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Efficacy of zoledronic acid with percutaneous kyphoplasty/vertebroplasty in the treatment of osteoporotic vertebral compression fractures: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The purpose of this study was to conduct a systematic review and meta-analysis analyzing the efficacy of zoledronic acid in improving outcomes with percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP) surgeries for osteoporotic vertebral compression fracture (OVCF).

MATERIALS AND METHODS: We electronically searched the databases of PubMed, Embase, ScienceDirect, CENTRAL, and Google Scholar up to 15th September 2020. All types of studies assessing the use of zoledronic acid with PKP/PVP surgeries were included.

RESULTS: Seven studies were included. On meta-analysis of data from five studies reporting bone mineral density (BMD) as g/cm², we found a statistically significant increase in BMD in the zoledronic group (MD: 0.14; 95% CI: 0.07, 0.21, I^2=97%; p<0.001). On pooled analysis of two studies reporting T scores, a similar result in favour of the zoledronic acid group was noted (MD: 0.60; 95% CI: 0.23, 0.98, I^2=76%; p=0.002). We also found a statistically significant reduction in pain scores (MD: -1.23; 95% CI: -1.59, -0.86, I^2=97%; p<0.00001), ODI scores (MD: -9.54; 95% CI: -12.76, -6.31, I^2=95%; p<0.00001) and serum type I procollagen peptide (CTX) levels (MD: -0.19; 95% CI: -0.25, -0.12, I^2=98%; p<0.00001) with zoledronic acid as compared to control. Our analysis also found a significantly reduced risk of further vertebral fractures in patients receiving zoledronic acid as compared to control (RR: 0.17; 95% CI: 0.07, 0.39, I^2=0%; p<0.00001).

CONCLUSIONS: Our review indicates that the use of once-yearly zoledronic acid in the peri-operative period of PVP/PKP procedures for patients with OVCF leads to significant improvement of BMD, reduced pain scores, better ODI scores, and reduced incidence of further vertebral fractures. Our results have clinical significance as it encourages the use of zoledronic acid for such patients for better clinical outcomes.

Key Words:
Bisphosphonate, Osteoporosis, Fracture, Bone.

Introduction

Osteoporosis has become a common systemic illness owing to a large aging population worldwide. According to estimates, the disease is ranked the world's 7th most common illness[1,2]. Osteoporosis is characterized by reduced bone mass along with low mechanical strength leading to increase bone fragility. As a result, osteoporotic patients have a higher risk of hip, ankle, and vertebral fractures as compared to those not affected by the disease[3,4].

Osteoporotic vertebral compression fracture (OVCF) of the thoracic or lumbar vertebrae is the most common type of fragility fracture with a prevalence in 1.4 million individuals around the world[5,6]. It can lead to considerable pain which further leads to limited mobility, loss of independence, and additional bone loss due to the associated inactivity. It is commonly seen in the elderly population who are in poor physical condition along with other comorbidities. Conservative treatment for managing OVCF consisting of bed rest, pain-killers, anti-osteoporosis medication, physical therapy, and bracing is usually not recommended in the elderly owing to the high risk of complications[7]. In this context, the two minimally invasive surgical treatments, namely, percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP) are commonly used for rapid pain relief and to achieve spinal stabilization in this cohort of patients[8]. In PVP, bone cement is injected into the fractured vertebrae via percutaneous incisions to increase the strength and stiffness of

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the bone. The procedure arrests further vertebral collapse and spinal deformity and relives OVCF associated pain. In 1998, Garfin et al[9] first introduced PKP as an alternative to PVP wherein an inflatable balloon is used to create a cavity in the vertebral body which is then filled with bone cement. Both techniques are effective in managing OVCF patients by reducing pain, drug dependence, and improving the quality of life[10].

Several drugs like calcium, vitamin D, calcitonin, parathyroid hormone, and bisphosphonates are used to manage osteoporosis in routine clinical practice[11]. Amongst these, bisphosphonates have been shown to improve bone mineral density (BMD) and reduce the risk of OVCF by reducing bone turnover. These drugs act by inhibiting the osteoclastic function and inducing osteoclast apoptosis which prevents bone resorption[12]. Recently, several studies[13,14] have combined the use of zoledronic acid, a third-generation, nitrogen-containing bisphosphonate, along with PVP/PKP to improve clinical outcomes. However, to the best of our knowledge, there have no systematic efforts to pool the available evidence. Therefore, the purpose of this study was to conduct a systematic review and meta-analysis analyzing the efficacy of zoledronic acid in improving outcomes with PVP/PKP surgeries for OVCF.

