European Review for Medical and Pharmacological Sciences 2021; 25: 5176-5188

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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Abstract. – 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.

MATERIALS AND METHODS: The systematic review was performed following PRISMA guidelines. Data were retrieved from PubMed, EMBASE, Cochrane Library, Google Scholar, Web of Science, and ClinicalTrial.gov, from database inception to March 2020. Eligible studies were those that assessed subsequent adjacent fractures after PVA in comparison with conservative treatment (CT). The number of patients with adjacent secondary vertebral fractures was calculated, and the pooled risk ratio (RR) with its 95% confidence intervals (95% CI) was used. Moreover, heterogeneity, sensitivity, and publication bias analyses were performed.

RESULTS: Twenty-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.

CONCLUSIONS: 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 fractures at adjacent vertebral levels.

Key Words:

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

Introduction

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[1]. As a minimally invasive therapy for OVCFs, percutaneous vertebral augmentation (PVA) has shown promising and encouraging outcomes compared with conservative treatment (CT)[2,3]. 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[4,5]. Subsequent fractures can occur at adjacent, non-adjacent, or even previously treated vertebral levels. Many meta-analyses[6-11] have shown that a subsequent fracture is related to the natural progression of osteoporosis and not to PVA with cement. However, only one study[7] 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

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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.

Materials and Methods

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses [PRISMA] Statement and was registered at International Prospective Register of Systematic Reviews (number: INPLASY202150097).

Search Strategy and Study Selection

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. To avoid missing any additional studies, references were also searched. Search strategy had been done without language restrictions. Our literature had rough search strategy and accurate search strategy. The details referred to our previous research[44].

Inclusion Criteria

Participants: Patients (age ≥ 50 years old) with OVCF were included.

Intervention and control: Experimental group had PVA, and control group had CT.

Outcomes: New adjacent vertebral fractures.

Study type: Prospective cohort study, Non-RCT, and RCT.

Data Extraction

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 new adjacent levels fractured was separately extracted and classified. If new fractures were not defined clearly, we considered them the radiological fracture, because diagnosis of OVCF needed imaging examination. If a patient had subsequent adjacent vertebral fractures at two or more levels at one time, the incidence was counted as one.

Risk of Bias Assessment and Quality Evaluation

Two independent reviewers appraised bias risk 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[12,13]. The main domains included: (1) selection bias; (2) performance bias; (3) detection bias; (4) attrition bias; (5) reporting bias; (6) other sources of bias. Risk of bias was graded as low, high, or unclear risk.

According to the Jadad scale[14], the quality of RCTs was assessed by (1) generation of random sequence; (2) allocation concealment; (3) implementation of blind method, and (4) description of case follow-up. The quality was graded as low quality (1-3scores) and high quality (4-7 scores).

Statistical Analysis

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 I^2 statistic. If the *p*-value was < 0.1, the chi-squared statistic was defined as significant. The I^2 statistic was used to assess the variation across the included trials based on the following standard: $I^2 < 25\%$, low heterogeneity; $I^2 = 25\%$-50%, moderate heterogeneity; and $I^2 > 50\%$, high heterogeneity. For $I^2 > 50\%$, 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.

Results

Description of Studies

Figure 1 presents the PRISMA flow diagram, including the search and selection process of related studies. A total of 1259 studies were retrieved, and 68 studies were evaluated according to the inclusion criteria. Finally, 14 serial studies (total 24 studies, including 5 serial non-RCTs[16-23] and 9 serial RCTs [24-38]) were selected. Details

of the included studies are presented in Tables I-III.

Risk of Bias and Quality Evaluation of Included Studies

The assessment for risk of potential bias in the included serial studies is shown in Table III. As cement appears opaque in imaging, it was difficult to blind the studies for patients, surgeons, and observers; hence, only two of the serial studies (control group had sham operation) were blinded for patients. Six serial studies reported an adequate blinding for outcomes assessors.

From the Jadad scale, eight serial studies[16,20,21,24-35,37,38] were considered high quality, and others were considered low quality (Table IV).

