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ORIGINAL ARTICLE

Which is the best treatment of osteoporotic vertebral compression fractures: balloon kyphoplasty, percutaneous vertebroplasty, or non-surgical treatment? A Bayesian network meta-analysis

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Abstract

Summary The aim of the current study was to use a Bayesian network meta-analysis to evaluate the relative benefits and risks of balloon kyphoplasty (BK), percutaneous vertebroplasty (PVP), and non-surgical treatment (NST) for patients with osteoporotic vertebral compression fractures (OVCFs). The results demonstrate that for pain and functional status, PVP was significantly better than NST, while the three treatments did not significantly differ in other outcomes.

Introduction BK, PVP, and NST are widely used to treat OVCFs, but preferable treatment is unknown. The aim of the current study was to use a Bayesian network meta-analysis to evaluate the relative benefits and risks of BK, PVP, and NST for patients with OVCFs.

Methods PubMed, EMBASE, and the Cochrane Library were screened. Based on the preplanned eligibility criteria, we screened and included randomized controlled trials that compared BK, PVP, and NST in treating patients with OVCFs. The risk of bias for individual studies was appraised. The data were pooled using a Bayesian network meta-analysis and a traditional direct comparison meta-analysis.

Results Of the 1057 relevant studies, 15 were eligible and included. Compared with NST, PVP significantly reduced pain, Oswestry Disability Index (ODI), and Roland–Morris Disability Questionnaire (RMDQ). The comparative efficacy of BK and PVP was similar for pain (mean difference (MD) 0.51, 95% credible interval (CrI) − 0.35 to 1.4), ODI (MD 0.11, 95% CrI − 13 to 13), and RMDQ (MD 1.2, 95% CrI − 2.7 to 5.4). The European Quality of Life–5 Dimensions (EQ–5D) and Physical Component Summary subscales of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36 PCS) did not differ significantly. There were also no substantial differences in the risks of subsequent vertebral fractures, adjacent vertebral fractures, and re-fractures at the treated level across all comparators. The results of pairwise meta-analyses were almost consistent with those of network meta-analyses. The treatment ranking indicated that PVP had the highest probability of being the most effective for pain, ODI, RMDQ, and EQ-5D. BK had the highest probability of improving SF-36 PCS and of reducing the risk of subsequent vertebral fractures and re-fractures at the treated level. NST was ranked first in preventing adjacent vertebral fractures.

Conclusion PVP was the most effective method for improving pain, functional status, and quality of life (based on EQ-5D). BK emerged as the best intervention for decreasing the risk of subsequent vertebral fractures and re-fractures at the treated level. NST could be ranked first in reducing adjacent vertebral fractures. The future directions of OVCFs treatment will depend on the outcomes of additional and larger randomized trials in comparing BK with PVP.

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Keywords Balloon kyphoplasty · Network meta-analysis · Non-surgical treatment · Osteoporotic vertebral compression fractures · Percutaneous vertebroplasty

Introduction

Osteoporosis is a systemic bone disorder with reduced bone mass and degradation of skeletal microarchitecture [1]. Patients with osteoporosis frequently experience vertebral compression fractures [2]. Osteoporotic vertebral compression fractures (OVCFs) constitute a major health problem, which commonly causes both acute and chronic back pain, substantial spinal deformity, functional disability, decreased quality of life, and high treatment expenses [3, 4]. It has been reported that the incidence of OVCFs in individuals 50 years or older may be 307 per 100,000 person years, and the direct expenses concomitant with new-onset OVCFs in the first year approximately 6490 Euros [5]. Furthermore, OVCFs also increase the risk of future vertebral fractures and mortality [6].

Non-surgical treatments (NST), including bed rest, various pharmacologic agents, back braces, and physical therapy are recommended to relieve symptoms and strengthen the spine [7, 8]. However, some patients still have lasting pain and disability even though they received NST and require invasive intervention [9]. Percutaneous vertebroplasty (PVP) has been widely used in patients suffering from OVCFs and concomitant back pain [10]. Balloon kyphoplasty (BK) is a technique that alleviates pain and improves function by using an inflatable bone tamp to compress the cancellous bone [11, 12].

However, little is known about which treatment is preferred. Most existing meta-analyses are pairwise design (see Supplementary Table 1) that compare the PVP with the BK, and few contrast NST with PVP or BK. Although Chen et al. [13] performed a network meta-analysis on a similar topic, their analysis focused on elderly people, and only five studies with 777 participants were included. Zhao et al. [14] and Zhang et al. [15] also performed similar network meta-analyses, but they did not perform subgroup analyses and meta-regression analyses to test the heterogeneity, nor did they perform sensitivity analyses to examine the robustness of the outcomes. Consequently, we found a need to perform a comprehensive network meta-analysis to ascertain the relative efficacy and safety of BK, PVP, and NST for patients with OVCFs.

Methods

Literature search and study selection

The protocol of this study was registered with PROSPERO (CRD42016039452) and was published [16]. In May 2017, we comprehensively searched PubMed, EMBASE, and the Cochrane Library for randomized controlled trials that compared BK, PVP, or NST for OVCFs. The search strategy comprised relevant text words and medical subject headings regarding OVCFs, BK, PVP, NST, and randomized controlled trials. The detailed search strategies are presented in Supplementary Table 2. No language or publication date restrictions were imposed. The references of all related studies were manually searched for additional publications. Based on the titles and abstracts, two researchers chose potentially eligible publications. Furthermore, the full text of the selected publications was reviewed for eligibility. Any divergence was settled through consensus.

