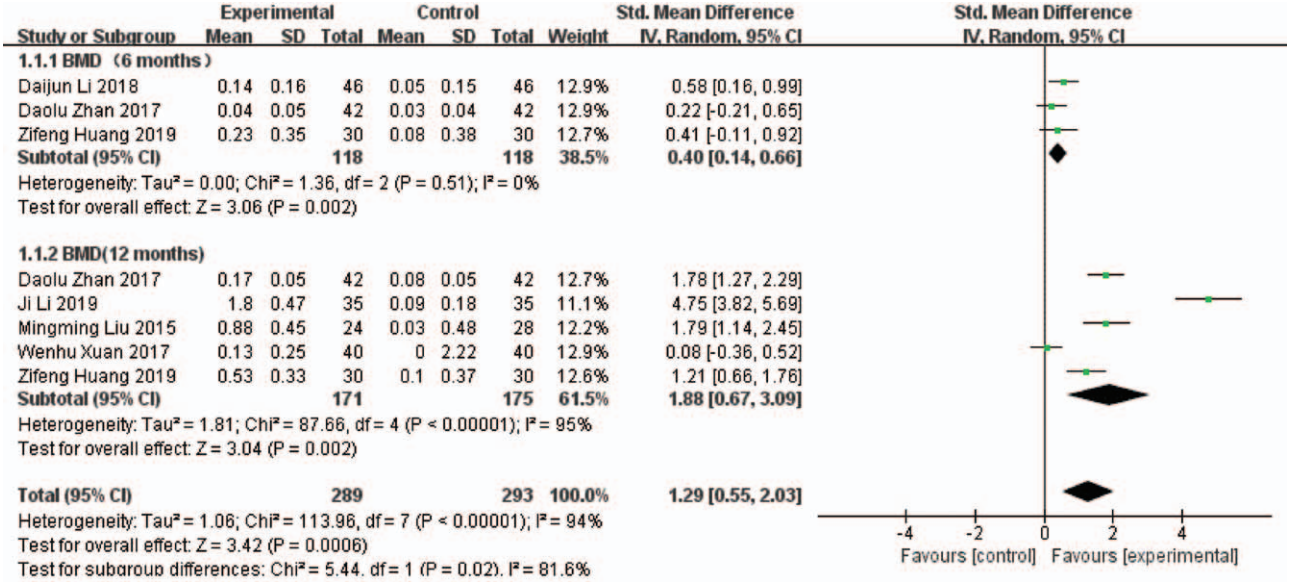

Figure 4. Forest plot and meta-analysis of BMD scores (6 and 12 mo).