Results

Incidence of Clinical Subsequent Adjacent Fractures after PVA

As shown in Figure 2, 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, I^2 = 31%).

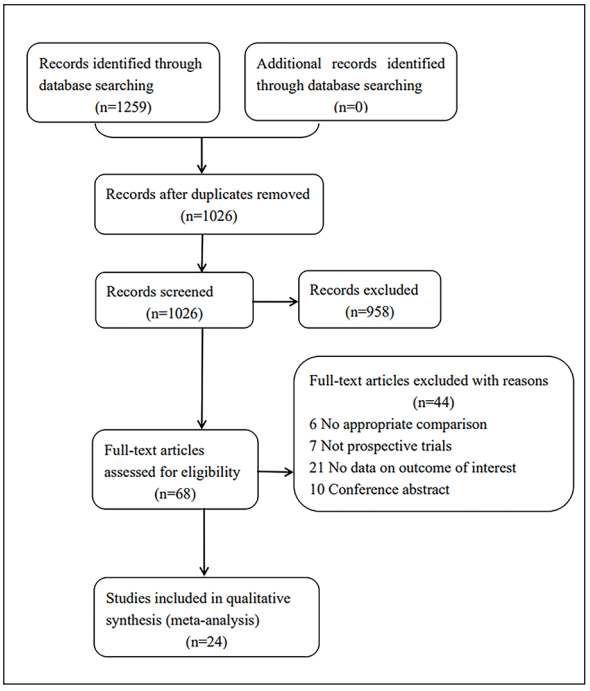

Figure 1. Flow diagram of the study selection process on the meta-analyses of subsequent adjacent fractures after PVA in the treatment for OVCF.

Incidence of Radiological Subsequent Adjacent Fractures after PVA

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 (Figure 3). 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, I^2 = 0%).

Number of Subsequent Adjacent Fractured Vertebrae after PVA

As regards the number of fractured vertebrae (Figure 4), 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, I^2 = 0%).

Sensitivity and Publication Bias Analyses

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 (Figures 5-7).

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.

Discussion

PVA, a minimally invasive technique, has become the most popular treatment for OVCFs. However, PVA also has some complications, such as cement leakage and subsequent fractures. Although the incidence of cement leakage is high, most patients are asymptomatic. Hence, it is generally believed that cement leakage is a phenomenon rather than a complication. By contrast, subsequent fractures seriously influence the effect of PVA. Regarding the cause, no convincing conclusion has been obtained from current stud-

Table I. Summary of study characteristics.

