INPLASY PROTOCOL

To cite: Sun et al. Percutaneous Vertebral Augmentation for Osteoporotic Vertebral Compression Fractures Will Increase the Number of Subsequent Fractures at Adjacent Vertebral Levels: A Systematic Review and Meta-analysis. Inplasy protocol 202150097. doi: 10.37766/inplasy2021.5.0097

Received: 27 May 2021

Published: 27 May 2021

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Support: **N/A.**

Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
None declared.

Percutaneous Vertebral Augmentation for Osteoporotic Vertebral Compression Fractures Will Increase the Number of Subsequent Fractures at Adjacent Vertebral Levels: A Systematic Review and Meta-analysis

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Review question / Objective: **This study aimed to investigate whether percutaneous vertebral augmentation (PVA) was associated with clinical and radiological subsequent adjacent fractures in patients with osteoporotic vertebral compression fractures.**
Eligibility criteria: **Participants: Only adult patients (age ≥ 50 years) diagnosed with OVCFs based on clinical and imaging examinations were included. Intervention and control groups: Patients who underwent PVA (PVP/PKP) were included in the experimental group, and patients who underwent CT (including sham operation) were included in the control group. Outcomes: The incidence of subsequent adjacent vertebral fractures. Study type: Prospective cohort study, non-randomized controlled trial (RCT), and RCT.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 May 2021 and was last updated on 27 May 2021 (registration number INPLASY202150097).

INTRODUCTION

Review question / Objective: **This study aimed to investigate whether percutaneous vertebral augmentation (PVA) was associated with clinical and radiological subsequent adjacent fractures in patients with osteoporotic vertebral compression fractures.**

Condition being studied: **Osteoporotic vertebral compression fractures (OVCFs) are common complications of osteoporosis and often result in back pain, spinal deformity, functional disability, and even death. Hence, they have become one of the most serious diseases, threatening the health of older patients and increasing the economic burden of the society. As a**

minimally invasive therapy for OVCFs, percutaneous vertebral augmentation (PVA) has shown promising and encouraging outcomes compared with conservative treatment (CT). Moreover, depending on the features of a fracture, percutaneous vertebroplasty (PVP), percutaneous kyphoplasty (PKP), or any other operation methods can be selected. However, PVA may also lead to subsequent fracture, which disputes the efficacy and safety of PVA. Subsequent fractures can occur at adjacent, non-adjacent, or even previously treated vertebral levels. Many meta-analyses have shown that a subsequent fracture is related to the natural progression of osteoporosis and not to PVA with cement. However, only one study has detailed the influence of PVA on subsequent adjacent vertebral fractures . Furthermore, no study has distinguished clinical fractures from radiological fractures and the number of fractured patients from the number of fractured vertebrae for analysis. Thus, this study aimed to explore the characteristics of subsequent adjacent fractures after PVA and to provide evidence regarding the treatment strategy of OVCFs.

