

Risk of subsequent adjacent fractures after vertebral augmentation: A systematic review

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Abstract

Background: The incidence of vertebral fractures is high and the new treatment options developed in recent years represent a significant improvement, although they are not without complications. **Objectives:** The aim of this study was to investigate whether percutaneous vertebral augmentation (PVA) was associated with clinical and radiological subsequent adjacent fractures. **Methods:** A systematic review and meta-analysis was performed searching on PubMed, EMBASE, Cochrane library, Google Scholar, Web of Science, and ClinicalTrial.gov from the establishment of the database to January 2020. Eligible studies assessing the subsequent adjacent fractures after PVA compared with conservative treatment (CT) were incorporated. The pooled risk ratio (RR) with its 95% confidence intervals (95% CI) was used. Heterogeneity, sensitivity, and publication bias analyses were performed. **Results:** Twenty-four studies were considered eligible and were included finally. 20/421 patients (4.75%) had clinical subsequent adjacent fractures from the PVA group, and 25/359 patients (6.96%) had from the CT group, and 46/440 patients (10.45%) from the PVA group and 36/444 patients (8.10%) from the CT group had radiological subsequent adjacent fractures. There both had no significant difference between 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, in fractured vertebrae, number in the PVA group was more than that in the CT group (RR=1.41, 95%CI: [1.03, 1.93], $p = 0.03$). **Conclusion:** Collectively, currently available literature provides data showed that PVA did not increase the incidence for subsequent adjacent fractures, no matter it was clinical or radiological fracture. However, PVA may increase the number of fractured vertebrae.

Key words: Osteoporotic vertebral compression fracture. Percutaneous vertebral augmentation. Vertebroplasty. Kyphoplasty. Subsequent adjacent fracture. Meta-analysis.

Riesgo de fracturas adyacentes en el tratamiento de las fracturas de compresión vertebral: Metaanálisis

Resumen

Antecedentes: La incidencia de fracturas vertebrales es elevada y las nuevas opciones de tratamiento desarrolladas en los últimos años suponen una mejoría importante, aunque no se encuentran exentas de complicaciones. **Objetivos:** El objetivo de este estudio fue investigar si el tratamiento vertebral percutáneo se asoció con fracturas en los niveles adyacentes, tanto clínicas como radiológicas, en los controles posteriores. **Métodos:** Se realizó una revisión sistemática y un metanálisis buscando en PubMed, EMBASE, la biblioteca Cochrane, Google Scholar, Web of Science y ClinicalTrial.gov desde el establecimiento de

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Date of reception: 16-06-2020

Date of acceptance: 16-03-2021

DOI: 10.24875/RMN.20000064

Available online: 25-05-2021

Rev Mex Neuroci. 2021;22(3):89-95

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la base de datos hasta enero de 2020. Se eligieron estudios elegibles que evalúan las fracturas adyacentes posteriores después de PVA en comparación con tratamiento conservador (CT). Se utilizó la razón de riesgo (RR), agrupada con sus intervalos de confianza del 95% (IC del 95%). Se realizaron análisis de heterogeneidad, de sensibilidad y de sesgo de publicación. **Resultados:** Se consideraron elegibles 24 estudio, que se incluyeron finalmente. Del total de pacientes estudiados, 20/421 pacientes (4.75%) tuvieron fracturas adyacentes clínicas posteriores del grupo PVA, y 25/359 pacientes (6.96%) tuvieron del grupo CT, y 46/440 pacientes (10.45%) del grupo PVA y 36/444 pacientes (8.10 %) del grupo CT tenía fracturas adyacentes radiológicas posteriores. No existieron diferencias significativas entre los dos grupos ($RR = 0.67$, IC 95%: [0.38, 1.19], $p = 0.17$) / ($RR = 1.13$, IC 95%: [0.75, 1.70], $p = 0.576$). Sin embargo, en las vértebras fracturadas, el número en el grupo PVA fue mayor que en el grupo CT ($RR = 1.41$, IC 95%: [1.03, 1.93], $p = 0.03$). **Conclusión:** Desde un punto de vista general, la literatura actualmente disponible proporciona datos que muestran que el PVA no aumentó la incidencia de fracturas adyacentes posteriores, sin importar si fue una fractura clínica o radiológica. Pero el PVA puede aumentar el número de vértebras fracturadas.