Eligibility criteria

Type of study

All relevant randomized controlled trials were included. Only published reports with full texts, not congress abstracts, were considered for inclusion.

Participants

Trials enrolling adults, aged at least 18 years, with a diagnosis of OVCFs of any duration were included. Studies with vertebral compression fracture caused by major trauma or malignancy were not included.

Types of interventions

We included trials that evaluated BK versus PVP, BK versus NST, PVP versus NST, or BK versus PVP versus NST for patients with OVCFs.

Outcomes of interest

The efficacy outcome included the pain measured on the visual analogue scale (VAS), the Oswestry Disability Index (ODI), the score on a modified 23-item version of the Roland–Morris Disability Questionnaire (RMDQ), the European Quality of Life–5 Dimensions (EQ–5D) scale, and the Physical Component Summary (PCS) subscales of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36).

The outcome regarding safety contained subsequent vertebral fractures, re-fractures at the treated level, and adjacent vertebral fractures.

Data extraction

Two researchers independently abstracted the information from the original publications, including the study characteristics, patient characteristics, intervention details for each treatment group, and outcome measures. Data that could not be obtained directly from the texts were recalculated, if possible. When the included studies did not provide standard deviations, the standard deviations were recalculated using the formula that was suggested in the Cochrane Handbook for Systematic Reviews of Interventions [17]. If either the final values or the change from baseline values for the same outcome was reported in different studies, we selected the measure that was most used. Any disagreements were solved by consensus among all of the researchers.

Risk of bias assessment

Two researchers evaluated the risk of bias for the included studies according to the Cochrane Handbook [17]. The criteria for assessment contain randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases. Each of the domains was determined to be "low risk," "unclear risk," or "high risk."

Statistical analysis

First, we did a traditional pairwise meta-analysis for all available direct evidence in comparing the two treatments. The I^2 statistics were used to detect the extent of between-trial heterogeneity, with $I^2 > 50\%$ indicating significant heterogeneity. The random-effect model was used as the main model. Furthermore, the results of the random-effect model were compared with that of the fixed-effect model to test the stability of the results. The odds ratio (OR) with 95% confidence interval (CI) was estimated for a dichotomous variable. The mean difference (MD) with 95% CI was calculated for a continuous outcome.

A network meta-analysis was conducted using a Bayesian Markov chain Monte Carlo (MCMC) framework. The posterior distribution of the parameter, which was used for inference, was summarized by its median (OR or MD) and 95% credible interval (CrI). Three chains with different initial values were run simultaneously. For the analyses, the inference was based on 150,000 iterations of MCMC after a 50,000-iteration burn-in period [18].

To check whether a model's fit was satisfactory, the posterior mean residual deviance was calculated. Then, we compared the value of the posterior mean residual deviance with the number of independent data points to test whether the model fits the data well [19]. A random-effect model was applied, because it is probably the most appropriate and conservative methodology to account for between-trial heterogeneity within each comparison [20, 21]. The deviance information criterion (DIC) is a measure of the model fit that penalizes the model complexity. A difference in the DIC by five or more units was regarded as meaningful [22]. The consistency was evaluated by comparing the DIC from a consistency model with that from an inconsistency model [20] and by comparing the direct evidence with the indirect evidence by using the node-splitting approach [23].

Statistical heterogeneity was evaluated based on the magnitude of the heterogeneity parameter (I^2 or τ^2) estimated from the network meta-analysis models [24]. The heterogeneity was investigated by fitting covariates (i.e., mean age, female ratio, sample size, the duration of symptoms and the duration of follow-up) in the network meta-regression [25]. Subgroup meta-analyses were further performed based on the duration of symptoms (acute (≤ 6 weeks), subacute (6–12 weeks), or long-standing (> 12 weeks)) and the duration of follow-up (short-term (< 1 year) or long-term (≥ 1 year)), if possible. Sensitivity analyses were performed to examine the robustness of the outcomes by excluding studies with a follow-up of less than 6 months, excluding studies in which the comparator group consisted of fewer than 50 participants, and restricting the analyses to studies with adequately concealed allocation.

For each outcome, we assessed the probability that each treatment regimen is the best (superior to all other interventions), second best, third best, etc., according to the rank order of the treatment regimens in each iteration of the Markov chain. To visually assess the presence of the publication bias and the small-study effects in the network, comparison-adjusted funnel plots were used [26].

All analyses were conducted by using R software, version 3.2.4 (https://cran.r-project.org/src/base/R-3/) via the gemtc version 0.81 package, Stata, version 13.0 (Stata Corp, College Station, TX), and Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014).

Results

Study search

Of the 1057 relevant publications that were identified through the electronic search and additional sources, 341 were excluded because they were duplicates. After the title and abstract were screened, further 682 studies were excluded. After verifying the remaining 34 full-text reports, 15 studies met the inclusion criteria and were included in the network meta-analysis. The study selection process is shown in Fig. 1.

