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Comparison of the efficacy and safety of 3 treatments for patients with osteoporotic vertebral compression fractures

A network meta-analysis

Song Zhao, MD, PhD[a], Chang-yan Xu, MM[b], Ao-ran Zhu, BM[a], Long Ye, MM[a], Long-long Lv, MM[a], Long Chen, MM[a], Qi Huang, MM[a], Feng Niu, MD, PhD[a,*]

Abstract

Background: Osteoporotic vertebral compression fractures (OVCFs) constitute an age-related health problem that affects approximately 200 million people worldwide. Currently, various treatments are performed with the goal of reducing pain, stabilizing the vertebrate, and restoring mobility. In this study, we aimed to assess the efficacy and safety of vertebroplasty (VP), kyphoplasty (KP), and conservative treatment (CT) for the treatment of OVCFs.

Methods: We performed a network meta-analysis. PubMed and Embase databases were searched to identify randomized controlled trials (RCTs) that contained at least one of the following outcomes: visual analog scale (VAS), Roland–Morris Disability Questionnaire (RDQ), European Quality of Life-5 Dimensions (EQ-5D), and new fractures. Odds ratios with 95% confidence intervals (CIs) were used to calculate the risk of new fractures, and mean differences (MDs) with 95% CIs were utilized to express RDQ, EQ-5D, and VAS outcomes.

Results: Sixteen RCTs with 2046 participants were included in this meta-analysis. Compared with CT, patients treated with VP had improved pain relief, daily function, and quality of life; however, no significant differences were found between VP and KP for these 3 outcomes. All treatment options were associated with comparable risk of new fractures. When the rank probability was assessed to distinguish subtle differences between the treatments, VP was the most effective treatment for pain relief, followed by KP and CT; conversely, KP was the most effective in improving daily function and quality of life and decreasing the incidence of new fractures, followed by VP and CT.

Conclusion: VP might be the best option when pain relief is the principle aim of therapy, but KP was associated with the lowest risk of new fractures and might offer better outcomes in terms of daily function and quality of life.

Abbreviations: ADDIS = Aggregate Data Drug Information System, CI = confidence interval, CT = conservative treatment, EQ-5D = European Quality of Life-5 Dimensions, KP = kyphoplasty, MD = mean difference, NMA = network meta-analysis, OR = odds ratio, OVCF = osteoporotic vertebral compression fracture, PSRF = Potential Scale Reduction Factor, RCTs = randomized controlled trials, RDQ = Roland–Morris Disability Questionnaire, VAS = visual analog scale, VP = vertebroplasty.

Keywords: conservative treatment, kyphoplasty, network meta-analysis, osteoporotic vertebral compression fractures, vertebroplasty

1. Introduction

Osteoporotic vertebral compression fractures (OVCFs) constitute an age-related health problem that affects approximately 200 million people worldwide.[1] In addition, they are the most common osteoporotic fractures, occurring in approximately 20% individuals older than 70 years.[2] Patients with severe OVCFs suffer from acute pain, disability, and even mortality.[3] Thus, OVCFs represent a serious health concern in old people, particularly the elderly.

Currently, various treatments are performed with the goal of reducing pain, stabilizing the vertebrate, and restoring mobility.[4–6] Conservative treatment (CT), which includes rest, external fixation, anti-inflammatory drugs, and analgesics, is effective only for a small portion of patients with OVCFs,[7] but it is associated with undesirable adverse effects and often fails in preventing kyphotic deformity.[8,9] Conversely, vertebroplasty (VP) and kyphoplasty (KP) are minimally invasive surgical treatments for OVCFs that can relieve pain quickly, improve mobility, and restore vertebral height.[10,11]

Numerous pairwise meta-analyses have been performed for head-to-head comparisons of KP with VP with respect to the aspects of complications,[12] pain reduction,[13] and disability.[13–15] In addition, a more comprehensive meta-regression analysis has been conducted,[16] but an integrated and credible conclusion remains elusive because CT has not

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[a] Department of Spine Surgery, [b] Medical Record Department, The First Hospital of Jilin University, Changchun, Jilin, China.

[*] Correspondence: Feng Niu, Department of Spine Surgery, The First Hospital of Jilin University, Chaoyang District, Changchun, Jilin, China (e-mail: fengniufengniu@163.com).