Palabras clave: Fractura por compresión vertebral osteoporótica. Tratamiento vertebral percutáneo. Vertebroplastia. Cifoplastia. Fractura adyacente posterior. Metaanálisis.

Introduction

As one of the most common complications of osteoporosis, osteoporotic vertebral compression fractures (OVCFs) often result in back pain, spinal deformity, functional disability, and even death. Hence, it has become one of the serious diseases threatening the health of elderly patients and increased the economic burden of society¹⁻⁴.

As a minimally invasive therapy for OVCFs, percutaneous vertebral augmentation (PVA) has shown promising and encouraging outcomes compared with conservative treatment (CT)^{2,5-7}. Moreover, according to different feature of fracture, PVA can choose percutaneous vertebroplasty (PVP), percutaneous kyphoplasty (PKP), or other operation methods. However, PVA can also lead to serious complications, the most serious of which is subsequent fracture, so the efficacy and safety of PVA are still in dispute^{3,8-10}. The subsequent fractures can occur at adjacent, non-adjacent, or even previously treated vertebral levels. However, there were few meta-analyses^{1,11-15} only to probe subsequent adjacent fractures, and RCTs as much as possible were not included in those reviews.

Furthermore, none of these studies distinguished clinical and radiological fracture, as well as the number of fractured patients and fractured vertebrae for analysis¹⁶⁻¹⁹. The purpose of this study is to explore the characteristics of subsequent adjacent fracture after PVA, so as to provide evidence for the treatment strategy of OVCF²⁰⁻²³.

Materials and methods

Search strategy and study selection

Two independent reviewers respectively conducted rough and accurate computerized retrieval in online

databases, including PubMed, EMBASE, Cochrane library, Google Scholar, Web of Science, and ClinicalTrial.gov, from the establishment of the database to January 2020. We also searched references to selected literatures to avoid missing any additional research. There are no language restrictions when searching (Fig. 1).

Rough search strategy: (vertebroplasty OR kyphoplasty OR vertebral augmentation) AND (conservative treatment) AND ((new fracture) OR (secondary fracture) OR (subsequent fracture) OR (adjacent fracture)).

Inclusion criteria

PARTICIPANTS

Only adult patients (age ≥ 50 years old) diagnosed with OVCF by clinical and imaging examination were included in the study.

Intervention and control

PVA (PVP/PKP) was performed in the experimental group and CT (including sham operation) was performed in the control group.

Outcomes

Analyzing the incidence of posterior adjacent vertebral fractures. Study type: prospective cohort study, non-RCT, and RCT.

Study selection and data extraction

Endnote X9 software was used to check, sort, and summarize the literatures; then, each study was carefully read and selected by two independent reviewers by