Materials and Methods

Search Strategy

The authors designed and implemented this review adhering to the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[15] and the Cochrane Handbook for Systematic Reviews of Intervention[16]. We electronically searched the databases of PubMed, Embase, ScienceDirect, CENTRAL, and Google scholar. Two of the study reviewers were involved in this process independently. Search limits were from the inception of databases to 15th September 2020. To identify relevant studies a mix of MeSH terms and free-text keywords were used. The keywords in different combinations were: "bisphosphonate", "zoledronic acid", "anti-resorptive", "percutaneous vertebroplasty", "percutaneous kyphoplasty", "compression fracture", "vertebrae", "spine", "osteoporosis", and "thoracolumbar fracture". For every database, the search results were screened by the titles and abstracts by both reviewers. After identifying potentially pertinent articles, full texts of the articles were extracted. Both the reviewers assessed individual articles based on the inclusion and exclusion criteria. Any disagreements were resolved by discussion. After screening, the reference list of studies meeting the inclusion criteria were hand searched for any more references.

Inclusion Criteria

All randomized controlled trials (RCTs), prospective, and retrospective studies were eligible for inclusion in this review. We further defined the inclusion criteria based on the PICO (Population, Intervention, Comparison, Outcome) framework as follows:- *Population*: studies conducted on osteoporotic patients with vertebral compression fracture undergoing PVP/PKP. *Intervention*: zoledronic acid administered in the perioperative period. *Comparison*: placebo or no drug. *Outcomes*: BMD and other outcomes like pain scores, Oswestry Disability Index (ODI), or drug-related adverse events. We included only English language studies. We excluded studies conducted on patients undergoing conservative management of the fracture or any other surgical procedures except PVP/PKP. We also excluded studies not using zoledronic acid, non-comparative studies, single-arm studies, studies with non-available full-texts, and studies not reporting relevant data.

Data Extraction

Data from the included studies were extracted by two reviewers independently. Data regarding authors, publication year, study type, surgical procedure, sample size, demographic details, intervention protocol, fracture site, pre-op BMD, study outcomes, and follow-up time were extracted. The primary outcome of the interest of our analysis was BMD. The secondary outcomes were pain scores, ODI, serum type I procollagen peptide (CTX) levels, the incidence of new vertebral fractures, and drug-related adverse events.

Risk of Bias Assessment

As both RCTs and non-RCTs were included in the review, we used different tools for assessing the risk of bias in these study types. The Cochrane Collaboration risk assessment tool was used for RCTs[17]. Studies were assessed by two reviewers independently for: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. For non-RCTs, the risk of a bias assessment tool for non-randomized studies (RoBANS) was used[18]. Studies were assessed for the selection of partici-

pants, confounding variables, intervention measurements, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

Statistical Analysis

We conducted a meta-analysis when at least three trials reported the same outcomes. "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) was used for the meta-analysis. Outcome data was fed into meta-analysis software and cross-checked for correctness. Continuous outcomes were summarized using the mean difference (MD) with 95% confidence intervals (CI). Risk ratios (RR) were calculated for the incidence of vertebral refractures. We used a random-effects model to calculate the pooled effect size for all our analyses. Sub-group analysis was carried out for study types. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial heterogeneity. Due to the inclusion of fewer than 10 studies per meta-analysis, funnel plots were not used to assess publication bias. In studies where data were presented only graphically, "Engage digitizer software version 12.1" (http://markummitchell.github.io/engauge-digitizer) was used to extract numerical data.

Results

Characteristics of Studies

The study flow-chart depicting the search results and selection of studies is presented in Figure 1. Seven studies[13,14,19-23] fulfilled the inclusion of criteria. The characteristics of included studies are presented in Table I.