	Author	Year	Study assessment design result	Intervention/ comparison	No. of sample size	Female (%)	Age, years	BMD lumbar T-score (No. < -2.5)	Fracture age, (weeks)	No. of fractured vertebra (1/2 more than 2)	Distribution of fractured vertebra, total (~T10/T11-L2/L3-L5)	Severity of fractured vertebra (I/II/III)	Follow-up	No./rate of successful follow-up
1	Blasco J/ Martinez-Ferrer A	2012 2013	RCT	PVP CT	125 (64/61)	47 (73%) 50 (82%)	71.33 ± 9.95 75.27 ± 8.53	-2.48 ± 1.77 -2.80 ± 1.32	Less than 12 months 20.04 ± 13.73/ 20.44 ± 18.62	3.55±2.82 (14/16/34) 3.02 ± 2.14 (19/15/27)	(N/A) (N/A)	N/A N/A	1 year	95 (47/48) 76%
2	Buchbinder R/ Kroon F/ Staples MP	2009 2013 2015	RCT	PVP Sham	78 (38/40)	31 (82%) 31 (78%)	74.2±14.0 78.9±9.5	21 21	Less than 12 months 9.0 (3.8-13.0)/ 9.5 (3.0-17.0)	31/7/0 33/7/0	N/A N/A	13/21/11 12/24/11	2 years	57 (29/28) 73%
3	Diamond TH	2003 2006	Pro	PVP CT	126 (88/38)	56 (63%) 31 (81%)	76.8 ± 8.7 76.1 ± 10.0	-3.9 ± 1.1 -3.3 ± 1.5	Less than 6 weeks (N/A)	57/21/14 N/A	133 (62/45/26) N/A	N/A N/A	2 years	98 (67/31) 78%
4	Du JP	2018	Pro	PVP/PKP CT	470 (193/277)	147 (76.2%) 205 (74.0%)	69.7 ± 9.9 71.5 ± 11.3	-3.0± 0.6 -2.8± 0.6	Less than 1 month 1.3 ± 1.2/ 2.6 ± 2.49	2.3 ± 0.6 N/A 2.4 ± 0.7 N/A	377 (N/A) 540 (N/A)	N/A N/A	1 year	414 (186/228) 88%
5	FaRRokhi MR	2011	RCT	PVP OMT	82 (40/42)	30 (75%) 30 (71%)	72 (59-90) 74 (55-87)	N/A (34) N/A (40)	4 weeks ~ 1 year 27 (4-50)/ 30 (6-54) N/A (40)	2.5 (1-4) N/A 2 (1-3) N/A	100 (N/A) 90 (N/A)	24/12/4 29/12/1	2 years	76 (38/39) 93%
6	Firanescu CE	2018/ 2019	RCT	PVP Sham	176 (90/86)	67 (74%) 66 (77%)	74.7 ± 10.7 76.9 ± 8.1	-2.4 ±1.0 -2.4±0.9	Less than 6 weeks 6.1 (4.1-7.4) 5.1 (3.4-7.3)	70/15/5 6 weeks 66/15/4	115 36/59/20 108 24/69/15	37/51/27 30/49/30	1 year	152 (76/76) 86%
7	Grafe IA/ Kasperk C	2005 2010	Pro	PKP OMT	60 (40/20)	34 (85%) 15 (75%)	68.7 ± 8.5 70.1 ± 12.3	N/A N/A	More than 1 year (N/A)	4/6/30 3/3/14	72 (0/50/22) 105 (2/73/30)	N/A N/A	3 years	48 (34/14) 80%
8	Klazen CA	2010	RCT	PVP CT	202 (101/101)	70 (69%) 70 (69%)	75.2 ± 9.8 75.4 ± 8.4	-3.0 ± 1.17 -3.0 ± 1.05	Less than 6 weeks 4.2 ± 2.4/ 3.8 ± 2.3	2.4 ± 1.9 N/A 2.1 ± 1.5 N/A	139 (19/91/29) 126 (32/66/28)	57/58/21 55/45/20	1 year	163 (86/77) 81%

Continued

Table I *(Continued)*. Summary of study characteristics.

	Author	Year	Study assessment design result	Intervention/ comparison	No. of sample size	Female (%)	Age, years	BMD lumbar T-score (No. < -2.5)	Fracture age, (weeks)	No. of fractured vertebra (1/2 more than 2)	Distribution of fractured vertebra, total (~T10/T11-L2/L3-L5)	Severity of fractured vertebra (I/II/III)	Follow-up	No./rate of successful follow-up
9	Movrin I	2012	Pro CT	PKP CT	107 (46/61)	36 (78%) 49 (60%)	67.8 ± 5.4 73.8 ± 7.5	Less than 6 weeks N/A	41/N/A/N/A 58/N/A/N/A	51 (N/A) 64 (N/A)	N/A N/A	1 year	107 (46/61)	100%
10	Rousing R	2009 2010	RCT	PVP CT	50 (26/24)	19 (73%) 21 (88%)	80 (65-96) 80 (71-93)	N/A N/A	Less than 8 weeks 1.2 1.0	19/6/0 18/4/2	31 2/20/9 32 3/22/7	N/A N/A	1 year	45 (23/22) 90%
11	Voormolen MHJ	2007	RCT	PVP OPM	34 (18/16)	14 (78%) 14 (88%)	72 (59-84) 74 (55-88)	N/A N/A	6 weeks- 6 mouths 12 (6-20) 10 (6-20)	N/A N/A	28 (N/A) 21 (N/A)	3/6/19 3/5/13	2 weeks	34 (18/16) 100%
12	Wardlaw D/ Boonen S/ Meirhaeghe JV	2009 2011 2013	RCT	PKP NSC	300 (149/151)	115 (77.2%) 117 (77.5)	72.2 (44.5-95.2) 74.1 (52.8-89.1)	(53) (51)	Less than 3 months (N/A)	(100/34/15) (115/28/8)	214 (49/127/38) 195 (41/130/24)	N/A N/A	2 years	210 (115/95) 70%
13	Wang HK	2010	Pro CT	PVP CT	55 (32/23)	27 (84%) 20 (87%)	72.9±12.4 72.7±9.1	-2.7± 0.9 -2.6±0.7 N/A N/A	Less than 6 weeks N/A	(22/10/0) 27 (3/16/8)	42 (8/23/11) N/A	N/A	1 year	52 (32/20) 95%
14	Yi XD	2014	RCT CT	PVP/PKP	290 (169/121)	113 (67%) 68 (56%)	70.9 ± 10.04 73.1 ± 8.93 63.9 ± 15.51 69.5 ± 8.92	N/A N/A	N/A N/A	(139/18/12) (98/18/5)	N/A N/A	N/A N/A	4.1 years	290 (169/121) 100%