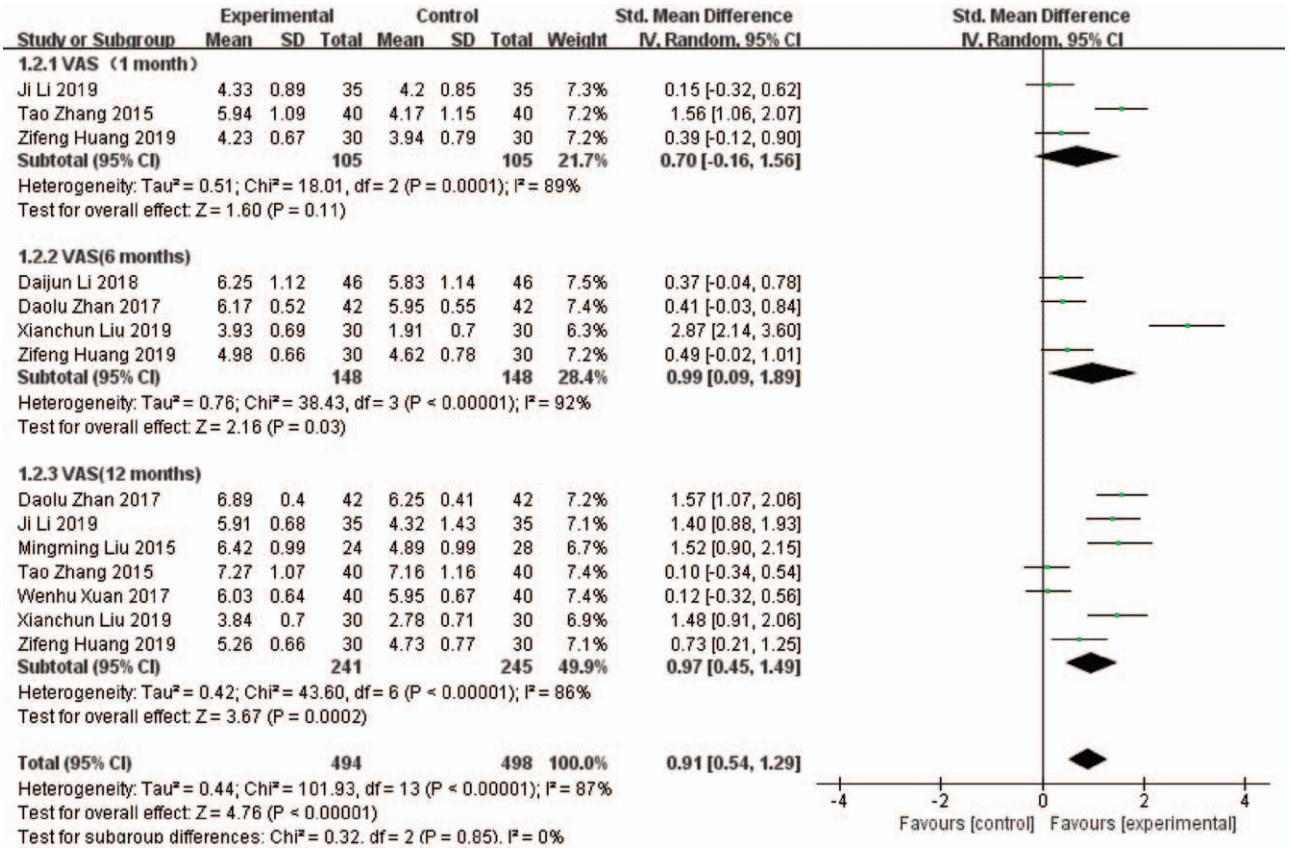

Figure 5. Forest plot and meta-analysis of VAS scores (1, 6, 12 mo).

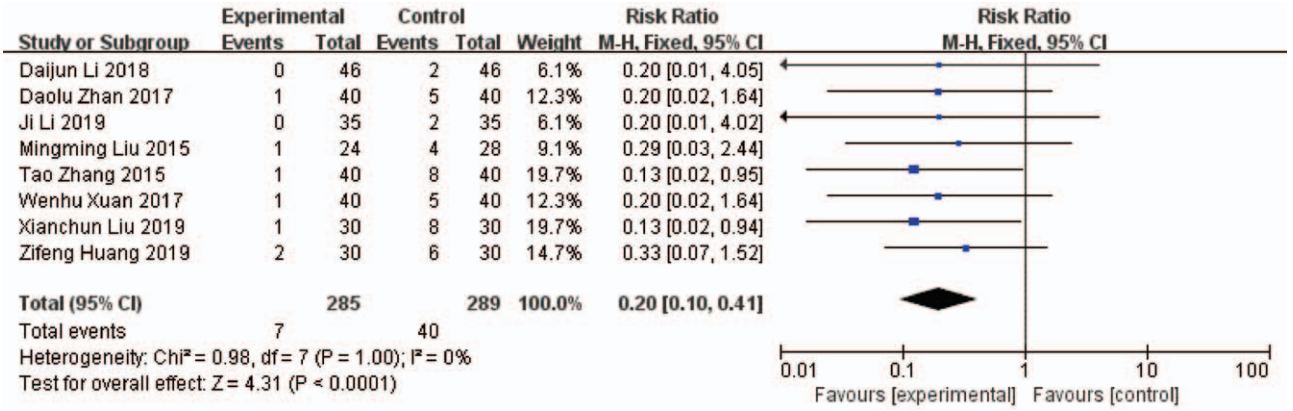

Figure 6. Forest plot and meta-analysis of RVF scores.