METHODS

Search strategy: Two reviewers independently conducted rough and accurate computerized retrieval from online databases, including PubMed, EMBASE, Cochrane library, Google Scholar, Web of Science, and ClinicalTrial.gov, from the establishment of the database to March 2020. References of selected studies were also searched to avoid missing any additional studies. There were no language restrictions in the literature search. Our literature search strategy was as follows: Rough search strategy: (vertebroplasty OR kyphoplasty OR vertebral augmentation) AND (conservative treatment) AND ((new fracture) OR (secondary fracture) OR (subsequent fracture) OR (adjacent fracture)). Accurate search strategy: (Taking retrieval strategy of PubMed as an example) 1#: ((Osteoporosis[Mesh]) OR ((((((((((((((((((((Osteoporoses) OR Osteoporosis, Post-Traumatic) OR Osteoporosis, Post Traumatic) OR Post-Traumatic Osteoporoses) OR Post-Traumatic Osteoporosis) OR Osteoporosis, Senile) OR Osteoporoses, Senile) OR Senile Osteoporoses) OR Osteoporosis, Involutional) OR Senile Osteoporosis) OR Osteoporosis, Age-Related) OR Osteoporosis, Age Related) OR Bone Loss, Age-Related) OR Age-Related Bone Loss) OR Age-Related Bone Losses) OR Bone Loss, Age Related) OR Bone Losses, Age-Related) OR Age-Related Osteoporosis) OR Age Related Osteoporosis) OR Age-Related Osteoporoses) OR Osteoporoses, Age-Related)) 2#: ((Fractures, Compression [Mesh]) OR ((((((Compression Fracture) OR Fracture, Compression) OR Compression Fractures) OR compressive fractures) OR Vertebral Fractures) OR vertebral compression fracture)) 3#: ((vertebroplasty[Mesh]) OR (augmentation) OR ((kyphoplasty[Mesh]) OR ((Balloon Vertebroplasty) OR Vertebroplasty, Balloon)) OR (VP OR PVP OR PKP)) 4#: ((Conservative Treatment[Mesh]) OR ((((((((((((((Conservative Treatments) OR Treatment, Conservative) OR Treatments, Conservative) OR Conservative Management) OR Conservative Managements) OR Management, Conservative) OR Managements, Conservative) OR Conservative Therapy) OR Conservative Therapies) OR Therapies, Conservative) OR Therapy, Conservative) OR conservatively) OR Treated Conservatively) OR Conservative care)) OR (((((nonsurgical approach) OR nonsurgical management) OR nonsurgical care) OR Pain medication treatment) OR Medical management) OR ((((sham procedure) OR sham trial) OR Placebo controlled)) 5#: ((secondary fracture) OR (subsequent fracture) OR (new fracture) OR (recompression in new levels) OR (nonsurgical level fracture) OR (new levels recompression) OR (remote level fracture) OR (adjacent fracture)) 6#: ((Prospective study) OR (Randomized controlled study) OR (Non randomized controlled study) OR (Prospective cohort study)) 7#: (1# AND 2#) AND 3# AND 4# AND 5# AND 6#.

Participant or population: Only adult patients (age ≥ 50 years) diagnosed with

OVCFs based on clinical and imaging examinations were included.

Intervention: Patients who underwent PVA (PVP/PKP) were included in the experimental group.

Comparator: Patients who underwent CT (including sham operation) were included in the control group.

Study designs to be included: Prospective cohort study, non-randomized controlled trial (RCT), and RCT.

Eligibility criteria: Participants: Only adult patients (age ≥ 50 years) diagnosed with OVCFs based on clinical and imaging examinations were included. Intervention and control groups: Patients who underwent PVA (PVP/PKP) were included in the experimental group, and patients who underwent CT (including sham operation) were included in the control group. Outcomes: The incidence of subsequent adjacent vertebral fractures. Study type: Prospective cohort study, non-randomized controlled trial (RCT), and RCT.

Information sources: Two reviewers independently conducted rough and accurate computerized retrieval from online databases, including PubMed, EMBASE, Cochrane library, Google Scholar, Web of Science, and ClinicalTrial.gov, from the establishment of the database to March 2020. Records identified through database searching (n=1259) Additional records identified through database searching (n=0) Records after duplicates removed (n=1026) Records screened (n=1026) Records excluded (n=958) Full-text articles assessed for eligibility (n=68) Full-text articles excluded with reasons (n=44) 6 No appropriate comparison 7 Not prospective trials 21 No data on outcome of interest 10 Conference abstract Studies included in qualitative synthesis (meta-analysis) (n=24).

Main outcome(s): 20/421 (4.75%) patients in the PVA group and 25/359 (6.96%) patients in the CT group had clinical subsequent adjacent fractures. No significant difference was found between the two groups (RR = 0.67, 95% CI [0.38, 1.19], p = 0.17. M-H. Fixed-effect model, I2 = 31%). Radiological subsequent adjacent fractures were reported in 46/440 (10.45%) patients from the PVA group and in 36/444 (8.10%) patients from the CT group. No significant difference was observed between the two groups (RR =1.13, 95% CI [0.75, 1.70], p = 0.576. M-H. Fixed-effect model, I2 = 0%). 69/126 (54.76%) vertebral bodies from the PVA group and 40/105 (38.10%) vertebral bodies from the CT group had subsequent adjacent fractures. A significant difference was found between the two groups (RR = 1.41, 95% CI [1.03, 1.93], p = 0.03. M-H. Fixed-effect model, I2 = 0%).