PVP: percutaneous vertebroplasty, PKP: percutaneous kyphoplasty, CT: conservative treatment, NSC: non-surgical care, OMT: optimal medical treatment.

Table II. Definition of subsequent fractures.

No.	Author	Year	Types of fracture in result	Definition
1	Blasco J/ Martinez-FerrerA	2012/ 2013	Clinical/radiological fracture	Radiological fracture: A reduction of 20% or more in the anterior, middle, or posterior height of the vertebral body compared with adjacent, undeformed vertebrae and/ or when MRI or bone scan confirmed acute VF.
2	Buchbinder R/ Kroon F/ Staples MP	2009/ 2013/ 2015	Clinical/radiological fracture	Radiological fracture: New fractures were defined as development of abnormal vertebral body morphology with loss of normal height. Progression of preexisting fractures was defined as increased loss of vertebral body height or change in fracture morphology according to this semi-quantitative technique. Clinical fracture: adverse events, including incident clinical fractures, were assessed at each time point with the use of open-ended questions.
3	Diamond TH	2003/ 2006	Radiological fracture	Radiological fracture: A decrease (compared with baseline radiographs) of 20% or more, and at least 4 mm, in any of the three vertebral heights (anterior, middle or posterior) on follow-up
4	Du JP	2018	Radiological fracture	N/A
5	FaRRokhi MR	2011	Clinical fracture	N/A
6	Firanescu CE	2018/ 2019	Clinical/radiological fracture	Radiological fracture: A new OVCF was defined as a decrease of at least 4 mm in vertical dimension
7	Grafe IA/ Kasperk C	2005/ 2010	Radiological fracture	Radiological fracture: New fractures were assessed in previously unfractured and pre-fractured vertebrae and defined as a height reduction of at least 20%
8	Klazen CA	2010	Radiological fracture	Radiological fracture: A “new VCF” was defined as a decrease of at least 4 mm in vertical dimension
9	Movrin I	2012	Clinical/radiological fracture	N/A
10	Rousing R	2009/ 2010	Clinical/radiological fracture	N/A
11	Voormolen MHJ	2007	Clinical/radiological fracture	N/A
12	Wang HK	2010	Clinical/radiological fracture	Clinical/radiological fracture: Patients were encouraged to have radiography or MRI for recurrent back pain. Recurrent vertebral compression fractures were defined as a decrease of body height of more than 20% and bone edema change on MRI.
13	Wardlaw D/ Boonen S / Meirhaeghe JV	2009 2011 2013	Clinical/radiological fracture	Radiological fracture : A new or worsening fracture was defined by consensus that deformity increased by one or more grades. Clinical fracture: Clinical fractures identified by investigators as adverse events MedDRA coded to musculoskeletal disorders
14	Yi XD	2014	Clinical/radiological fracture	Clinical/radiological fracture: high T2 MRI signal was observed in new segments and A VAS score > 7

ies[39-43], including biomechanical research, finite element analysis, and clinical studies.