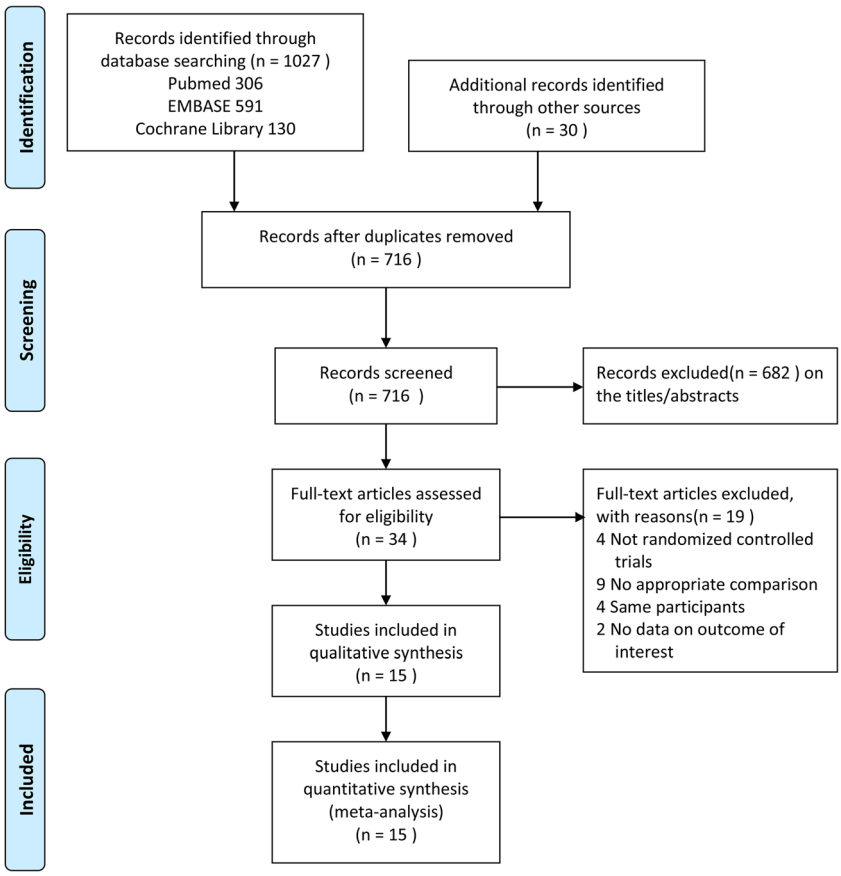

Fig. 1 The flow diagram of study selection

Study characteristics

Of the included studies, only one trial had 3 study groups, and the rest had 2 study groups. The included studies were published between 2007 and 2016. A total of 2092 randomly assigned patients were included in the final analysis. In the studies, the average age of the patients was between 61.3 and 80, and the female ratio ranged from 55.95 to 82.35% of the participants. The duration of symptoms ranged from 1.1 to 28.54 weeks. Five trials [27–31] did not report detailed information about the duration of symptoms. According to the duration of symptoms, six trials [32–37] were conducted during the acute period, one [38] trial was conducted during the subacute period, and three trials [39–41] were conducted during the chronic period. The duration of follow-up ranged from 2 weeks to 49.4 months. In the two studies [27, 38], the duration of the follow-up was less than 1 year and was classified as short-term. Then, the rest were classified as long-term. Table 1 summarizes the main characteristics of the trials that were included.

Risk of bias

The risk of bias for the included trials is shown in Fig. 2. One trial [33] was graded as having a low risk of bias, 12 trials were at a high risk of bias, and the rest were classified as an unclear risk of bias. Fourteen trials reported an appropriate randomization, and seven trials described the methods of allocation concealment. Twelve trials did not blind the participants or the outcome assessors.

Bayesian network meta-analyses

The evidence networks of eligible comparisons for the efficacy and safety outcomes are displayed in Supplementary Fig. 1.

Pain

With respect to the efficacy endpoint (Fig. 3), the use of PVP was the most effective treatment for pain on the VAS [27–30, 32–41], while use of NST presented the highest mean difference in pain. PVP emerged as the best intervention in treatment ranking (probability of 88.75%), followed by BK or PVP (Fig. 4), but the extent of pain reduction compared with BK was minor (MD = − 0.51, 95% CrI − 1.4 to 0.35).

Functional status

Six trials [28–30, 37, 40, 41] with 658 patients were included in the analysis of the ODI (Fig. 3). PVP had a