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always been the control treatment and non-randomized trials have been included. A Bayesian network meta-analysis (NMA) is superior to traditional analyses when comparing multiple treatments because it combines direct and indirect comparisons and provides a posterior probability distribution for distinguishing subtle differences among treatments.[17,18] To the best of our knowledge, there has only been 1 NMA focusing on the efficacy and tolerability of the 3 main treatments (KP, VP, and CT) for OVCFs.[19] However, this only included 5 randomized controlled trials (RCTs) and restricted outcomes to visual analog scale (VAS) results, all-cause discontinuation, and new fractures.

In this study, we performed a Bayesian NMA with larger RCTs that included more outcome measures. Our aim was to achieve a more integrated and comprehensive comparison of the 3 treatments for OVCFs.

2. Methods

2.1. Data acquisition and search strategy

PubMed and Embase databases were searched until December 31, 2016, using the following keywords: vertebroplasty, kyphoplasty, compression, fracture, fractures, osteoporotic, and osteoporosis. Reference lists of relevant articles were also searched manually to identify additional eligible studies. Because this was a meta-analysis of study data, ethical approval was not necessary.

2.2. Selection criteria

Studies were included if they were RCTs, published in full in English, included patients with OVCFs, and had a control group that underwent CT, and an intervention group that underwent VP or KP. In addition, studies were required to contain at least of one of the following outcome measures: pain relief (VAS; scores ranging from 0 to 10, with 10 indicating the worst pain imaginable),[20] daily function [Roland–Morris Disability Questionnaire (RDQ); scores ranging from 0 to 24, with a higher score indicating worse physical functioning],[21] quality of life [European Quality of Life-5 Dimensions (EQ-5D); scores ranging from 0 to 1, with 1 indicating perfect health],[22] and new fractures. Nonrandomized trials, reviews, reports, comments, and letters were excluded.

2.3. Data extraction and quality assessment

Two reviewers extracted data from eligible literatures independently. This included the following: name of the first author, year of publication, location of the study, year of the study, type of intervention, demographic characteristics (number, sex, and age), duration of follow-up, and outcomes. The quality of eligible trials was assessed using following the Cochrane Handbook for Systematic Reviews of Interventions[23] and Jadad score. Any disagreement was settled by group discussion with a third investigator.

2.4. Statistical analysis

For the dichotomous outcome of new fractures, results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes of VAS, RDQ, and EQ-5D, the mean difference (MD) was used to evaluate effects of the 3 treatments. If the 95% CI included 1 for OR or zero for MD, the results were not considered to be significantly different.

The pairwise meta-analysis was performed using R software version 3.12 (R Foundation for Statistical Computing, Beijing1, China, meta package). The potential heterogeneity across the studies was examined using the Q statistic[24] and I^2 index. A random-effects model was used to pool the effect size if there was significant heterogeneity ($P < .05$ or $I^2 > 50\%$); otherwise, a fixed-effects model was adopted.[25]

To incorporate indirect comparisons, NMA was conducted using the Aggregate Data Drug Information System (ADDIS) software (Version 1.16.5, Erasmus University, The Netherlands). ADDIS is a nonprogramming software that can assess and process data using Markov chain Monte Carlo methods in a Bayesian framework.[26,27] The parameters in the ADDIS software were set as follows: number of chains = 4, tuning iterations = 20,000, simulation iterations = 50,000, thinning interval = 10, inference samples = 10,000, and variance scaling factor = 2.5. A random-effects model was used to pool the effect size. A node-splitting analysis was applied in the ADDIS software for evaluating any inconsistencies within NMA, and a consistency model was adopted when a P-value $> .05$ was observed during the comparison between direct and indirect evidence, and an inconsistency model was chosen otherwise.[28] The convergence of iterative simulation was interpreted by the potential scale reduction factor (PSRF) calculated by the Brooks–Gelman–Rubin method.[29] The rank probability for each treatment was also estimated graphically with the ADDIS software. Finally, Egger's test was used to verify the potential for publication bias.