We have recently published a systematic review[44] and reported that PVA does not increase the incidence of subsequent fractures on un-operated levels in both clinical and radiological fractures. These may be associated with the natural process of osteoporosis, because osteoporosis of spinal zones is considered to deteriorate across several levels simultaneously.

The same method[44] has been applied to the study of subsequent adjacent fractures. The study showed no significant differences in the incidence of subsequent adjacent fractures between PVA and CT. PVA was a safe and feasible treatment for OVCFs, and it did not increase the risk of secondary adjacent fractures, regardless of clinical or radiological fractures.

However, the number of adjacent levels fractured in the PVA group was higher than that in

Table III. Summary of subsequent fractures.

	Author	Year	Intervention/ comparisons	No. of clinical fracture	No. of radiological fracture	No. of radiological fractured vertebra	No. of clinical adjacent fracture	No. of radiological adjacent fracture	No. of radiological adjacent fractured vertebra	Total patients
1	Blasco J/	2012	PVP	12	17	29	N/A	N/A	24	64
	Martinez-FererA	2013	CT	1	8	8	N/A	N/A	2	61
2	Buchbinder R/	2009	PVP	14	N/A	27	N/A	N/A	10	29
	Kroon F/	2013	Sham	13	N/A	21	N/A	N/A	5	28
	Staples MP	2015								
3	Diamond TH	2003/	PVP	N/A	21	29	N/A	9	N/A	67
		2006	CT	N/A	9	11	N/A	4	N/A	31
4	Du JP	2018	PVP/PKP	N/A	N/A	N/A	N/A	5	N/A	186
			CT	N/A	N/A	N/A	N/A	5	N/A	228
5	FaRRokhi MR	2011	PVP	N/A	N/A	N/A	1	N/A	N/A	38
			OMT	N/A	N/A	N/A	6	N/A	N/A	39
6	Firanescu CE	2018/	PVP	6	15	31	N/A	N/A	17	76
		2019	Sham	6	19	28	N/A	N/A	15	76
7	Grafe IA/	2005	PKP	N/A	14	21	N/A	N/A	7	34
	Kasperk C	2010	OMT	N/A	10	18	N/A	N/A	4	14
8	Klazen CA	2010	PVP	N/A	15	18	N/A	N/A	11	91
			CT	N/A	21	30	N/A	N/A	14	85
9	Movrin I	2012	PKP	N/A	N/A	N/A	0	3	N/A	46
			CT	N/A	N/A	N/A	2	10	N/A	61
10	Rousing R	2009	PVP	0	4	N/A	N/A	1	N/A	23
		2010	CT	3	v3	N/A	N/A	0	N/A	22
11	Voormolen	2007	PVP	2	N/A	N/A	2	N/A	N/A	18
	MHJ		OPM	0	N/A	N/A	0	N/A	N/A	16
12	Wang HK	2010	PVP	8	N/A	N/A	4	N/A	N/A	32
			CT	1	N/A	N/A	0	N/A	N/A	20
13	Wardlaw D/	2009	PKP	26	56	N/A	5	28	N/A	118
	Boonen S /	2011	NSC	17	45	N/A	11	17	N/A	102
	Meirhaeghe JV	2013								
14	Yi XD	2014	PVP/PKP	14	N/A	18	8	N/A	9	169
			CT	17	N/A	24	6	N/A	6	121

Table IV. Risk of Bias Summary.