Data management: Endnote X9 software was used to check, sort, and summarize the studies. Then, each study was carefully read and selected by two independent reviewers by a double-blind method. Any disagreement was resolved by discussion or consultation with a third reviewer. The number of clinical and radiological subsequent adjacent fractures was separately extracted and classified. If the subsequent adjacent fractures were not defined clearly in the article, it was considered a radiological fracture because most fractures need imaging for diagnosis. If a patient had subsequent adjacent vertebral fractures at two or more levels at one time, the incidence was counted as one.

Quality assessment / Risk of bias analysis: Two independent reviewers applied the risk of bias tool to appraise all included studies according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). The methodological quality was assessed according to Cochrane Collaboration's domain-based evaluation framework. The main domains were assessed in the following sequence: (1) selection bias (randomized sequence generation and allocation concealment), (2) performance bias (blinding of participants and personnel), (3) detection bias (blinding of outcome assessment), (4) attrition bias (incomplete outcome data, e.g., due to dropouts), (5) reporting bias (selective reporting), and (6) other sources of bias.

The score for each bias domain and the final score for the risk of systematic bias were graded as low, high, or unclear risk. According to the Jadad scale, the quality of RCTs was evaluated based on the following aspects: (1) generation of random sequence, (2) allocation concealment, (3) implementation of blind method, and (4) description of case follow-up. A score of "1–3" was considered low quality, and "4–7" was considered high quality.

Strategy of data synthesis: To compare the differences in the incidence of subsequent adjacent fractures after PVA, dichotomous data were calculated by risk ratio (RR) and its 95% confidence interval (95% CI). Heterogeneity was tested using the chi-squared statistic and the I2 statistic. If the p-value was < 0.1, the chi-squared statistic was defined as significant. The I2 statistic was used to assess the variation across the included trials based on the following standard: I2 < 25%, low heterogeneity; I2 = 25%–50%, moderate heterogeneity; and I2 > 50%, high heterogeneity. For I2 > 50%, a random-effect model was adopted; otherwise, a fixed-effect model was used 15. Sensitivity analyses were performed to investigate the influence of each study by removing them one at a time and by calculating the effect on the overall results of the meta-analysis. Publication bias was detected using Begg's and Egger's tests. Statistical analysis was performed using Review Manager 5.3 and Stata 15.0.

Subgroup analysis: N/A.

Sensitivity analysis: Sensitivity analyses were conducted owing to the discrepancy between studies. Each study was removed at a time to test whether the removed study would influence the overall effects. No specific trials were found as the main source of heterogeneity. The results of publication bias, based on the Begg's test (clinical fractures, p = 0.707 > 0.05/ radiological fractures, p = 0.806 > 0.05/ fractured vertebrae, p = 0.086 > 0.05) and Egger's test (clinical fractures, p = 0.599 > 0.05/ radiological fractures, p = 0.659 > 0.05/fractured vertebrae, p = 0.061 > 0.05), did not indicate the existence of any publication bias.

Language: English.

Country(ies) involved: China.

Other relevant information: wenty-four studies were included finally. Moreover, 20/421 (4.75%) patients from the PVA group and 25/359 (6.96%) patients from the CT group had clinical subsequent adjacent fractures, and 46/440 (10.45%) patients from the PVA group and 36/444 (8.10%) patients from the CT group had radiological subsequent adjacent fractures. Both had no significant difference between the two groups (RR = 0.67, 95% CI [0.38, 1.19], p = 0.17)/(RR = 1.13, 95% CI [0.75, 1.70], p = 0.576). However, the number of fractured vertebrae was higher in the PVA group than in the CT group (RR = 1.41, 95% CI [1.03, 1.93], p = 0.03). A sensitivity analysis did not identify specific trials that seriously deflected. No obvious publication bias was identified. The systematic review revealed that PVA did not increase the incidence for subsequent adjacent fractures regardless of whether they were clinical or radiological fractures. However, PVA can increase the number of subsequent fracture at adjacent vertebral levels.

Keywords: Osteoporotic vertebral compression fracture, Percutaneous vertebral augmentation, Vertebroplasty, Kyphoplasty, Conservative treatment, Subsequent adjacent fracture, Meta-analysis, TRIAL.

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H T, HB S and JL S have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. HB S and JL S are involved in drafting the manuscript or revising it critically for important intellectual content.