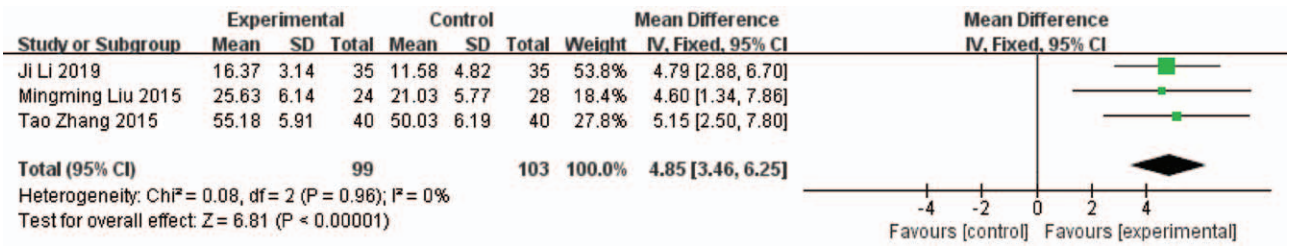

Figure 7. Forest plot and meta-analysis of ODI scores (12 mo).

RVF in the experimental group showed significant differences from the control group ($P < .05$) (Fig. 6).

3.3.4. ODI. Three studies[18,22,23] reported ODI scores at 12 months after treatment. The heterogeneity test suggested a low degree of homogeneity ($I^2 < 50\%$, MD: 4.85, 95% CI: 3.46–6.25), and a fixed-effects model was used for meta-analysis. The results showed that there were significant differences between the 2 groups ($P < .05$) (Fig. 7).

3.3.5. PINP. PINP was reported in 3 studies[17,18,21] at the follow-up period after operation. The heterogeneity test showed a low degree ($I^2 = 0\%$, MD: 4.21, 95% CI: 3.39–5.04), and a fixed-effects model was used for meta-analysis. The results showed that there were significant differences in the experimental group ($P < .05$) (Fig. 8).

3.3.6. β-CTX. β-CTX was reported in 2 studies[18,21] at the follow-up period after operation. The heterogeneity test showed that the homogeneity was a low degree ($I^2 = 0\%$, MD: 0.07, 95% CI: 0.06–0.09), and a fixed-effects model was used for meta-analysis. The analysis results showed that the β-CTX scores in the experimental group indicated better improvement than those in the control group ($P < .05$) (Fig. 9).

3.4. Bone cement leakage

A total of 4 studies[16,19–21] reported the comparison of bone cement leakage between the 2 groups during follow-up. The heterogeneity test showed a low degree ($I^2 = 0\%$, RR: 0.42, 95% CI: 0.22–0.82), and a fixed-effects model was used for meta-analysis. The analysis results revealed the significant differences between 2 groups ($P < .05$) (Fig. 10).

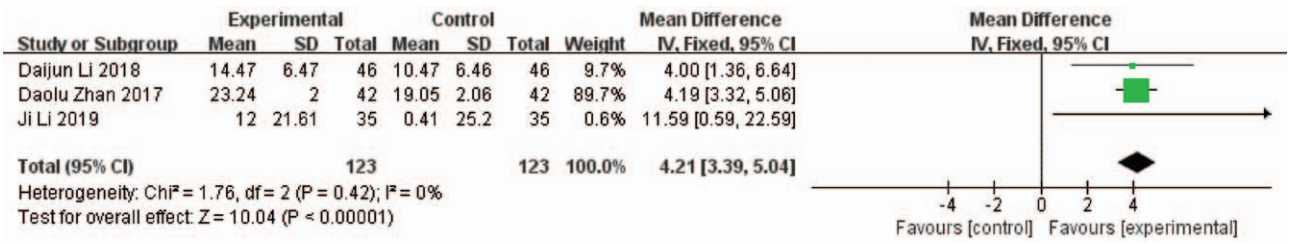

Figure 8. Forest plot and meta-analysis of PINP scores.

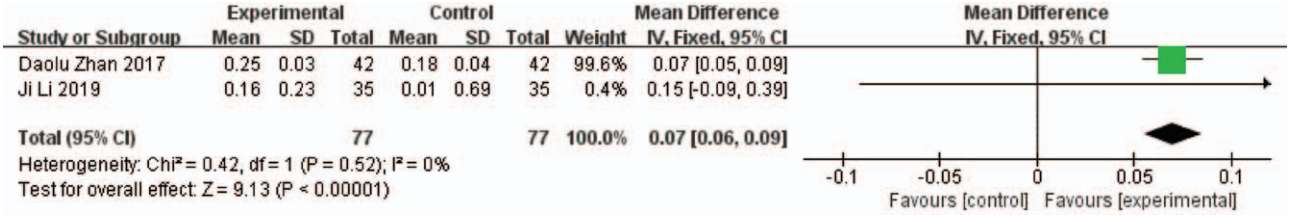

Figure 9. Forest plot and meta-analysis of β-CTX scores.