No.	Study	Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and Personnel (performance bias)	Blinding of measurement detection (bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other source of bias	Jadad scale	Quality of study
1	Blasco J/ Martinez-Ferrer A	2012/ 2013	Low	Unclear	High	High	Unclear	Unclear	Low	4	High
2	Buchbinder R/ Kroon F/ Staples MP	2009/ 2013/ 2015	Low	Low	Low	Low	Low	Low	Low	7	High
3	Diamond TH	2003/ 2006	High	High	High	High	Low	Low	Unclear	1	Low
4	Du JP	2018	High	High	High	Low	Low	High	Unclear	1	Low
5	Farrokhi MR	2011	Low	Low	High	Low	Low	High	Low	5	High
6	Firanescu CE	2018/ 2019	Low	Low	Low	Unclear	Low	Low	Low	7	High
7	Grafe IA/ Kasperk C	2005/ 2010	High	High	High	High	Low	High	Unclear	1	Low
8	Klazen CA	2010	Low	Low	High	High	Low	High	Unclear	5	High
9	Movrin I	2012	High	High	High	Unclear	Low	Low	Unclear	1	Low
10	Rousing R	2009/ 2010	Low	Low	High	Unclear	Low	Low	Unclear	5	High
11	Voormolen MHJ	2007	Unclear	Unclear	High	High	Unclear	High	Unclear	2	Low
12	Wardlaw D/ Boonen S/ Meirhaeghe JV	2009 2011 2013	Low	Low	High	Low	Low	Low	Low	5	High
13	Wang HK	2010	High	High	High	Low	High	High	Unclear	0	Low
14	Yi XD	2014	Unclear	Unclear	Unclear	Low	Low	Low	Low	4	High

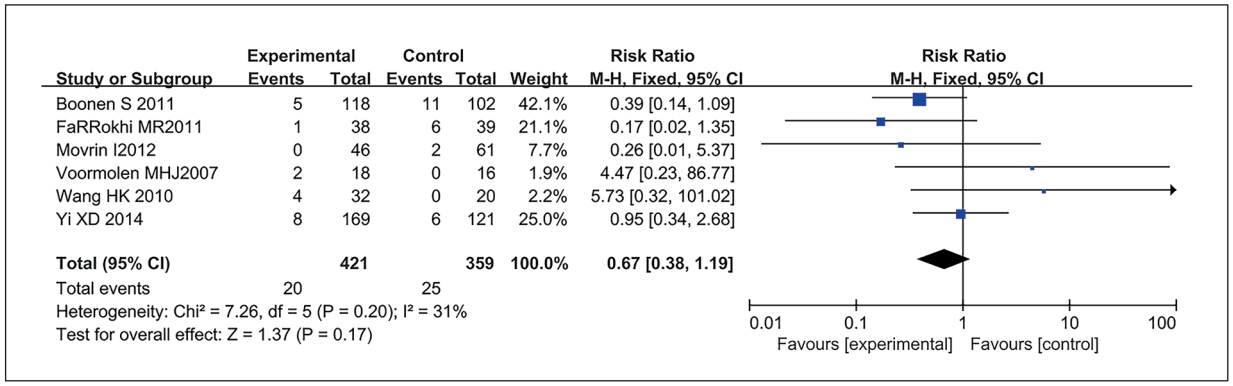

Figure 2. Forest plot of the incidence of clinical subsequent adjacent fractures between the PVA group and CT group.

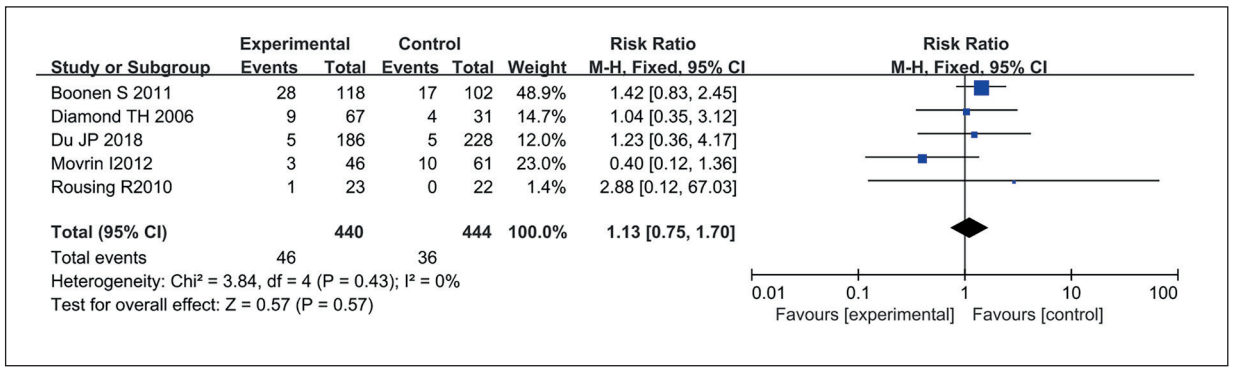

Figure 3. Forest plot of the incidence of radiological subsequent adjacent fractures between the PVA group and CT group.