Table 1 Characteristics of the included studies

Study	Country	Study characteristics	Interventions	Sample size	Age (years)*	Female ratio (%)	Duration of symptoms (weeks)*	Follow-up (months)
Blasco 2012	Spain	April 2006 to January 2010, single-center study	G1: PVP; G2: NST	G1: 64; G2: 61	G1: 71.33 ± 9.95; G2: 75.27 ± 8.53	G1: 73; G2: 82	G1: 20.0 ± 13.7; G2: 20.4 ± 18.6	12
Boonen 2011	Eight[a]	February 2003 to December 2005, multi-center study	G1: BK; G2: NST	G1: 149; G2: 151	G1: 72.2 (44.5–95.2); G2: 74.1 (52.8–89.1)	G1: 77.2; G2: 77.5	G1: 5.6 ± 4.4; G2: 6.4 ± 5.2	24
Chen 2010	China	January 2007 to January 2010, single-center study	G1: PVP; G2: NST	G1: 18; G2: 22	G1: 77.5 ± 0.8; G2: 76.3 ± 0.5	G1: 77.78; G2: 72.73	G1: NA; G2: NA	3
Chen 2014	China	January 2007 to December 2012, single-center study	G1: PVP; G2: NST	G1: 46; G2: 43	G1: 64.63 ± 9.10; G2: 66.49 ± 9.11	G1: 69.57; G2: 69.77	G1: 28.28 ± 12; G2: 27.24 ± 10.04	31
Chen 2015	China	January 2010 to September 2014, single-center study	G1: PVP; G2: NST	G1: 42; G2: 42	G1: 67.04 ± 8.37; G2: 66.09 ± 8.74	G1: 57.14; G2: 54.76	G1: NA; G2: NA	34.7
Dohm 2014	USA	October 2006 to May 2011, multi-center study	G1: BK; G2: PVP	G1: 191; G2: 190	G1: 75.5 ± 10.3; G2: 75.7 ± 10.5	G1: 79.1; G2: 75.8	G1: NA; G2: NA	24
Evans 2016	USA	NA, multi-center study	G1: BK; G2: PVP	G1: 59; G2: 56	G1: 75.1 ± 10.1; G2: 76.1 ± 10.0	G1: 64.8; G2: 77.6	G1: 2.57 ± 1.47; G2: 2.5 ± 1.67	12
Farrokhi 2011	Iran	September 2004 to January 2006, single-center study	G1: PVP; G2: NST	G1: 40; G2: 42	G1: 72 (59–90); G2: 74 (55–87)	G1: 75; G2: 71	G1: 27 (4–50); G2: 30 (6–54)	36
Klazen 2010	Two[b]	October 2005 to June 2008, multi-center study	G1: PVP; G2: NST	G1: 93; G2: 95	G1: 75.2 ± 9.8; G2: 75.4 ± 8.4	G1: 75.27; G2: 73.68	G1: 4.2 ± 2.4; G2: 3.8 ± 2.3	12
Liu 2015	China	NA, single-center study	G1: BK; G2: PVP	G1: 50; G2: 50	G1: 72.3 ± 7.6; G2: 74.3 ± 6.4	G1: 78; G2: 76	G1: 2.4 ± 1.1; G2: 2.3 ± 1.0	60
Rousing 2010	Denmark	January 2001 to January 2008, single-center study	G1: PVP; G2: NST	G1: 26; G2: 24	G1: 80 (76.9–83.2); G2: 80 (77.6–82.6)	G1: 73.08; G2: 87.5	G1: 1.2 (0.5–1.9); G2: 1.0 (0.3–1.6)	12
Voormolen 2007	Netherlands	July 2003 to June 2005, multi-center study	G1: PVP; G2: NST	G1: 18; G2: 16	G1: 72 (59–84); G2: 74 (55–88)	G1: 78; G2: 88	G1: 12.1 (6.7–19.7); G2: 10.9 (6.6–20.1)	0.5
Wang 2015	China	January 2012 to February 2014, single-center study	G1: BK; G2: PVP	G1: 54; G2: 53	G1: 68.63 ± 8.39; G2: 69.43 ± 8.94	G1: 74.07; G2: 77.36	G1: NA; G2: NA	12
Yang 2016	China	January 2009 to December 2011, single-center study	G1: PVP; G2: NST	G1: 56; G2: 51	G1: 77.1 ± 6.0; G2: 76.2 ± 5.6	G1: 64.29; G2: 64.71	G1: 1.2 ± 0.66 G2: 1.2 ± 0.66	12
Yi 2014	China	November 2005 to July 2009, single-center study	G1: BK; G2: PVP; G3: NST	G1: 79; G2: 90; G3: 121	G1: 61.3 (48–75); G2: 61.3 (48–75); G3: 61.3 (48–75)	G1: 62.41 G2: 62.41 G3: 62.41	G1: NA; G2: NA; G3: NA	49.4

G, group; *BK*, balloon kyphoplasty; *PVP*, percutaneous vertebroplasty; *NST*, non-surgical treatment; *NA*, not available

[a] Austria, Belgium, France, Germany, Italy, Sweden, the Netherlands, and the UK

[b] Netherlands and Belgium

* Data are expressed as mean ± SD or mean (range)