4. Discussion

4.1. Symptoms and complications of osteoporosis

Osteoporosis is a systemic chronic bone disease, mainly characterized by the reduction of bone mass and the increase of bone fragility, and it has a devastating burden on public health and social economy, especially the quality of life for the elderly people.[24] According to statistics, the osteoporosis has become the world's common diseases, and it affects an estimated 10 million elderly people aged over 50 years in the USA.[25] The clinical main symptoms of osteoporosis are low back pains, height reduction, and humpback, especially the increased risk of fracture. Patients with osteoporosis have increased bone fragility and are prone to fracture under external force, especially OVCF, which is the main complication of osteoporosis.[26] The incidence rate of OVCF in women is higher than that in men, especially in postmenopausal women. This may be related to the change of estrogen level in postmenopausal women. The traditional non-surgical treatment often has poor effectivity and many complications. It requires long-term bed rest, and brings further bone loss, deterioration of osteoporosis, easy to cause deep vein thrombosis and organ failure, increase mortality, etc.[27]

4.2. Advantages and disadvantages of PKP

In recent years, with the development of minimally invasive spine surgery, PKP has been applied by many doctors in the treatment of OVCF. In 1998, Garfin[28] first reported PKP for correction of kyphosis and restoration of vertebral height. It has gradually become the first choice for the treatment of OVCF. Several studies[29,30] have reported that PKP can quickly relieve pain, stabilize the spine, significantly improve the quality of life of patients, restore the height of fractured vertebral body, get out of bed within 24 hours, and improve kyphosis. At present, PKP has become the "gold standard" for the treatment of OVCF. The analgesic mechanism of PKP is exothermic reaction and coagulation of bone cement, which can lead to degeneration and necrosis of nerve endings, reduce the stimulation of painful nerve endings, and relieve the pain symptoms of patients. On the other hand, the perfusion of bone cement can occlude micro-fracture of vertebral body, increase strength, reduce internal pressure, restore height, restore biomechanics, and spinal stability.[31] However, studies have shown that osteoporosis, as a systemic disease, is the main influencing factor of refracture after PKP. PKP alone cannot effectively prevent the progression of osteoporosis and the recurrence of fracture. From the perspective of biomechanics, bone cement can change the local biomechanical properties of fractured vertebrae in a short time, affect the mechanical conduction of adjacent vertebral bodies, and increase the risk of recurrence of adjacent segments after operation.[12] Therefore, in order to ensure the curative effect of PKP, systematic anti-osteoporosis treatment is very important and necessary.

4.3. Efficacy and safety of ZOL

ZOL is the third generation of bisphosphonates, 5 mg per year. It can block the mevalonate pathway, strongly inhibit the formation of osteoclasts, bone turnover and resorption regulated by osteoclasts, and promote the absorption of calcium, thus producing the effect of anti-osteoporosis treatment.[32] After intravenous injection, ZOL could be rapidly distributed in the bone and preferentially concentrated in the sites with high degree of bone transformation.[33] Its main molecular target is trans-isoprene in osteoclasts, but whether it has other effects is unclear. Gaines et al[34] found that ZOL could promote functional recovery, alleviate pain, improve BMD and bone metabolism by inhibiting function of osteoclasts, which was one of its main advantages as a new treatment in patients with osteoporosis. In addition, Molvik et al[35] showed that although oral bisphosph-

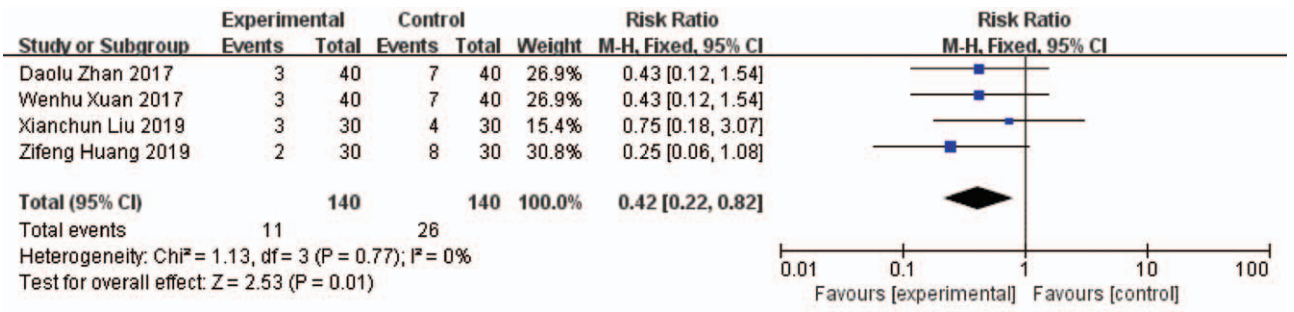

Figure 10. Forest plot and meta-analysis of bone cement leakage scores.