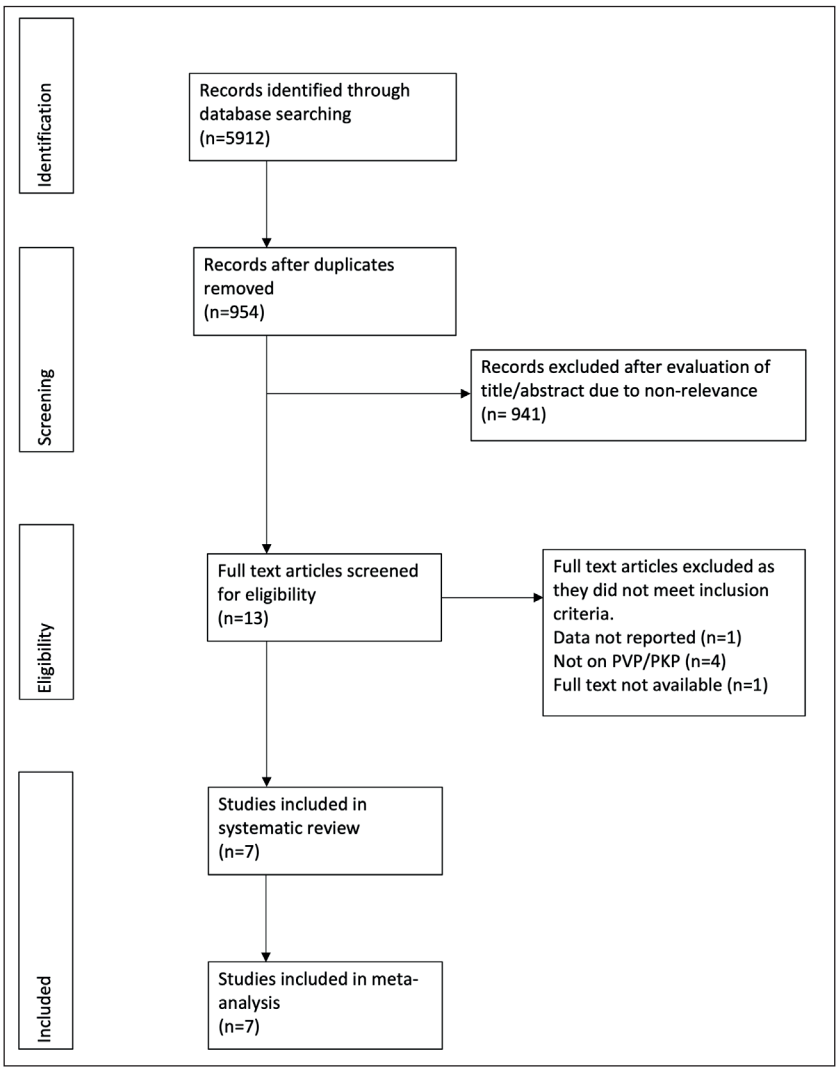

Figure 1. Study flow chart.

Table I. Characteristics of included studies.

Author/Year	Study type	Surgery	Study drug protocol	Sample size	Mean age	Male Gender (%)	BMI	Fracture site	Pre-operative BMD (g/cm² or T scores)	Follow-up
Li et al[23]/ 2020	RT	PVP	5 mg of Zoledronic acid administered 3-5 days postoperatively. Tab Rosuvastatin 10mg OD for 12 months	Study: 60 Control: 60	71.5± 2.2 71.0± 2.2	66.6 63.3	24.1± 1.0 24.0± 1.0	NR	0.36± 0.08 0.38± 0.05	12 months
Hu et al[22]/ 2020	RCT	PVP	5 mg of Zoledronic acid administered preoperatively	Study: 121 Control: 121	62.6± 7.2 67.4± 4.1	40.5 33.1	26.1± 3.2 26.7± 5.4	T:89, L:57 T:101, L:51	0.41± 0.05 0.41± 0.05	12 months
Huang S et al[21]/ 2019	RT	PKP	4 mg of Zoledronic acid administered on 2nd postoperative day	Study: 52 Control: 52	50.7± 3.2 51.6± 3.3	NR	22.9± 1.9 23.5± 1.8	T: 40, L:42 T: 28, L:34	0.83± 0.14 0.83± 0.13	3 months
Zhang et al[20]/ 2019	RCT	PKP	5 mg of Zoledronic acid administered preoperatively	Study: 50 Control: 51	64.6± 6.7 63.9± 7.5	0 0	26.1± 1.8 26.1± 2.2	T: 28, L:22 T: 24, L:27	0.67± 0.07 0.66± 0.05	12 months
Huang ZF et al[19]/ 2019	RCT	PKP	5 mg of Zoledronic acid administered on 3rd postoperative day	Study: 30 Control: 30	76.1± 8.3 74.3± 9.0	33.3 23.3	18.3± 1.2 18.3± 1.4	T:17, L:13 T: 14, L:20	-3.14± 0.38* -3.15± 0.41*	12 months
Shi et al[14]/ 2018	RT	PKP	5 mg of Zoledronic acid administered on 3rd postoperative day	Study: 29 Control: 34	77.7± 5.5 76.6± 4.8	54.2 53	30.2± 3.1 31.5± 3.2	T:10, L:19 T: 18, L:12	-3.51± 0.47* -3.8 ± 0.67*	24 months
Liu et al[13]/ 2017	RCT	PKP	Zoledronic acid administered preoperatively	Study: 52 Control: 52	67.7± 7.6 70.9± 10.6	25 24.6	NR	T:22, L:45 T: 20, L:43	0.61 ± 0.13 0.59 ± 0.14	12 months