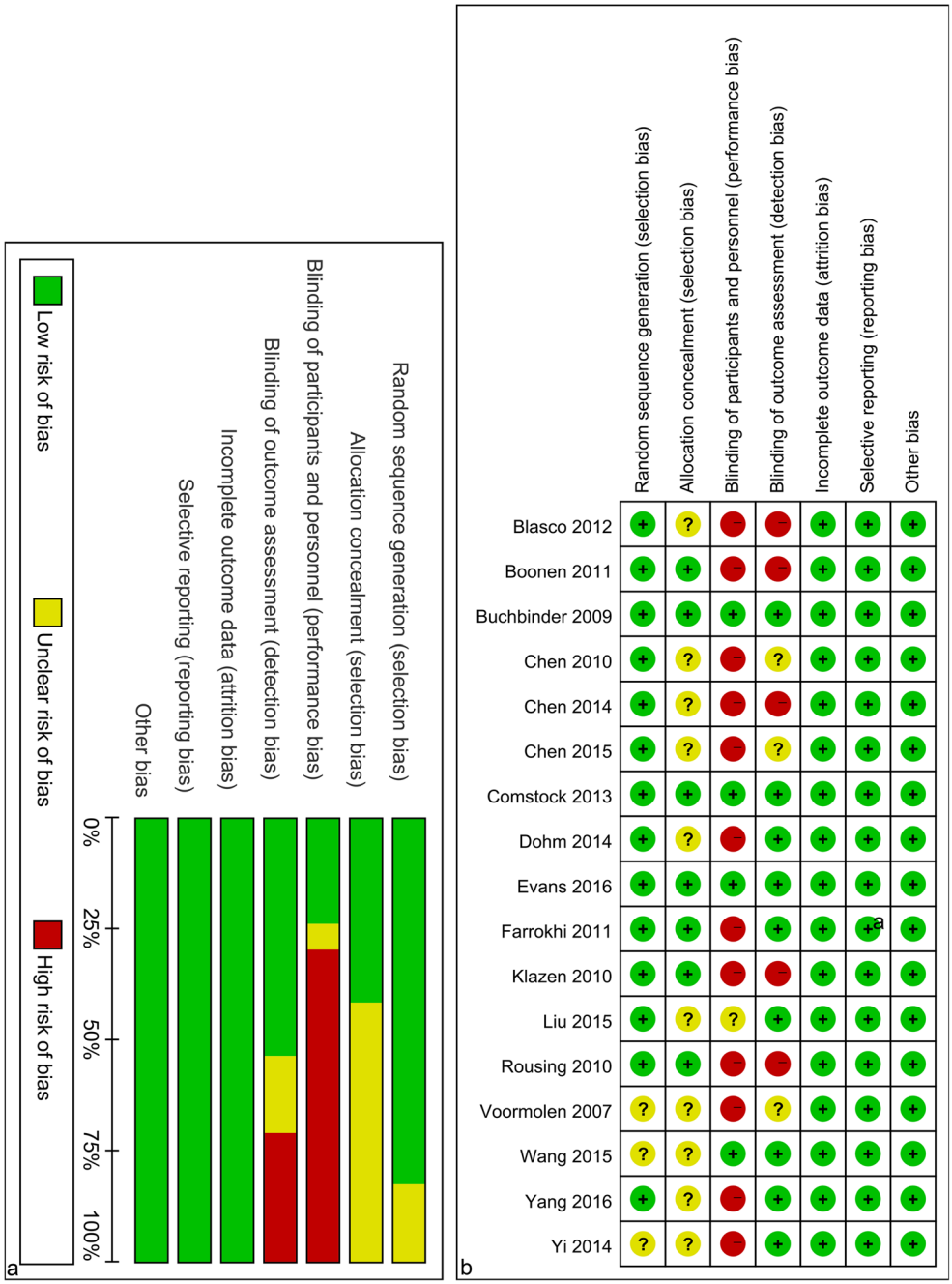

Fig. 2 Risk of bias assessment of each included study: **a** Risk of bias graph. **b** Risk of bias summary

statistically significant lower ODI than NST (MD = − 11, 95% CrI − 20 to − 1.4), with the 95% CrI excluding the null effect. BK had a lower ODI compared with NST, with the results narrowly failing to reach statistical significance. PVP was the best intervention in treatment ranking (probability of 50.24%) (Fig. 4).

A total of four studies [32, 33, 38, 40] (441 patients) contributed to the analysis of the RMDQ (Fig. 3). The use of PVP presented lower RMDQ scores than NST (MD = − 3, 95% CrI − 6.6 to − 0.27), with the 95% CrI excluding the null effect. PVP (79.90%) ranked the first, BK (19.19%) ranked second and NST (0.91%) ranked last (Fig. 4).

Quality of life

With respect to EQ-5D [29, 32, 36] (Fig. 3), the use of PVP or BK was associated with higher EQ-5D levels compared with that of NST (MD = 0.11, 95% CrI − 0.024 to 0.24 and MD = 0.094, 95% CrI − 0.03 to 0.22, respectively), although the difference was not statistically significant. According to the treatment ranking, PVP had the highest probability (64.22%) of being the best treatment, BK (33.74%) ranked second and NST (2.04%) ranked last (Fig. 4).

Three studies [29, 32, 36] with a total of 473 patients were included in the analysis of SF-36 PCS (Fig. 3). The use of BK

VAS

BK	0.20 (-0.35, 0.75)	-0.83 (-1.41, -0.25)
0.51 (-0.35, 1.4)	PVP	-0.94 (-1.49, -0.39)
-0.34 (-1.2, 0.49)	**-0.85 (-1.4, -0.28)**	NST

ODI

BK	-0.44 (-2.73, 1.85)	/
0.11 (-13, 13)	PVP	-10.53 (-17.46, -3.60)
-10 (-26, 5.3)	**-11 (-20, -1.4)**	NST

RMDQ

BK	0.80 (-2.42, 4.02)	-1.60 (-3.08, -0.12)
1.2 (-2.7, 5.4)	PVP	-3.39 (-5.60, -1.18)
-1.8 (-6.0, 1.8)	**-3 (-6.6, -0.27)**	NST

EQ-5D

BK	-0.02 (-0.08, 0.04)	0.10 (-0.00, 0.20)
-0.017 (-0.13, 0.096)	PVP	0.10 (-0.04, 0.25)
0.094 (-0.03, 0.22)	0.11 (-0.024, 0.24)	NST

SF-36 PCS

BK	0.22 (-2.75, 3.19)	2.03 (-0.19, 4.25)
0.25 (-3.1, 3.6)	PVP	1.60 (-4.63, 7.83)
2 (-0.99, 4.9)	1.7 (-2.2, 5.6)	NST

Subsequent vertebral fractures

BK	0.86 (0.58, 1.28)	0.84 (0.25, 2.78)
1.0 (0.52, 2.2)	PVP	0.96 (0.57, 1.60)
1.0 (0.47, 2.3)	0.98 (0.56, 1.7)	NST

Adjacent vertebral fractures

BK	0.76 (0.32, 1.82)	1.38 (0.54, 3.54)
0.34 (0.069, 1.2)	PVP	2.22 (0.66, 7.53)
1.5 (0.26, 8.0)	3 (0.83, 14)	NST

Re-fractures at treated level

BK	0.39 (0.12, 1.25)	0.41 (0.15, 1.12)
0.60 (0.082, 6.6)	PVP	0.19 (0.01, 3.67)
0.20 (0.016, 1.2)	0.33 (0.011, 3.0)	NST

Fig. 3 For pain on VAS, ODI, and RMDQ, mean difference lower than 0 favors the column-defining treatment. For EQ-5D and SF-36 PCS, mean difference greater than 0 favors the column-defining treatment. For subsequent vertebral fractures, adjacent vertebral fractures, and re-fractures at treated level, odds ratio lower than 1 favors the column-defining treatment. Results of standard pairwise meta-analyses were shown in the upper right. Results of Bayesian network meta-analyses were shown in the bottom left. Statistically significant results are in bold. VAS, visual analogue scale; ODI, Oswestry Disability Index; EQ-5D, European Quality of Life–5 Dimensions; RMDQ, Roland–Morris Disability Questionnaire; SF-36 PCS, Physical Component Summary subscales of the Medical Outcomes Study 36-Item Short-Form General Health Survey