3. Results

3.1. Eligible studies

The flow diagram for the literature selection is shown in Fig. 1. The search strategy originally yielded 2775 articles (1324 articles from the PubMed database and 1451 articles from the Embase database) and 1614 articles remained after removing duplicates. Another 1424 irrelevant articles were then removed after screening study titles and abstracts. Finally, 174 articles (53 reviews, 21 letters to editors, 31 case series or reports, 22 non-RCTs, 16 articles with duplicated populations, and 31 articles with inadequate outcomes) were excluded after reviewing the full text of the remaining 190 articles. Thus, 16 eligible studies were included in NMA.[30–45]

3.2. Study characteristics and quality assessment

Characteristics of eligible studies are shown in Table 1. The number of patients who underwent KP, VP, and CT was 478, 816, and 752, respectively. The average age of patients ranged from 63 to 81 years, and the sex distribution was comparable between intervention and control groups. Follow-up durations lasted from 2 weeks to 3 years. Among the 16 RCTs, 11 compared the effect of VP with CT, 2 compared the effect of KP with CT, and 3 compared the effect of KP and VP. The Jadad scores were between 3 and 5, suggesting high quality of the included studies.

The bias of the eligible studies is summarized in Fig. 2A. Only 2 of the 16 studies had a low risk of performance bias with respect to the blinding of participants and personnel,[41,46] with the remaining studies having unclear risk. Two studies had high risk of reporting bias[40,42] and 3 studies had a high risk of other bias.[37,45,47] As illustrated in Fig. 2B, the quality of life of patients in most of the selected studies was rated as good.

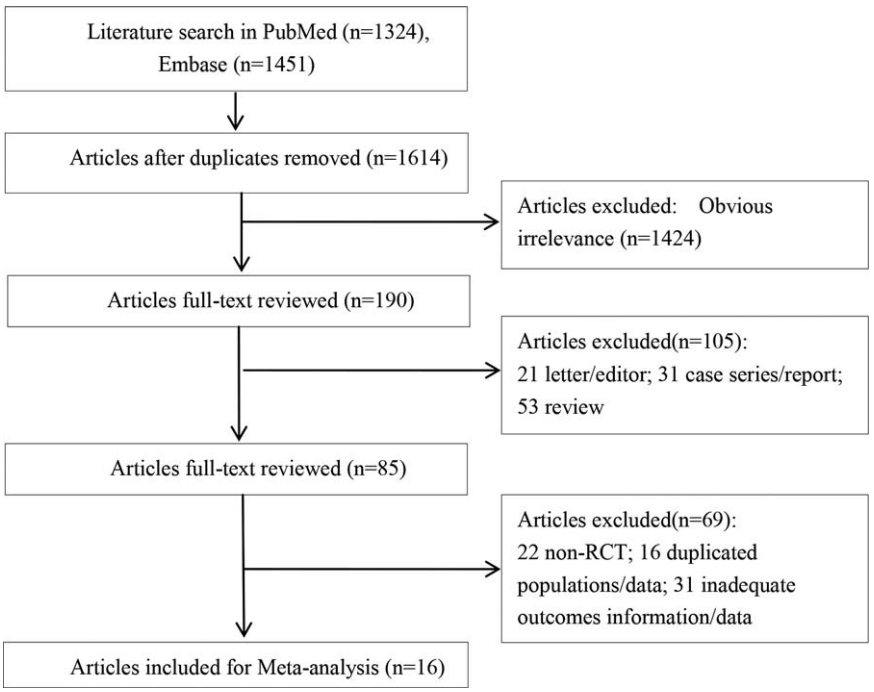

Figure 1. Flow chart of study selection.

3.3. Meta-analyses

Among the 4 outcomes, a closed triangle circular was shown for new fractures and EQ-5D only. A node-splitting analysis was performed to check for inconsistencies in these 2 outcomes (Table 2) and showed that *P*-values were all $> .5$, indicating a lack of significant inconsistency. In addition, PSRF for the 5 outcomes was between 1.00 and 1.01, suggesting a complete convergence and good iteration simulation. Given these results, a consistency model was adopted for NMA.

3.4. Pain

Table 3 summarizes the results of pairwise meta-analysis and NMA based on the VAS score for pain. Both NMA (MD, −1.12; 95% CI:−1.80, −0.51) and pairwise meta-analysis (MD, −1.13; 95% CI:−1.70, −0.56) showed that patients who underwent VP had a significantly greater pain relief than those who underwent CT.

3.5. Quality of life

As shown in Table 4, NMA (MD, 0.07; 95% CI: 0.00, 0.11) and pairwise meta-analysis (MD, 0.05; 95% CI: 0.02, 0.08) indicated that there was a significant improvement in quality of life among patients who underwent VP compared with those who underwent CT.

3.6. Functional outcome

NMA (MD, −2.51; 95% CI:−5.37, −0.28) and pairwise meta-analysis (MD, −2.50; 95% CI: −3.40, −1.60) suggested that VP was significantly associated with a greater beneficial effect on daily function than CT (Table 5).