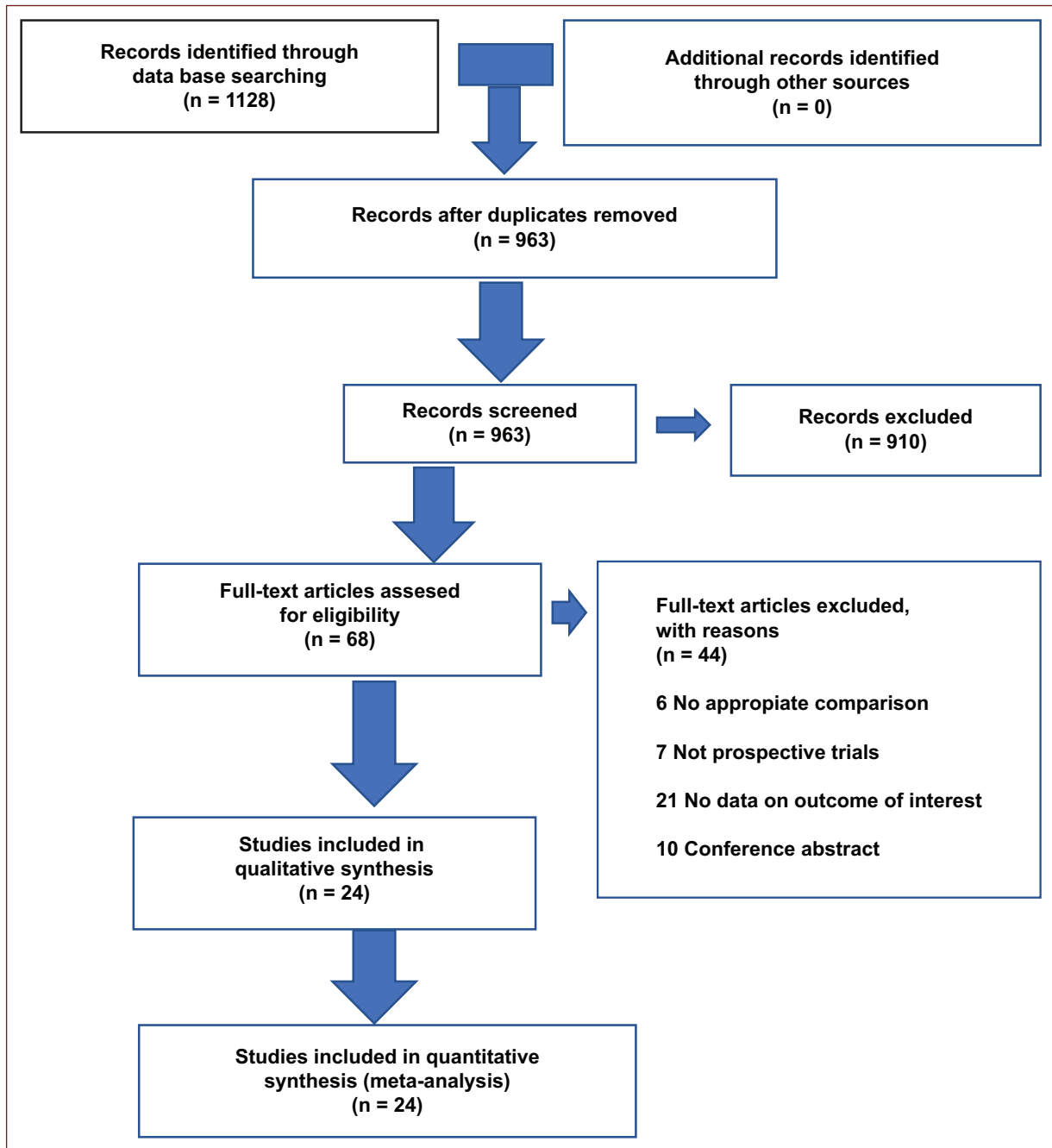


Figure 1. Inclusion scheme of the various studies analyzed.

double-blind method. Any disagreement was resolved by discussion or by consulting a third reviewer.

The number of clinical and radiological subsequent adjacent fracture was separately extracted and classified. If subsequent adjacent fracture did not have clear definition in the article, we deal with it as radiological fracture, because most fractures need imaging to be diagnosed. If the patient had subsequent adjacent

vertebral fractures equal to or more than 2 levels at once time, we just counted once for incidence.

Risk of bias assessment and quality evaluation

Two independent reviewers applied the risk of bias tool to appraise all the included literatures according to

the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0), respectively. The methodological quality was assessed according to the Cochrane Collaboration's domain-based evaluation framework^{11,12}. 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 representing low, high, or unclear risk.

According to the Jadad scale¹³, the quality of RCTs was evaluated, including the following four aspects: (1) generation of random sequence; (2) allocation concealment; (3) implementation of blind method; and (4) description of case follow-up. "1-3" was considered as low quality and "4-7" was considered as high quality.

Statistical analysis

To compare the differences from incidence for 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 $p < 0.1$, we defined the Chi-squared statistic as statistically significant. The I² statistic was used to assess the variation across the included trails as the following standard: I² < 25% means that heterogeneity is low; I²: 25-50% shows moderate heterogeneity; and I² > 50% demonstrates high heterogeneity. If I² > 50%, a random-effect model would be adopted; otherwise, a fixed effect model would be used¹⁴. Sensitivity analyses were conducted to investigate the impacts of each individual study by deleting them in turn on the overall meta-analysis results. Publication bias was detected using the method of Begg's and Egger's test. The statistical analysis was performed by Review Manager 5.3 and Stata 15.0.

Results

Description of studies

From the PRISMA Flow Diagram, the search and selection process of related literatures in this study were described. A total of 1,128 literatures were retrieved, and 68 literatures were evaluated according to

the inclusion criteria. Finally, 14 serial studies (total 24 literatures, including 5 serial non-RCTs^{16-21,24,25} and 9 serial RCTs)^{15,22,23,26-37} were selected.