BMD, bone mineral density; RCT, Randomized controlled trial; RT, retrospective study; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty. NR, not reported; T, thoracic; L, lumbar.
* T-scores

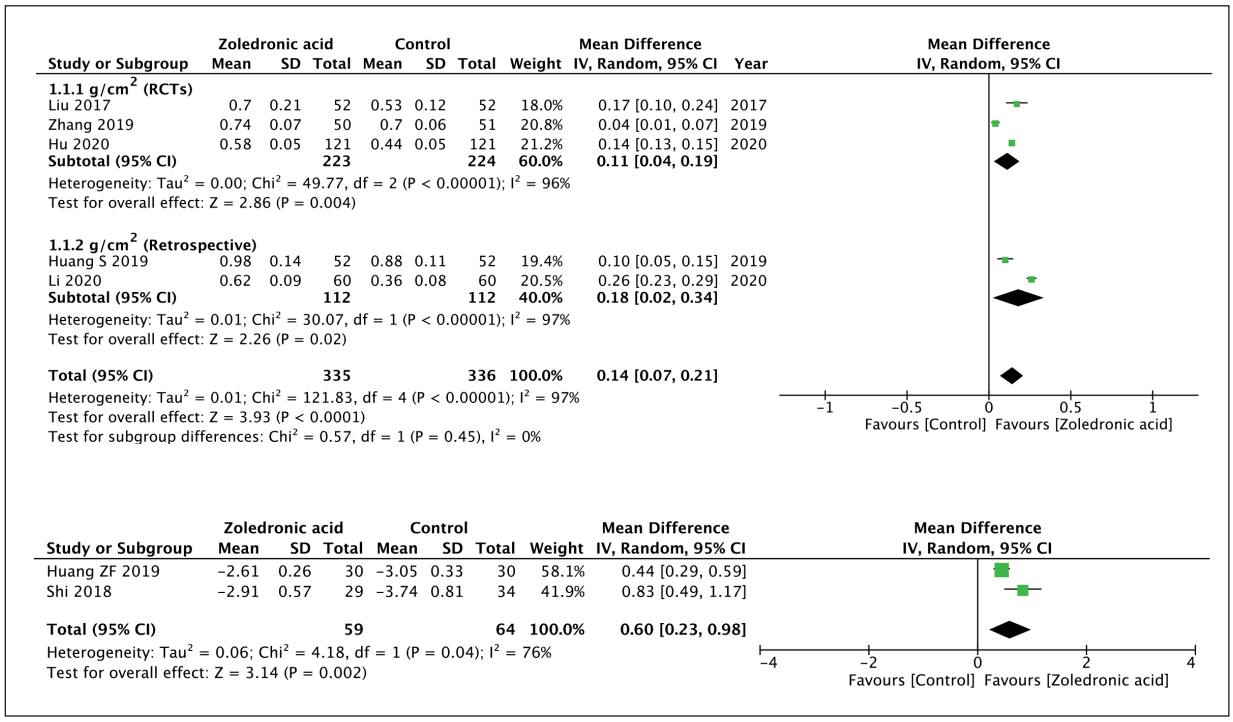

Figure 2. A, Forest plot of bone mineral density scores (g/cm2) with sub-group analysis based on study type. **B**, Forest plot of bone mineral density scores (T score).

All studies were conducted in China. Four were RCTs[13,19,20,22] while remaining were retrospective studies[14,21,23]. Zoledronic acid was administered pre-operatively in three studies[13,20,22] and post-operatively in the remaining studies. The total number of thoracic or lumbar fractures varied in the included studies. No statistically significant difference was noted in baseline BMD of the two groups by the included studies. Follow-up amongst studies ranged from 3 months to 24 months. For the report of Shi et al[14], data of 12 months of follow-up were extracted for the meta-analysis to maintain homogeneity amongst studies.