3.7. New fractures

According to the pooled estimates (Table 6) measured by pairwise meta-analysis and NMA, there was no significant difference among the 3 treatments in the incidence of new fractures.

3.8. Rank probability

Figure 3A–C summarizes rank probabilities of the 3 treatments with respect to VAS, RDQ, and incidence of new fractures, respectively, with rank 1 indicating the worst result. Figure 3D presents the rank probability for EQ-5D, with rank 1 being the best result. KP treatment had the most beneficial effect on daily function, quality of life, and incidence of new fractures, followed by VP and CT. In addition, VP was the most efficacious treatment for pain relief, followed by KP and CT.

3.9. Publication bias

No publication bias was observed among the eligible studies (Table S1, http://links.lww.com/MD/B777).

4. Discussion

In this study, we performed NMA for evaluating the efficacy (in terms of VAS, RDQ, and EQ-5D) and safety (in terms of new fractures) of 3 treatments for patients with OVCFs based on data from 16 RCTs. NMA and pairwise meta-analysis indicated that VP significantly decreased pain, improved the quality of life, and strengthened the daily function compared with CT. Moreover, no significant difference was observed in the incidence of new fractures among the 3 treatments. When aiming to alleviate pain, VP was more effective than KP; however, KP was more effective than VP when aiming to improve daily function and quality of life and to decrease the incidence of new fractures. In both cases, CT was the least effective.

Our results indicated that greater pain relief was achieved in patients with OVCFs who underwent VP than in those who underwent CT. Several pairwise meta-analyses provided robust

Table 1

Characteristics of the identified studies.

Author	Public year	Study location	Study year	Jadad score	Group	N	Age, years	Male	Duration of follow-up	Main outcomes
Chen D	2013	China	2007.1–2012.12	4	VP	46	64.63±9.10	30	12 mo	VAS, new fractures, RDQ
					CT	43	66.49±9.11	30		
Blasco J	2012	Spain	2006.4–2010.1	4	VP	64	71.33±9.95	27	12 mo	VAS
					CT	61	75.27±8.53	18		
Boonen S	2011	8 countries*	2003.2–2005.12	5	KP	149	72.2±8.45	23	24 mo	New fractures, RDQ, EQ-5D
					CT	151	74.1±6.05	23		
Farrokhi MR	2011	Iran	2004.9–2006.1	4	VP	40	72±7.75	25	36 mo	New fractures, VAS,
					CT	42	74±8.0	29		
Klazen CA	2010	Netherlands and Belgium	2005.10–2008.6	4	VP	101	75.2±9.8	31	11.4 mo	New fractures, VAS, RDQ
					CT	101	75.4±8.4	31		
Rousing R	2009	Denmark	2001.1–2008.1	4	VP	25	80±7.75	24	12 mo	New fractures, VAS, EQ-5D
					CT	24	80±5.5	12.5		
Kallmes DF	2009	United Kingdom, Australia	2004.6–2008.8	3	VP	68	73.4±9.4	22	1 mo	VAS, RDQ, EQ-5D
					CT	63	74.3±9.6	27		
Buchbinder R	2009	Australia	2004.4–2010.10	3	VP	38	74.2±14.0	18	6 mo	RDQ, EQ-5D
					CT	40	78.9±9.5	22		
Voormolen MH	2006	Netherlands and Belgium	2003.7–2005.6	4	VP	18	72±6.25	22	2 wk	VAS, RDQ
					CT	16	74±8.25	12		
Liu JT	2009	China	NA	4	KP	50	72.3±7.6	11	6 mo	VAS
					VP	50	74.3±6.4	12		
Endres S	2012	Germany	NA	3	KP	20	63.3 (53–77)	6	6 mo	VAS
					VP	21	71.3 (63–77)	8		
Dohm M	2014	USA	NA	4	KP	191	75.6 years	86	24 mo	New fractures, EQ-5D
					VP	190				
Clark W	2016	Australia	2011.11–2014.12		VP	61	80±7	13	6 mo	New fractures, VAS, RDQ, EQ-5D
				4	CT	59	81±7	19		
Staples MP	2015	Australia, New Zealand	2004.4–2010.10	4	VP	38	NA	NA	24 mo	New fractures
					CT	40	NA	NA		
Yang EZ	2015	China	2009.1–2011.12	4	VP	56	77.1±6.0	20	12 mo	New fractures, VAS
					CT	51	76.2±5.6	18		
Berenson J	2011	Australia, USA; Canada, Europe	2005.5–2008.3	4	KP; CT	68; 61	64.8 (37.6–88.0); 63.0 (39.5–83.4)	28; 26	1 mo	RDQ

* Austria, Belgium, France, Germany, Italy, Sweden, the Netherlands, and the United Kingdom.