onates could improve BMD of patients, its low bioavailability and complications limited its clinical application. At the same time, compared with other oral bisphosphonates, ZOL had the characteristics of fewer usage, longer duration, and better patient compliance, which promoted its clinical application. Liu et al[36] retrospectively analyzed 104 elderly patients with OVCF. Fifty-two patients were treated with PKP alone and 52 patients received ZOL infusion after PKP. The results showed that VAS, ODI, and BMD in the ZOL after PKP were significantly improved compared with the PKP alone ($P < .05$). It is confirmed that ZOL can improve BMD, reduce the risk of RVF, relieve pain, and improve the quality of life for OVCF patients after PKP. In summary, the clinical efficacy and safety of ZOL is significant, and it can be used for anti-osteoporosis treatment in patients after PKP.

4.4. Analysis of the result

In our study, the data from 8 RCTs reported clinical outcome scores in both groups over a 12-month follow-up period. Meta-analysis showed that there were significant differences in BMD and VAS between the 2 groups at 6 and 12 months after operation. In terms of RVF, the report found that patients in experimental group experienced significantly less than that of control group at the end of follow-up. In addition, ODI were significantly different after 12 months of follow-up. These results indicate that ZOL could increase BMD, relieve pain, and improve physical function. Huang et al[16] reviewed the effects of ZOL combined with PKP on BMD and VAS at 1, 6, and 12-months follow-up. The results showed that compared with the control group, the VAS was also significantly decreased ($P < .05$). After 12 months of follow-up, the BMD of the treatment group increased significantly, and showed a gradual increasing trend. PINP and β-CTX are identified as the secretion of osteocytes in the process of metabolism, reflecting the level of bone transformation. PINP is secreted by osteoblasts and is an important marker of bone formation. β-CTX is decomposition product of I collagen and a specific indicator of bone resorption.[37] Therefore, it can be used to predict the risk of fracture. In this meta-analysis, the improvement rate of PINP and β-CTX was significantly and gradually increased in the experimental group at the end of follow-up ($P < .05$), which was consistent with the relevant research results.[36] Meanwhile, we also analyzed the risk of bone cement leakage after PKP. There was a significant difference between the 2 groups ($P < .05$). But there were no obvious clinical symptoms, so these patients did not receive additional special treatment. In addition, some side-effects of ZOL were observed including fever, headache, nausea, fatigue, muscle aches, dizziness, and other acute-phase reactions.[38] The patients took water and nonsteroidal anti-inflammatory drugs after the infusion of ZOL, which significantly reduced the adverse reactions, and this confirmed the safety and feasibility of the clinical application of ZOL.

4.5. Strengths and limitations

The strengths of this investigation is the first systematic evaluation of all available high quality of the efficacy of ZOL combined with PKP in the prevention and treatment of OVCF, and all trails included are randomized controlled design, and quality assessment is of good level. However, the limitations of this results should also be noted. The difference of PKP operation technique, short follow-up periods, and different fracture vertebrae all may influence the level of heterogeneity and the results of study. In addition, all trials included only 1 article of English language, which may lead to selection bias. Moreover, the whole sample size is too small to objectively assess the quality of meta-analysis. All of these may affect the credibility of our conclusions.

5. Conclusions

Based on the results of systematic review and meta-analysis, the clinical efficacy and safety of ZOL in the treatment and prevention of OVCF after PKP are satisfactory. However, more long-term, multicenter, large sample sizes should be used to confirm the efficacy and safety of the ZOL. In general, ZOL combined with PKP should be widely used in the treatment of OVCF.

Author contributions

KML, HG, and RX participated in the design of the study; JY and XZH carried out data curation; CYL, SQW, and JYG performed the statistical analysis; LHL carried out supervision; KML and RX wrote the manuscript; KML and HG plotted the manuscript; QZ, LHL, and YKH revised the manuscript. All authors approved the final version of the manuscript.
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