Outcomes

BMD was evaluated by all included studies and data presented as g/cm^2 or as T scores. A separate analysis was carried out for these different scales. On meta-analysis of data from five studies reporting data as g/cm^2, we found a statistically significant increase in BMD in the zoledronic group as compared to the control group (MD: 0.14; 95% CI: 0.07, 0.21, I^2=97%; p<0.001) (Figure 2A). On subgroup analysis, statistically significant results were seen in both RCTs (MD: 0.11; 95% CI: 0.04, 0.19, I^2=96%; p=0.004) and retrospective studies (MD: 0.18; 95% CI: 0.02, 0.34, I^2=97%; p=0.02). On pooled analysis of two studies reporting T scores, a similar result in favor of the zoledronic acid group was noted (MD: 0.60; 95% CI: 0.23, 0.98, I^2=76%; p=0.002) (Figure 2B).

Pain was assessed on Visual Analog Scale (VAS) in all studies. On meta-analysis of all seven studies, we found a statistically significant reduction in pain scores with zoledronic acid as compared to control (MD: -1.23; 95% CI: -1.59, -0.86, I^2=97%; p<0.00001) (Figure 3). On subgroup analysis, statistically significant results were seen in both RCTs (MD: -1.04; 95% CI: -1.44, -0.64, I^2=92%; p<0.00001) and retrospective studies (MD: -1.45; 95% CI: -2.07, -0.84, I^2=97%; p<0.00001).

Five researches reported data on ODI scores. On pooled analysis, ODI scores were significantly reduced in the zoledronic acid group (MD: -9.54; 95% CI: -12.76, -6.31, I^2=95%; p<0.00001) (Figure 4). Significant reduction was seen in both RCTs (MD: -7.16; 95% CI: -11.19, -3.12, I^2=86%; p=0.0005) and retrospective studies (MD: -11.01; 95% CI: -14.72, -7.29, I^2=95%; p<0.00001).

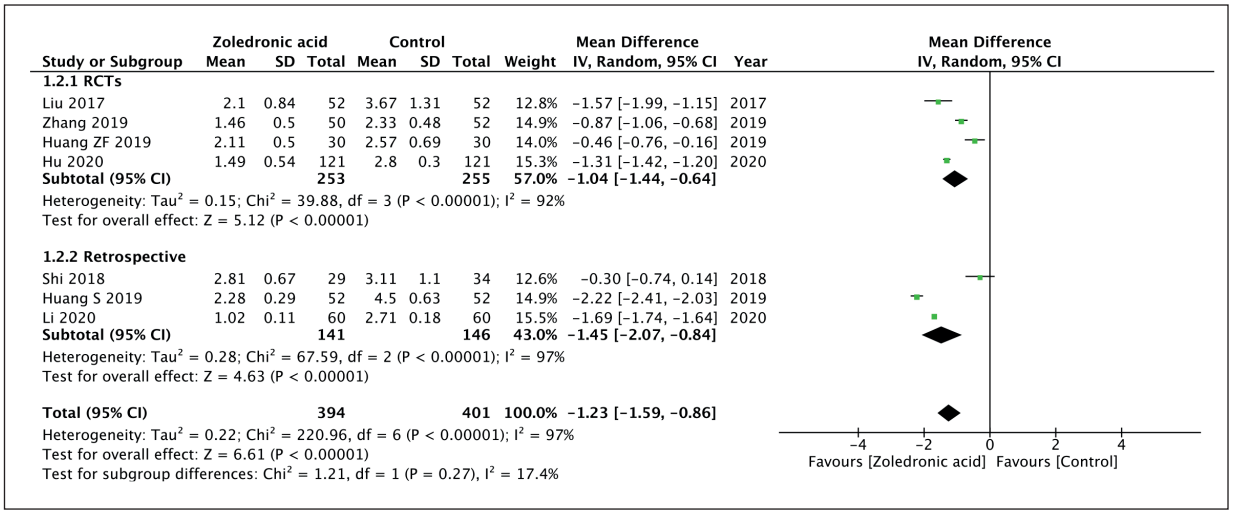

Figure 3. Forest plot for pain scores on Visual Analog scale with sub-group analysis based on study type.

Data on CTX was reported by four studies. Meta-analysis indicated a statistically significant reduction of CTX in patients receiving zoledronic acid (MD: -0.19; 95% CI: -0.25, -0.12, I^2=98%; p<0.00001) (Figure 5). Since only one investigation was retrospective in the meta-analysis of CTX scores, a sub-group analysis was not conducted. Our analysis also found a significantly reduced risk of further vertebral fractures in patients receiving zoledronic acid as compared to control (RR: 0.17; 95% CI: 0.07, 0.39, I^2=0%; p<0.00001) (Figure 6). The results were significant in both RCTs (RR: 0.20; 95% CI: 0.07, 0.53, I^2=0%; p=0.001) and retrospective studies (RR: 0.11; 95% CI: 0.02, 0.57, I^2=0%; p=0.009). Data regarding zoledronic acid-related adverse events are presented in Table II. Fever, flu-like symptoms, and muscle pain were the most common adverse events reported.