CT = conservative treatment, EQ-5D = European Quality of Life-5 Dimensions, KP = Kyphoplasty, RDQ = Roland-Morris Disability Questionnaire, VAS = visual analog scale, VP = vertebroplasty.

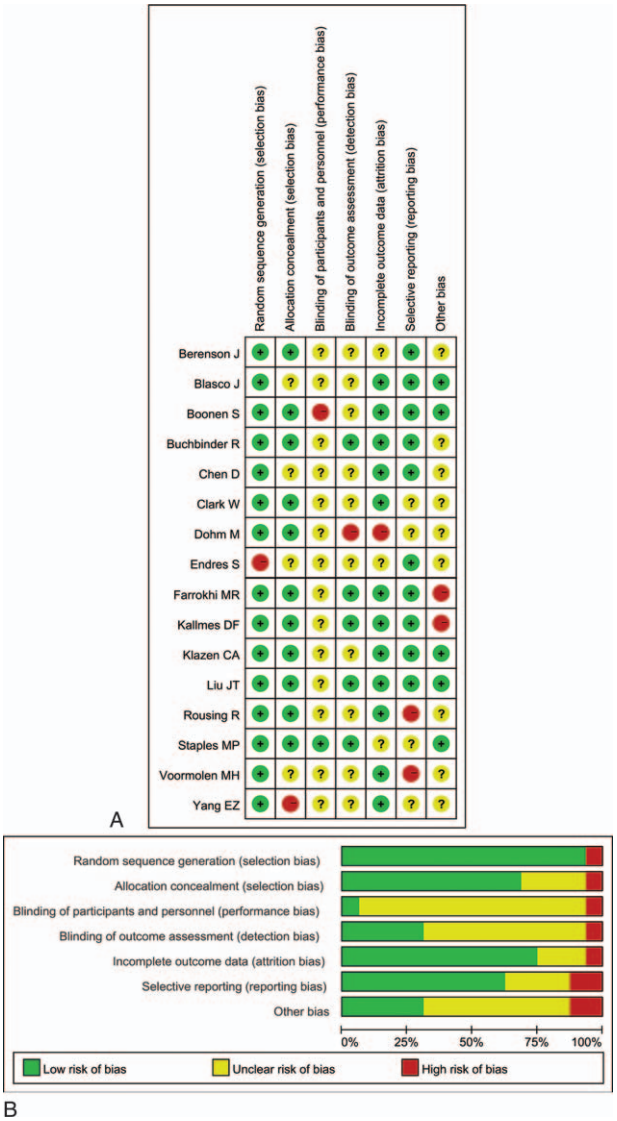

Figure 2. Results of quality assessment. (A) Summary of the risk of bias. (B) Graph of the risk of bias.

support for this conclusion.[48–50] In addition, our findings suggested that there was no significant difference between VP and KP in pain reduction. Although a number of meta-analyses have compared the effects of these 2 treatments on pain relief,[13,51,52] there are controversies in the results probably because of the inclusion of nonrandomized controlled trials. Consistent with our analysis, in NMA of 5 RCTs, Chen et al[19] concluded that

Table 3

Multiple treatments comparison regarding VAS.

CT	/	−1.13 (−1.70, −0.56)*
0.94 (−0.40, 2.39)	KP	0.05 (−0.18, 0.27)†
1.12 (0.51, 1.80)	0.19 (−1.08, 1.43)	VP

The number in the cell represents the mean difference (95% confidence interval) of the column defining treatment relative to the row defining treatment.
CT = conservative treatment, KP = kyphoplasty, VP = vertebroplasty, VAS = visual analog scale.
Empty cell = network comparison; gray filled cell = pairwise comparison.
* Random-effects model
† Fixed-effects model.

Table 4

Multiple treatments comparison regarding EQ-5D.