the CT group, which meant that the severity of subsequent adjacent vertebral fractures in the PVA group was worse than that in the CT group. First, although the clinical characteristics at baseline in studies included were similar, the number of OVCFs and the severity of fracture at baseline in the PVA group were worse than that in the CT group. Second, because of the high incidence of vertebral body fractures, the phenomenon of "sandwich-type fracture" after PVA was higher. As a special type of OVCF, sandwich-type fracture may lead to subsequent adjacent fractures

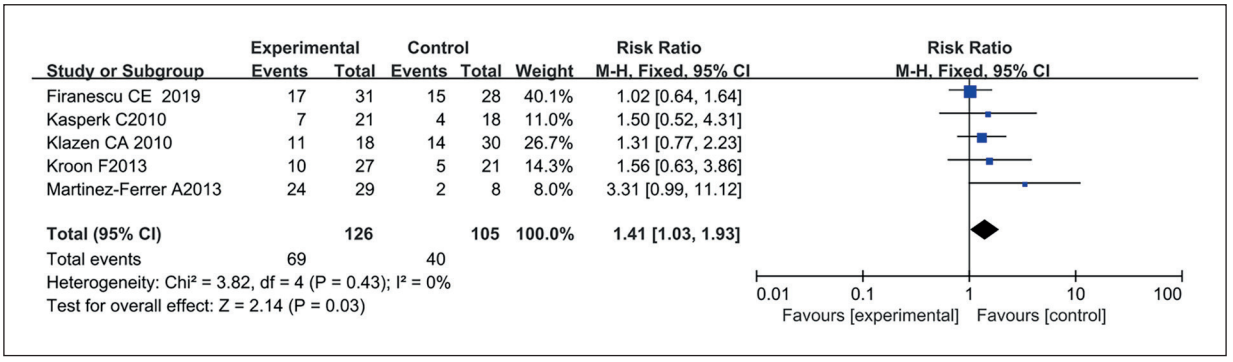

Figure 4. Forest plot of the incidence of subsequent adjacent fractured vertebrae between the PVA group and CT group.

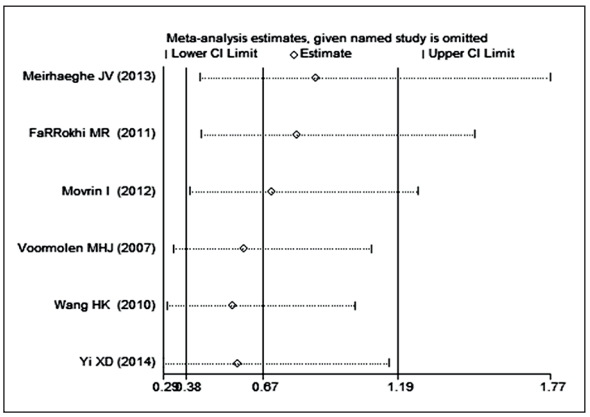

Figure 5. Sensitivity analyses for clinical subsequent adjacent fractures depicting the effect of a trial on the pooled analysis by removing one trial at a time.

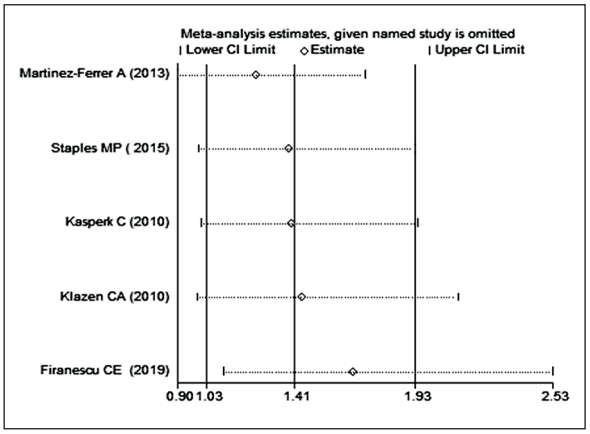

Figure 7. Sensitivity analyses for subsequent adjacent fractured vertebrae depicting the effect of a trial on the analysis by removing one trial at a time.

more easily. Third, because of rapid relief from pain after PVA, patients may begin to exercise early without protective measures and without short-term treatment using anti-osteoporosis medications, thus increasing the risk of subsequent vertebral fractures.