Risk of Bias Analysis

Details of the risk of bias in included studies are presented in Table III. Only one RCT[20] mentioned the randomization method. All RCTs had a high risk of bias for blinding. Likewise, the retrospective studies had a high risk of bias for confounding factors and blinding of outcome assessment.

Discussion

The results of our review suggest that the use of a single dose of zoledronic acid to PVP/PKP procedures for the management of OVCF leads to significant improvements in BMD, pain scores, and ODI. The drug also leads to a significant reduction in CTX levels with decreased risk of further vertebral fractures.

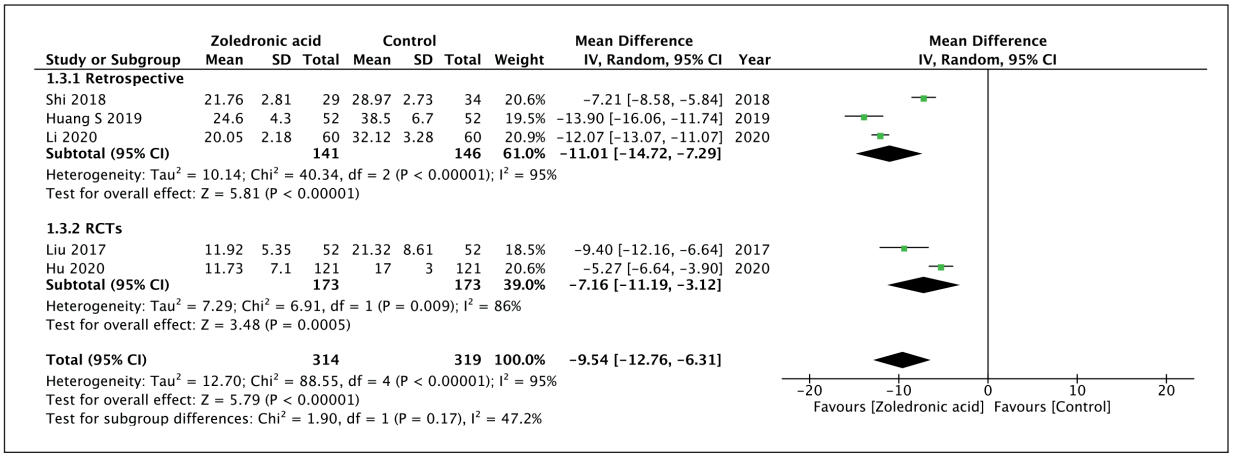

Figure 4. Forest plot for Oswestry Disability Index with sub-group analysis based on study type.

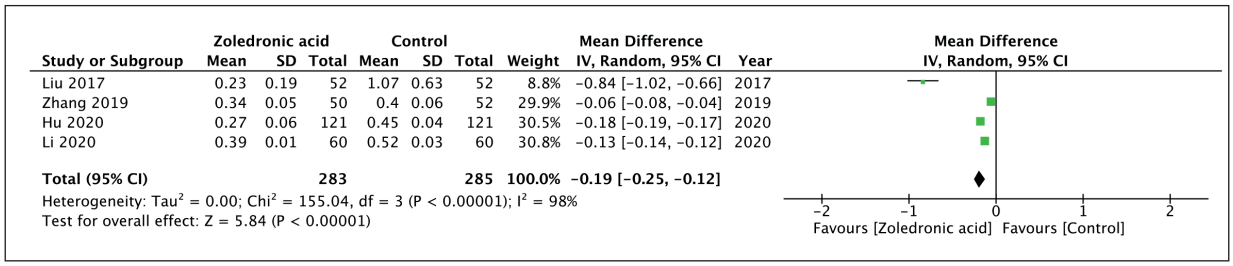

Figure 5. Forest plot for CTX levels.