CT	0.10 (−0.07, 0.27)	0.05 (0.02, 0.08)*
−0.10 (−0.17, −0.01)	KP	−0.02 (−0.06, 0.02)
−0.07 (−0.11, −0.00)	0.03 (−0.05, 0.11)	VP

The number in the cell represents the mean difference (95% confidence interval) of the column defining treatment relative to the row defining treatment.
CT = conservative treatment, EQ-5D = European Quality of Life-5 Dimensions, KP = kyphoplasty, VP = vertebroplasty.
Empty cell = network comparison; gray filled cell = pairwise comparison.
* Fixed-effects model.

there was no significant difference between VP and KP with respect to VAS. Also, consistent with the analysis performed by Chen et al,[19] we showed that VP was the most efficacious therapy for relieving acute pain, followed by KP and CT.

All 3 investigated treatments had comparable effects on the incidence of new fractures in this NMA. Meta-analyses showed that KP and VP were associated with similar risks of new fractures,[13,14,51] but that there was no significant difference in risk of new fractures between VP and CT.[48,53] Of the few studies that directly compared KP and CT in terms of the incidence of new fractures, NMA reported that there was no significant difference between KP, VP, and CT, but that there was a subtle difference after ranking.[19] Inconsistent with this result, we were able to rank KP first in our investigation. The inclusion of fewer RCTs may account for this disagreement.

As shown in our analysis, patients who underwent VP had significantly improved the daily function and quality of life compared with those who underwent CT, whereas no significant difference was found between VP and KP for these measures. Several investigations provided support for the superiority of VP over CT on recovery in function and improvement in the quality of life.[48,53] Xing et al[14] detected no significant difference between KP and VP in the improvement of short- and long-term function. However, conflicting result was shown in a meta-analysis based on

Table 2

The node-splitting analysis for new fractures and EQ-5D.

Outcome	Name	Direct effect	Indirect effect	Overall	*P*
New fractures	CT, KP	0.29 (−0.80, 1.44)	−0.67 (−1.91, 0.54)	−0.11 (−1.05, 0.77)	.16
	CT, VP	−0.41 (−1.00, 0.14)	0.54 (−1.02, 2.20)	−0.25 (−0.88, 0.27)	.17
	KP, VP	0.24 (−0.87, 1.35)	−0.67 (−1.97, 0.49)	−0.12 (−1.10, 0.74)	.17
EQ-5D	CT, KP	0.10 (−0.02, 0.22)	0.07 (−0.08, 0.20)	0.09 (0.01, 0.16)	.55
	CT, VP	0.04 (−0.04, 0.11)	0.08 (−0.09, 0.25)	0.06 (−0.01, 0.10)	.55
	KP, VP	−0.02 (−0.14, 0.10)	−0.05 (−0.20, 0.08)	−0.04 (−0.11, 0.04)	.58

CT = conservative treatment, EQ-5D = European Quality of Life-5 Dimensions, KP = kyphoplasty, VP = vertebroplasty.

Table 5

Multiple treatments comparison regarding RDQ.

CT	−5.75 (−11.92, 0.43)a	−2.50 (−3.40, −1.60)*
5.72 (1.05, 10.60)	KP	/
2.51 (0.28, 5.37)	−3.22 (−8.78, 2.49)	VP

The number in the cell represents the mean difference (95% confidence interval) of the column defining treatment relative to the row defining treatment.
CT = conservative treatment, RDQ = Roland–Morris Disability Questionnaire, KP = kyphoplasty, VP = vertebroplasty.
Empty cell = network comparison; gray filled cell = pairwise comparison.
* Random-effects model.

Table 6

Multiple treatments comparison regarding new fractures.

CT	1.35 (0.83, 2.21)	0.69 (0.47, 1.02)*
1.11 (0.46, 2.86)	KP	1.29 (0.84, 1.99)
1.29 (0.77, 2.41)	1.13 (0.48, 3.00)	VP

The number in the cell represents the odds ratio (95% confidence interval) of the column defining treatment relative to the row defining treatment.
CT = conservative treatment, KP = kyphoplasty, VP = vertebroplasty.
Empty cell = network comparison; gray filled cell = pairwise comparison.
* Fixed-effects model.

the cohort study.[13] Limited RCT data might be the main obstacle for providing a definitive conclusion on the comparison of the effect of KP with that of VP on daily function. Furthermore, few studies have compared the effects of KP and VP on quality of life. Our findings provided additional evidence on relative merits of VP and KP on daily function and quality of life, with the probability analysis suggesting that KP might be superior to VP.