The main novelties of the work were that clinical and radiological subsequent adjacent fractures were distinguished, as well as the number of fracture cases and the number of fractured vertebrae. In some cases, older patients were not sensitive to pain in OVCFs caused by minor trauma. If imaging examinations are not implemented regularly, potential misdiagnosis may occur. In this study, clinical and radiological subsequent adjacent fractures were separately analyzed, which would improve the accuracy. Moreover, to avoid a false-positive rate in the frequency of subsequent adjacent vertebral fractures, we counted the incidence of two or more fractures at different vertebral levels in the same patient as one. In addition, our study incorporated some non-RCTs. As an adverse consequence, subsequent adjacent fractures were objective outcomes during follow-ups and would not be obviously affected by randomization and blinding method, which may not greatly influence the reliability. Inclusion of non-RCTs increased our sample size, provided more convincing results, and made the results more convincing.

From the sensitivity analyses, no apparent deviation was observed in all the included trials, indicating that no specific trial influenced the overall results of the analysis. Additionally, the results of Begg's and Egger's tests showed no potential publication bias. This shows that poor-quality RCTs and non-RCTs would still provide relatively accurate data for subsequent fractures as an objective outcome from another aspect.

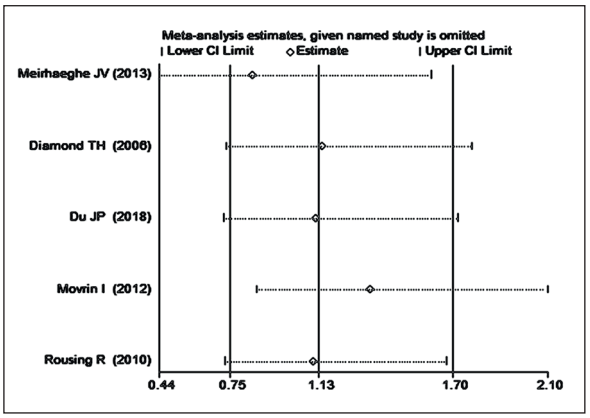

Figure 6. Sensitivity analyses for radiological subsequent adjacent fractures depicting the effect of a trial on the analysis by removing one trial at a time.

Limitations

This study had some limitations. First, subgroup analysis was not performed for different operation methods (PVP/PKP). As the review compared clinical and radiological fractures separately, there were few eligible studies for the subgroup analysis. However, some previous studies[6-11,45,46] have clearly shown that the above factors have no effect on subsequent fractures. Second, most studies mainly focused on pain relief and functional recovery; therefore, other factors influencing subsequent fractures, such as age, sex, low body mass index, age at fracture onset, cement leakage, bilateral or

unilateral involvement, multiple levels treated, cement volume, anti-osteoporosis treatment, and low bone mineral density, were not considered[47-50]. These limitations warrant the need for further RCTs of high quality, large sample sizes, and long-term follow-ups after PVA and CT to offer more valuable and convincing conclusions.

Conclusions

PVA does not increase the incidence of clinical or radiological subsequent adjacent fractures. Subsequent fractures could be related to higher risk of osteoporosis occurring simultaneously at several spinal levels. However, PVA appear to increase the number of subsequent fractures to adjacent vertebral levels.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval and Consent to Participate

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.

Funding

None of the authors has any potential conflict of interest. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Availability of Data and Materials

The datasets supporting the conclusions of this article are included within the article. We state that we have full control of all primary data and that we agree to allow the journal to review our data if requested.

Authors' Contribution

HT, 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. H T agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved of the final manuscript.

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