Risk of bias and quality evaluation of included studies

Because cement is opaque in imaging, it is difficult to blind patients, surgeons, and observers, so only two of the serial studies (control group had sham operation) were blinded to the patients. Six serial studies reported an adequate blinding for outcomes assessors. From the Jadad scale, eight serial studies^{16,20-23,26-39} were considered as high quality, and the others were considered as low quality.

Meta-analysis results

The incidence of clinical subsequent adjacent fractures after PVA:

A total of 20/421 patients (4.75%) had clinical subsequent adjacent fractures from the PVA group, and 25/359 patients (6.96%) had from the CT group. There showed no significant difference between two groups (RR = 0.67, 95%CI: [0.38, 1.19], $p = 0.17$. M-H. Fixed effect model, I² = 31%).

The incidence of radiological subsequent adjacent fractures after PVA:

As far as radiological subsequent adjacent fractures were concerned, the results showed that 46/440 patients (10.45%) from the PVA group and 36/444 patients (8.10%) from the CT group had this complication form. There always had no significant difference between two groups (RR = 1.13, 95%CI: [0.75, 1.70], $p = 0.576$. M-H. Fixed effect model, I² = 0%).

The number of subsequent adjacent fractures for vertebrae after PVA:

In number of fractured vertebrae, 69/126 vertebral bodies (54.76%) had subsequent adjacent fractures from the PVA group and 40/105 vertebral bodies (38.10%) had from the CT group. There showed a significant difference between two groups (RR = 1.41, 95%CI: [1.03, 1.93], $p = 0.03$. M-H. Fixed effect model, I² = 0%).

Sensitivity and publication bias analysis

Sensitivity analyses were conducted due to the discrepancy between studies. Each study was removed in turn to test whether the removed study would influence

the overall effects. No specific trials could be determined as the main source of heterogeneity.

From the results of publication bias, the results of Begg's test (clinical fractures: $p = 0.707 > 0.05$ /radiological fractures: $p = 0.806 > 0.05$ /fractures for vertebrae: $p = 0.086 > 0.05$) and Egger's test (clinical fractures: $p = 0.599 > 0.05$ /radiological fractures: $p = 0.659 > 0.05$ /fractures for vertebrae: $p = 0.061 > 0.05$) did not indicate the existence of publication bias.

Discussion

A low BMD is a well-known risk factor for fracture with advancing age. After the age of 50, 1 SD decrease in BMD value doubles the risk of fracture. In healthy young adults, a low but stable BMD is not a risk factor of imminent fracture, but detection of low BMD should lead to the implementation of non-pharmacological measures and to the prevention and/or treatment of any additional risk factors of BMD decline, as hypogonadism or tobacco smoking. Patients with added risk factors, including those requiring corticosteroid therapies, should benefit from a reinforced follow-up.

At present, there is no general consensus about the management of osteoporotic vertebral fractures (OVF). In the past, conservative treatment for at least 1 month was deemed appropriate for the majority of vertebral fractures. When pain persisted after conservative treatment, it was necessary to consider surgical interventions including vertebroplasty for vertebral fractures with < 30% loss of height of the affected vertebral body and kyphoplasty for vertebral fractures with greater than 30% loss of height. At present, this type of treatment is not feasible. We can consider the characteristics and methods of operation of the third-generation systems for the percutaneous treatment of osteoporotic fracture such as Vertebral Body Stenting® (VBS), OsseoFix®, and Spine Jack®. VBS is a titanium device accompanied by a hydraulic (as opposed to mechanical) working system which allows a partial and not immediate possibility to control the opening of the device. On the other hand, OsseoFix® and Spine Jack® are accompanied by a mechanical working system which allows a progressive and controlled reduction of the vertebral fracture. Another important aspect to consider is the vertebral body height recovery. OsseoFix® has an indirect mechanism of action: the compaction of the trabecular bone causes an increase in the vertebral body height. Unlike the Vertebral Body Stenting® and Spine Jack®, the OsseoFix® has no direct lift

mechanism. Therefore in our opinion, for these characteristics and for the force that this device is able to provide, Spine Jack® is the only device also suitable for the treatment OVF, traumatic fracture (recent, old, or inveterate), and primary or secondary bone tumors.