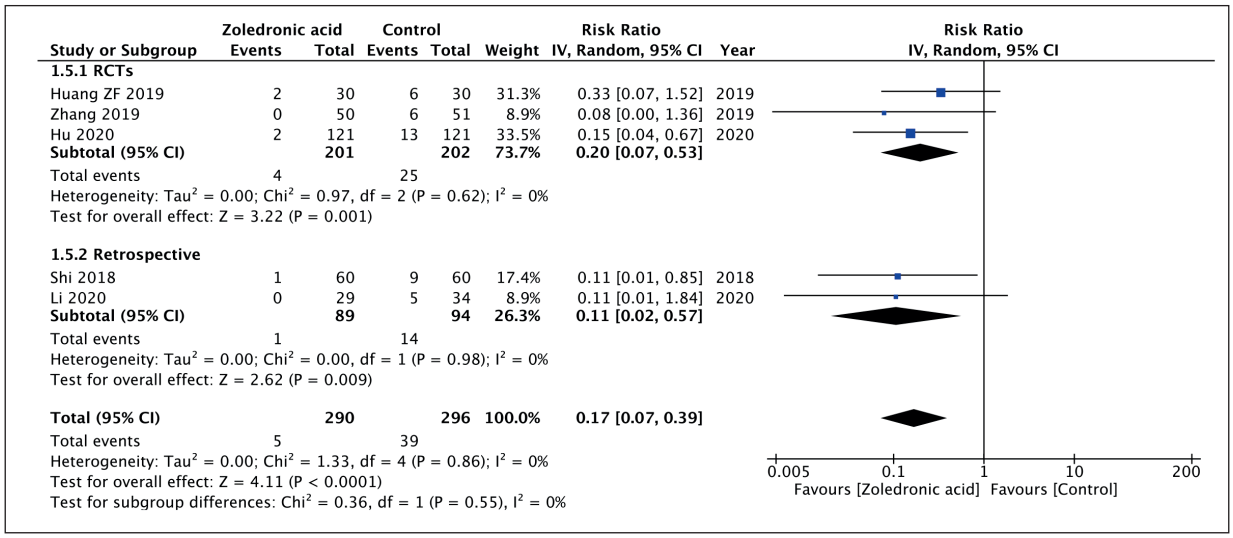

Figure 6. Forest plot for risk of new vertebral fractures with sub-group analysis based on study type.

Table II. Comparison of serum ACE activity and levels of RA, Ang II, and ALD in peripheral blood.

Variable	Control	Hypertension	*t*	*p*
ACE activity (U/L)	105.37±25.13	171.20±31.39	17.171	<0.001
RA (μg/L)	2.92±0.43	3.13±0.51	3.302	0.001
Ang II (ng/L)	51.99±18.27	104.73±34.29	14.237	<0.001
ALD (ng/L)	30.15±19.07	51.32±18.10	8.445	<0.001

ACE: Angiotensin converting enzyme; RA: Renin; Ang II: Angiotensin II; ALD: Aldosterone.

Table III. The influence of microRNA-136 on the therapeutic efficacy in EH.

Groups	Effect after one month			Effect after two months		
	Significant effect	Valid	Invalid	Significant effect	Valid	Invalid
High level of microRNA-136 (n=55)	28	9	18	34	16	5
Low level of microRNA-136 (n=55)	21	13	21	22	13	20
χ^2	1.803	0.909	0.358	5.238	0.421	11.647
p	0.25	0.475	0.69	0.035	0.666	0.001

A compression fracture of the thoracic or lumbar vertebrae is a significantly disabling complication of osteoporosis in the elderly. While OVCF may be managed by non-surgical methods consisting of complete bed rest for 3 months and anti-inflammatory drugs for pain relief, it may lead to additional bone loss and exacerbation of osteoporosis leading to several complications like hypothyroidism, pressure ulcers, and adverse cardiovascular events[21]. According to one study, non-surgical therapy for OVCF can lead to mortality rates of up to 20%[24]. Elderly patients with OVCF frequently undergo PVP or PKP wherein under radiological guidance, bone cement is injected in the centrum to reinforce the bone, restore vertebral height, and improve the kyphotic deformity. Wang et al[25] in a recent systematic review and meta-analysis of 16 studies have reported that there is no difference in clinical outcomes with either procedure. The authors found no statistically significant difference in VAS scores and ODI scores between patients undergoing PVP or PKP. However, there are concerns that the injected bone cement in PVP or PKP can lead to increased mechanical pressure and risk of new vertebral fractures[13,26]. Contrastingly, Yang et al[27] in a two-year follow-up research of 290 patients have shown that PVP does not increase the risk of new OVCF and the primary risk factor of further fractures was low BMD due to osteoporosis itself. Similar results have been demonstrated by Rho et al[28] in a cohort of PVP and PKP patients. Thus, to improve clinical outcomes, there is a need to manage the primary condition itself.