Our results should be interpreted cautiously because of the limitations of the study. First, no subgroup meta-analysis was performed because of the lack of conformity in the duration of follow-up and inadequacy of raw data. Second, no closed triangle circle was shown for VAS and RDQ outcomes, and there were limited RCTs for certain pairwise meta-analyses (e.g., only 1 RCT compared the effectiveness of KP and CT with VAS). This could decrease confidence in our conclusions. Third, the effect size was only pooled using a random-effects model, which was a restriction of the ADDIS software, and this might have produced conservative conclusions. Finally, heterogeneity such as caused by the follow-up times (from 2 weeks in 1 study to years in some), performance bias, and reporting bias might limit the reliability of our conclusions.

5. Conclusion

In conclusion, VP was the best procedure for relieving pain, whereas KP, which is associated with higher costs, was associated with the lowest incidence of new fractures and best improvement in daily function and quality of life. Our findings provide evidence-based support for applying these procedures in the treatment of OVCFs. However, because of the limitation of the present study, such as heterogeneity caused by the follow-up times, larger scale RCTs of higher quality are urgently needed to confirm these conclusions.

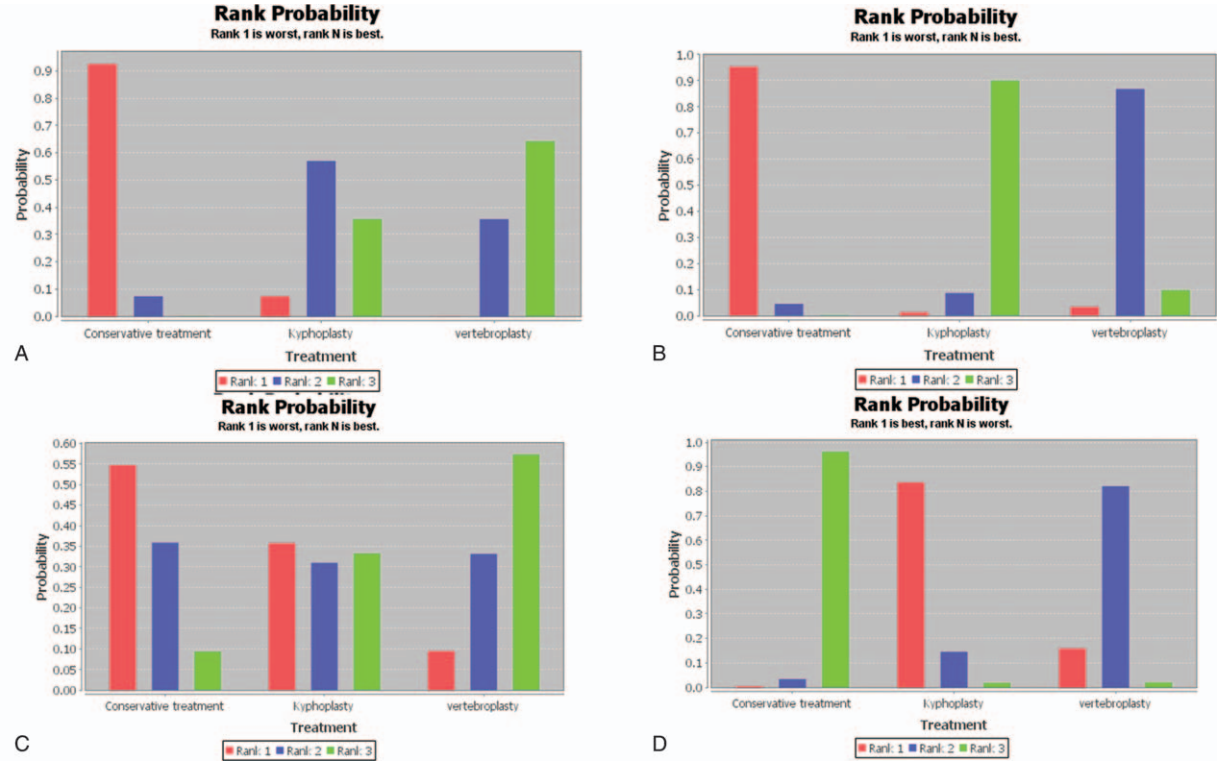

Figure 3. Rank probabilities for conservative treatment, kyphoplasty, and vertebroplasty: (A) visual analog scale; (B) Roland–Morris Disability Questionnaire; (C) new fractures; (D) European Quality of Life-5 Dimensions.

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