With the advantage of pain relief rapidly, PVA, as a minimally invasive technique, has become the most popular treatment for OVCFs. However, PVA also has some complications and risks, such as cement leakage and subsequent fractures. The incidence of cement leakage is high, but most of them are asymptomatic, so it is generally believed that the cement leakage is a phenomenon rather than a complication. However, subsequent fracture is different. Once it happens, it will seriously influence the effect of PVA. About the reason, no convincing conclusion has been obtained from current studies, including biomechanical research, finite element analysis, and clinical studies^{15,21,23,25,29,34,38-42}. Many meta-analyses^{7-10,36-41,43-45} have shown that subsequent fracture is related to the natural progression of osteoporosis, not due to the PVA with cement. However, only one⁴ has detailed the influence on subsequent adjacent vertebral fractures after PVA.

The most remarkable differences from the previous meta-analysis were that clinical and radiological subsequent adjacent fracture, as well as the number of fractured cases and fractured vertebrae, were analyzed separately. Because OVCFs were mostly caused by minor trauma, and some elderly patients were not sensitive to pain. If regular imaging examinations were not taken, misdiagnosis was inevitable. The clinical subsequent fractures and radiological ones are separately analyzed in this study, which was more persuasive. Moreover, if the patient had equal to or more than 2 fractured levels at once time, it only showed the more number of subsequent adjacent vertebral fractures, not the increasing frequency, so we just counted once for incidence.

This study showed that no significant differences were in the incidence of subsequent adjacent fractures between PVA and CT, regardless of fracture type, which came to conclusion that PVA was a safe and feasible treatment for OVCF, and would not increase the risk of secondary adjacent fracture^{21,25,44,45}. However, the number of vertebrae fractured in the PVA group was more than that in the CT group, which meant that the severity was worse.

First, although the clinical characteristics at baseline in those studies were similar (Except for Klazen's study, the number of OVCFs at baseline was statistically significant (2.4 ± 1.9 vs. 2.1 ± 1.5), the number of OVCFs

and severity of fracture at baseline in the PVA group was worse than that in the CT group.

Second, because of more vertebral body fractures, the phenomenon of “sandwich type” after PVA would increase. As a special type of OVCF, it may lead to subsequent adjacent fractures more easily.

Third, because rapidly relieve pain, the patients after PVA can make exercise early, so trauma without awareness of protection and short-term treatment of anti-osteoporosis would increase risk.

In addition, this study had incorporated some non-RCTs. As an adverse effect, subsequent fractures were objective outcomes during the follow-up and would not be obviously affected by randomization and blinding method, which may not influence the reliability too much. This can increased the sample size and made it more convincing.

In sensitivity analysis, no apparent deviation was observed in all trials included, indicating that no specific trial influenced the overall effects. From the results of Begg's and Egger's test, potential publication bias was not found. It showed RCTs of poor quality and non-RCTs would still provide relatively accurate data for subsequent fractures as an objective outcome from another aspect.

It would be very useful in the future to study the evolution of the patients, taking into account the moment in which the fracture occurred and the time that elapsed until the procedure was performed, because of the time to do the augmentation surgery shows the best results when it is performed before 7 weeks and after the second.

Limitation

There also had some limitations in our study. First, subgroup analysis was not done by different operation methods (PVP/PKP), follow-up time. Because this review compared clinical fracture and radiological one separately, so there were few eligible literatures for subgroup analysis. For another, the previous studies had clearly shown the factors above that has no effect on subsequent fractures. Second, most studies mainly focused on pain relief and functional recovery, so other influence factors for subsequent fractures are not considered, such as age, sex, low body mass index, the fracture age, cement leakage and pulmonary embolism, bilateral or unilateral, multiple levels treated, the volume of cement, anti-osteoporosis treatment, and low bone mineral density⁴⁴⁻⁴⁷. Therefore, further RCTs of high quality, large sample size, long-term follow-up between PVA and CT were demanded to offer more invaluable and convincing conclusion.

Conclusion

PVA may not increase the incidence for subsequent adjacent fractures, no matter it was clinical or radiological fracture. This could be explained by the own natural process of osteoporosis, where it is well known that there are various areas of the spine in which the risk of fracture at several levels, at the same time, is considered high.

On the other hand, PVA can really increase the total number of fractured vertebrae.

Authors' contributions

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

Funding

None.

Conflicts of interest

None of the authors have any potential conflicts of interest.

Ethical disclosures

The study was approved by the Institutional Review Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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