or PVP was superior to NST in SF-36 PCS (MD = 2, 95% CrI − 0.99 to 4.9 and MD = 1.7, 95% CrI − 2.2 to 5.6, respectively). The results did not reach statistical significance for the comparisons. The estimated probability of BK being the best treatment was 52.67% (Fig. 4). NST had the lowest probability (4.97%) of increasing SF-36 PCS.

Risk of vertebral fractures

Subsequent vertebral fractures data were available in 14 trials [27–32, 34–41] (Fig. 3). There were no significant differences in the subsequent vertebral fractures across all comparators. Based on the treatment ranking, BK had the highest probability (34.75%) of reducing the risk of subsequent vertebral fractures (Fig. 4).

As for the prevention of adjacent vertebral fractures [27, 30–32, 35, 36, 38, 39, 41] (Fig. 3), NST was ranked first, with a 67.80% probability of being the best therapy, followed by BK and PVP (Fig. 4). NST was associated with fewer adjacent vertebral fractures compared with PVP (OR = 0.34, 95% CrI 0.069 to 1.2) or BK (OR = 0.68, 95% CrI 0.12 to 3.9), although no prominent differences were observed.

Regarding the safety endpoint (Fig. 3), the use of BK or PVP reduced the risk of re-fractures at the treated level [29, 31, 32] compared with NST, although no notable differences were seen (OR = 0.20, 95% CrI 0.016 to 1.2 and OR = 0.33, 95% CrI 0.011 to 3.0, respectively). When compared directly, BK and PVP had similar risks of re-fractures at the treated level (OR = 0.60, 95% CrI 0.082 to 6.6). BK had the highest probability (67.92%) of being the best therapy, PVP (29.79%) ranked second and NST (2.29%) ranked last (Fig. 4).

Heterogeneity, model fit, and inconsistency

The Brooks-Gelman-Rubin plots indicated that the model had converged sufficiently. Heterogeneity (global I^2) was 87.51% for pain, 98.88% for ODI, 66.49% for RMDQ, 0% for SF-36 PCS, 0% for EQ-5D, 41.77% for subsequent vertebral fractures, 41.82% for adjacent vertebral fractures, and 44.79% for re-fractures at the treated level. The model fit was estimated by comparing the posterior mean residual deviance with the number of data points and was shown to be similar (Supplementary Table 3). There was no statistically apparent difference between the direct and indirect estimates for pain, RMDQ, SF-36 PCS, EQ-5D, the subsequent vertebral fractures, and the adjacent vertebral fractures. The DICs were analogous between the consistency and the inconsistency models, which suggested evidence of consistency in the network. However, this should be read cautiously, as there may be insufficient power to identify inconsistency.

Traditional pairwise meta-analysis

We also performed standard, frequentist, pairwise meta-analyses to complement the results of the network meta-analysis. The results of the corresponding standard pairwise meta-analyses (Fig. 3) were almost concordant with those of the network meta-analysis. The results of the random-effect model were similar with that of the