Zoledronic acid is a parenterally administered highly potent amino bisphosphonate that has been approved by the USA Food and drug administration for the treatment of postmenopausal osteoporosis, male osteoporosis, and glucocorticoid-induced osteoporosis[29]. The drug binds to the hydroxyapatite surface and inhibits osteoclast farnesyl pyrophosphate synthase. This leads to apoptosis of osteoclasts, reduction of osteolysis and bone turnover, and activation of osteoblastic activity which in turn increases bone mass[29]. The use of once a year zoledronic acid has been shown to reduce the risk of fragility fractures in several studies. In a two-year multicenter, randomized, placebo-controlled, double-blind trial on 665 patients, Nakamura et al[30] have demonstrated that 5 mg of once-yearly zoledronic acid reduced the cumulative risk of clinical fracture, clinical vertebral fracture, and non-vertebral fracture by 54, 70, and 45 %, respectively. The HORIZON-Pivotal Fracture Trial has shown that yearly infusion of zoledronic acid reduces the risk of vertebral fractures by 77% and increase BMD by 6.7% in women with postmenopausal osteoporosis[31].

Owing to the evidence supporting the clinical effects of zoledronic acid, in the past few years, there have been several reports of combining the drug with PVP/PKP surgeries. On a systematic search of the literature, we were able to pool data of 795 patients from seven studies in our analysis. For the primary outcome of interest, our results demonstrated that the use of zoledronic acid administered once in the perioperative period of PVP/PKP led to statistically significant improvement in the BMD. The results were significant irrespective of the type of study and method of measurement of BMD. Patients receiving zoledronic acid also had significantly reduced pain scores and better ODI scores. The serum marker CTX was also reduced in patients receiving zoledronic acid indicating reduced bone turnover. Our analysis also indicated that the administration of the bisphosphonate can reduce the risk of new vertebral fractures by 83% (95% CI: 61%-93%). The adverse events related to the drug administration were few and not serious. Our results are similar to studies reporting the use of zoledronic acid in lumbar fusion surgeries. Chen et al[32] in an RCT of 79 osteoporotic patients with single-level degenerative spondylolisthesis undergoing spinal fusion compared the efficacy of zoledronic acid and placebo in improving clinical outcomes. The authors reported significantly improved BMD, better ODI scores, suppressed CTX levels, and reduced risk of adjacent vertebral fractures with zoledronic acid after a follow-up of 12 months. In a retrospective study, Tu et al[33] have demonstrated that the administration of zoledronic acid with lumbar interbody fusion surgery for patients with degenerative lumbar spondylolisthesis and osteoporosis results in reduced VAS scores, better ODI scores, and reduced incidence of OVCF.

The results of our review should be interpreted in context with the following limitations. Firstly, our analysis consisted of a mix of RCTs and retrospective studies. Thus, the inherent limitations of retrospective studies could have influenced our results. Furthermore, the quality of the included studies was not high. There were concerns of bias with randomization and blinding amongst the included RCTs. Secondly, there was methodological heterogeneity in the included studies in the surgical procedure with both PVP and PKP being assessed. One of the studies used a statin along with zoledronic acid. Statins are known to improve bone density and inhibit bone tissue absorption[11]. Thus, the drug may have had a supplementary effect with zoledronic acid. Lastly, all studies were carried out

in China and hence the general application of results should be carried out with caution.

However, our review does have some novelties. Our study is the first systematic review and meta-analysis assessing the efficacy of zoledronic acid combined with PVP/PKP procedures for OVCF patients. A total of seven studies with 795 patients were assessed with appropriate sub-group analysis for study types. The absence of any difference in the significance of our results amongst retrospective studies and RCTs lend credibility to our conclusion.

To summarize, our review indicates that the use of once-yearly zoledronic acid in the peri-operative period of PVP/PKP procedures for patients with OVCF leads to significant improvement of BMD, reduced pain scores, better ODI scores, and reduced incidence of further vertebral fractures. Our results have clinical significance as it encourages the use of zoledronic acid for such patients for better clinical outcomes. Future studies should focus on five and ten-year outcomes and compare zoledronic acid with other anti-osteoporotic drugs to further refine current evidence.

Author Contributions

GO conceived and designed the study. HL, BS, LH, GC and WL collected the data and performed the literature search. GO was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

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None

Conflict of Interests

The authors declare that they have no conflict of interests.

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