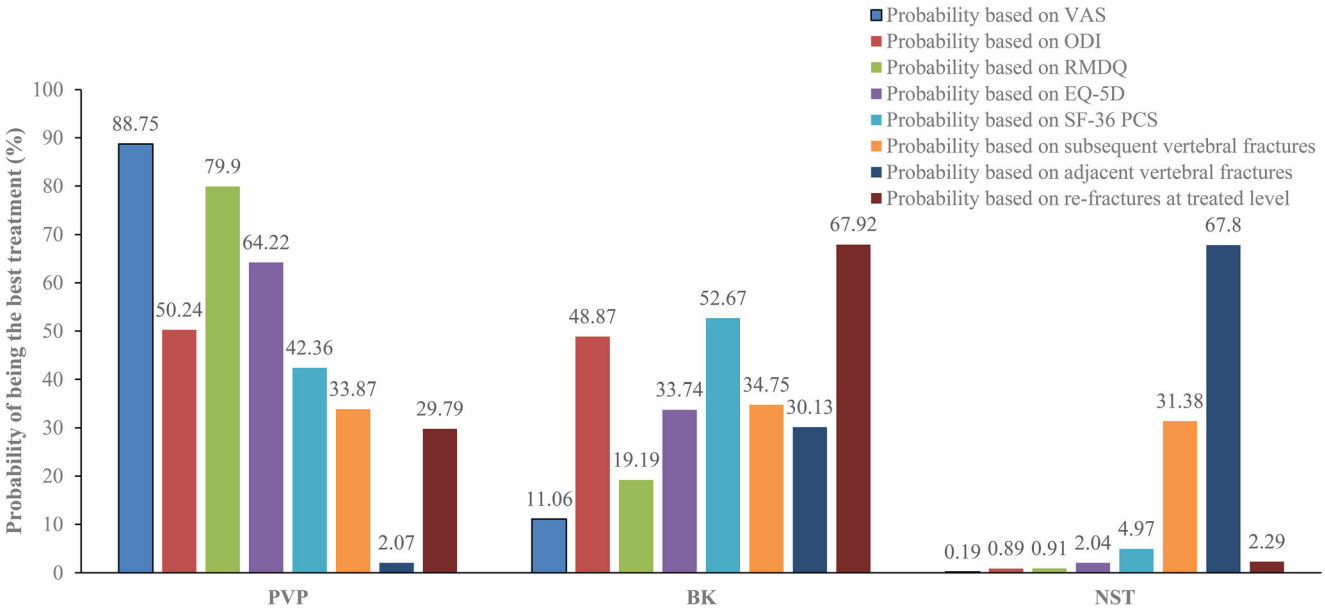

Fig. 4 Probability that each treatment is the most efficacious in the study network. BK, balloon kyphoplasty; PVP, percutaneous vertebroplasty; NST, non-surgical treatment; VAS, visual analogue scale; ODI, Oswestry Disability Index; RMDQ, Roland–Morris Disability Questionnaire; EQ-5D, European Quality of Life–5 Dimensions; SF-36 PCS, Physical Component Summary subscales of the Medical Outcomes Study 36-Item Short-Form General Health Survey

fixed-effect model (Supplementary Table 4), which indicated that the results were stable.

Meta-regression analyses

The meta-regression adjustment for the mean age, female ratio, sample size, duration of symptoms, and duration of follow-up almost did not alter the outcomes regarding the pain and subsequent vertebral fractures (Supplementary Table 5).

Subgroup analyses

In the preplanned stratified analyses based on the duration of symptoms and the duration of follow-up, the results of PVP with respect to pain, ODI, RMDQ, subsequent vertebral fractures, and adjacent vertebral fractures were significantly changed when compared with NST. Other results did not show clear differences (Supplementary Table 6).

Sensitivity analyses

The sensitivity analyses excluding studies with a follow-up of less than 6 months did not show any major change in all of the outcomes (Supplementary Table 7). However, sensitivity analyses excluding studies in which comparator groups consisting of fewer than 50 participants altered the summary estimates for pain and ODI, which thus became statistically non-significant when comparing PVP with NST. If we restricted the analyses to studies with adequately concealed allocation, almost all of the results were stable.

Publication bias

Generally, substantial asymmetry was not shown for the outcomes regarding pain, subsequent vertebral fractures, and adjacent vertebral fractures through visually estimating the comparison-adjusted funnel plots.

Discussion

Our network meta-analysis of randomized controlled trials compared BK, PVP, and NST and estimated their efficacy and safety for the treatment of OVCFs. We found that for pain, ODI, and RMDQ outcomes, PVP was significantly better than NST. The three treatments did not significantly differ in other outcomes. For the outcomes of pain, ODI, RMDQ, and EQ-5D, PVP had the highest probability of being the best treatment. BK emerged as the best intervention in the treatment ranking for SF-36 PCS, subsequent vertebral fractures and re-fractures at the treated level. NST could be ranked first in reducing adjacent vertebral fractures.

An ideal intervention for treating OVCFs should bring about a permanent improvement in the pain and avoid introducing new pain at a different vertebral level. Although the precise mechanism of pain relief is indistinct, two studies [42, 43] demonstrated that inhibiting and immobilizing the micromovement in the fractured vertebral body resulted in pain reduction. Heini et al. [44] reported that PMMA cement can destroy the terminal nerve endings in the fractured vertebral body and reduce the pain. It has been reported that pain tended to spontaneously improve during the acute phase [45].

In VERTOS II, 53% of participants who originally met the eligible criteria subsequently became unqualified due to their pain score spontaneously falling below 5 between screening and randomization [34]. Prior network meta-analyses [13, 46] have demonstrated that BK significantly decreased pain compared with NST for the long-term VAS scores. However, due to pooling randomized and nonrandomized controlled studies, or including a limited number of trials, the reliability of the results may have been compromised. Some studies [47, 48] found that BK was associated with significant improvements in pain compared with PVP at a long-term follow-up. Nevertheless, other meta-analyses [49, 50] indicated that no considerable differences between BK and PVP were observed in long-term pain relief. In these studies, some data came from observational studies, which are subject to bias. To offer more reliable evidence and diminish potential bias, we included only randomized controlled trials. The included studies were considered to be adequately homogenous, but there was statistically significant heterogeneity. The 15 studies included patients with comparable baseline pain and sex distribution, although follow-up periods varied from 2 weeks to 5 years. Large inconsistencies in the duration of follow-up may potentially cause the high heterogeneity that was observed in this analysis. Hence, we performed a sensitivity analysis by excluding studies with a follow-up of less than 6 months, a meta-regression analysis with covariate 'follow-up duration,' and a subgroup analysis (short-term (< 1 year) or long-term (≥ 1 year)). The sensitivity analysis and the meta-regression analysis did not alter the result. However, the subgroup analysis demonstrated that no significant difference between PVP and NST was observed at the short-term follow-up. The effect of the spontaneous healing process during the acute phase could have biased the results, which may have caused the patients who were treated with NST to improve spontaneously and lessened the difference in pain between PVP and NST at the short-term follow-up.

The ODI and RMDQ were used to evaluate the back-specific functional status. A review [45] indicated that BK and PVP provided better results than NST by improving functionality, which was determined by increased ODI scores. A previous study [47] showed that BK was associated with a significant improvement in the ODI scores compared with that of PVP. This finding was contrary to the result of the present analysis. Among the 11 included studies, there were ten observational studies in the previous study that were subject to bias. These observational studies may have disturbed the reliability of the result.

The quality of life was most often estimated with the EQ-5D, which were created to minimize subjective variability [51]. PVP and BK were each associated with a higher EQ-5D level compared with that of NST, although the difference was not statistically significant. Furthermore, PVP was shown to be nonsignificantly better than BK. However, there was a tendency towards favoring BK over PVP in terms of SF-36 PCS. Our analysis suggested a beneficial association of BK and PVP in improving the quality of life compared with NST. Improvement of lung function because of the modification of kyphotic deformity [52] and alleviation of impaired physical function through pain relief [52, 53] may account for why BK and PVP may improve the quality of life. However, only three studies using EQ-5D and SF-36 PCS to assess quality of life were eligible to be included. Therefore, the small size of the sample made the findings untrustworthy. Thus, more randomized controlled trials to assess the quality of life are required to tackle the areas of uncertainty.

We did not find an increased risk of subsequent vertebral fractures, adjacent vertebral fractures, or re-fractures at the treated level associated with the three interventions; however, a clinically crucial increased risk cannot be omitted based on this review, given the small number of events. The results of our review are consistent with a prior network meta-analysis [13], which indicated that these interventions (BK, PVP, and NST) had no significant differences with respect to the risk of subsequent vertebral fractures. However, data extracted from the randomized controlled trials that compared risk with using BK compared with using NST were inconsistent, as determined by the considerable statistical heterogeneity that was observed in the pooled analyses. Blasco et al. [39] found a substantially increased incidence of clinically further vertebral fractures associated with PVP over a 1-year follow-up period; another study observed a significantly lower risk of subsequent vertebral fractures in the PVP group (2.2%) compared with that of the NST group (13.3%) [41], while any significant differences in risk between groups were observed in other studies [27–30, 32, 34–38, 40]. Incompatible outcomes were also observed in observational studies that compared the risk of subsequent vertebral fractures after PVP with that in a cohort who did not undergo the procedure [54, 55]. As is well-known, patients suffering vertebral fractures caused by osteoporosis have a higher incidence of new vertebral fractures compared with patients who were not subjected to osteoporosis [56]. Approximately 20% of patients who have ever experienced OVCFs will suffer a further vertebral compression fracture within 1 year, which is influenced by the severity of the former fracture [57].

In an earlier meta-analysis [47] of 11 studies that compared BK and PVP for patients with OVCFs, no detectable differences between groups in the adjacent vertebral fractures were found. Another meta-analysis [58] that compared the vertebral augmentation with nonoperative treatment found there was no considerable difference in the risk of adjacent vertebral compression fractures. The above finding was further confirmed by the current analysis with the strength of the network meta-analysis. It was shown by Berlemann et al. [59] that the failure strength for functional spine units treated by the injection of

cement was lower than that of untreated controls. The mechanism for this may be that the increased stiffness of the augmented vertebrae changes the biomechanics of the load transfer to the adjacent vertebral bodies. It is possible that a 'stress-riser' effect and a considerable difference in the biomechanical properties between the augmented and the adjacent, non-augmented vertebrae result in the early failure of the adjacent level. This may be the reason that BK and PVP were associated with a higher risk of adjacent vertebral fractures than was NST in our analysis. However, to finally confirm whether or not the three interventions increase the risk of further vertebral fractures, especially adjacent vertebral fractures, further large randomized controlled trials with a prolonged follow-up were required.

The results of the present study should be interpreted with some limitations. First, treatment could not be masked in some comparisons. Different from the blinded randomized controlled studies [60, 61], knowledge of the assignment may have influenced patient responses to questions or investigator assessments. However, this weakness is challenging to conquer in this type of study, as a blinding strategy is rarely promising to use on a surgical topic, which is an inherent limitation of conducting randomized trials on such topics. Second, this study consisted of 17 studies, but almost half of them had a modest sample size ($n < 100$). Compared with large sample size studies, studies with a small sample size tended to exaggerate the treatment effectiveness, which may restrict the power of the findings. We included a sensitivity analysis that excluded studies in which any comparator group consisted of fewer than 50 participants and found that the summary estimates for pain and ODI became statistically non-significant when comparing PVP with NST. Moreover, given that the number of studies available for some outcomes (EQ-5D, SF-36 PCS scores, and re-fractures at treated level) was relatively limited, the estimates and the statistical power cannot be ensured; thus, some of the analyses may fail to detect a true treatment effect, and the publication bias may need further estimation. Further trials of high quality would be beneficial to increase the statistical power and shed further light on the efficacy and safety of BK, PVP, and NST on OVCFs. Furthermore, substantial heterogeneity was found in pairwise and network meta-analyses. The meta-regression with adjacent vertebral fractures demonstrated that the mean age, female ratio, sample size, and duration of follow-up induced substantial changes in the results. Other factors, including the proportion of current smokers, body mass index, and bone mass density, which were not accessible in a few of the trials included in the present analysis, may have affected the outcomes. Nevertheless, the outcomes are unlikely to be substantively biased in view of the consistency of outcomes between direct and indirect comparison meta-analyses.

Conclusion

In conclusion, our network meta-analysis indicated that for pain and functional status, PVP was significantly better than NST, while the three treatments did not significantly differ in other outcomes. PVP was the most effective strategy in improving the pain, functional status, and quality of life (based on EQ-5D). BK emerged as the best intervention for improving the quality of life (based on SF-36 PCS) and for decreasing the risk of subsequent vertebral fractures and re-fractures at the treated level. NST could be ranked first in reducing adjacent vertebral fractures. The future direction of treatment of OVCFs will depend on the outcomes of additional and larger randomized trials that compare BK with PVP.

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Compliance with ethical standards

Conflicts of interest None.

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