Pain Physician 2013; 16:277-290 • ISSN 1533-3159

Systematic Review

A Systematic Review and Meta-analysis of Randomized Controlled Trials of Unilateral Versus Bilateral Kyphoplasty for Osteoporotic Vertebral Compression Fractures

Li-yu Yang, MD, Xing-Li Wang, MD, Long Zhou, MD, and Qin Fu, MD, PhD

From: Department of Orthopedic Surgery, The Shengjing Hospital of China Medical University, China

Dr. Yang is a first year resident in the Department of Orthopedic Surgery, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China. Dr. Wang is a first year resident in the Department of Ophthalmology, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China. Dr. Zhou is a second year resident in the Department of Orthopedic Surgery, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China. Dr. Fu is Medical director, Department of Orthopedic Surgery, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China, and Professor, Department of Orthopedic Surgery, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China.

Address Correspondence:
Qin Fu, MD, PhD
Dept. of Orthopedic Surgery
The Shengjing Hospital of China Medical University
No.36 Sanhao Street
Heping District, Shenyang, Liaoning 110004
People's Republic of China
E-mail:qinfucmu@hotmail.com

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: None.

Manuscript received: 11-28-2012
Revised manuscript received: 01-25-2013
Accepted for publication: 02-25-2013

Free full manuscript: www.painphysicianjournal.com

Background: Kyphoplasty reduces the pain caused by osteoporotic vertebral compression fracture (OVCF). Although the procedure is typically carried out using a bilateral approach, it is now increasingly performed using a unilateral approach because of the concern for long-term adverse effects. However, little evidence is available to demonstrate superior safety of the unilateral approach.

Objective: The purpose of this study was to compare the short- and long-term safety and efficacy of unilateral vs. bilateral kyphoplasty.

Study Design: A systematic review and meta-analysis of randomized controlled trials.

Settings: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and abstracts published in the related orthopedic journals were systematically searched up to September 2012, using "unilateral kyphoplasty" and "osteoporotic vertebral compression fractures" as key words.

Methods: Two investigators independently searched and identified relevant reports and abstracts using the PRISMA statement criteria. Relevant studies cited by the identified papers were also included. The level of evidence was classified as good, fair, and limited (or poor) based on the quality of evidence developed by the U.S. Preventive Services Task Force (USPSTF).

Results: Four randomized controlled trials (RCTs) of 159 cases were enrolled. The methodological quality of the articles was determined as moderate. We did not find any significant difference between unilateral and bilateral kyphoplasty on pain relief, in either short-term or long-term follow-up ($P = 0.65$ and $P = 0.69$, respectively). The rate of adjacent vertebral fracture was not statistically different with a P value of 0.88 and 95% CI (confidence intervals) of 0.25-3.26. Cement leakage was comparable between unilateral and bilateral kyphoplasty ($P = 0.56$, 95% CI = 0.46-4.26). The loss of vertebral height in long-term follow-up was not different ($P = 0.10$, 95% CI = -0.39-4.54). Operation time and cement dosage were considerably less for unilateral kyphoplasty ($P < 0.01$ and $P < 0.05$, respectively).

Limitations: Only 4 RCTs and 159 patients were included in this systematic review. Publication bias also existed among the studies included.

Conclusions: Both unilateral and bilateral kyphoplasty are effective in alleviating the back pain caused by OVCF. Two approaches have the same degree of safety. More RCTs are needed to examine the efficacy and adverse reactions of the 2 approaches.

Key words: Unilateral kyphoplasty, bilateral kyphoplasty, osteoporotic vertebral compression fractures, systematic review, meta-analysis, randomized controlled trials

Pain Physician 2013; 16:277-290

Percutaneous kyphoplasty is a minimally invasive surgery that provides pain relief and vertebral height restoration for osteoporotic vertebral compression fractures (OVCFs) (1-8). Briefly, a large-bore needle is placed transpedicularly into the vertebral body under fluoroscopy. An inflatable balloon tamp is inserted into the fractured vertebral body between the end plates in the anterior two-thirds of the vertebral body. Expanding the balloon tamp creates a hollow cavity and elevates the endplate. The cavity is filled with viscous cement such as polymethylmethacrylate (PMMA). Under ideal conditions, the cement remains in the anterior three-fourths of the restored vertebra (9). The operation is typically carried out using a bilateral transpedicular or extra-pedicular approach. In recent years, unilateral kyphoplasty has been increasingly used because of less operative time, less radiation exposure, and lower risk of punctured pedicular fractures (10,11). The unilateral approach could also reduce the possibility of cement leakage through the cannula tract and the resulting nerve injury (12,13).

Kyphoplasty has been reported to increase the risk of secondary vertebral compression fractures (14). A recent systematic review (1) indicated no significant difference between vertebral augmentation and conventional nonsurgical management. However, the efficacy and adverse effects of unipedicular and bipedicular approaches have not been compared. Studies using cadavers did not reveal a significant difference between unipedicular and bipedicular kyphoplasty in terms of adverse effects (15,16). Generally, bilateral kyphoplasty is thought to be more stable as more cement is injected. In the current study, we carried out a systematic literature review of the published clinical studies that compared unilateral and bilateral kyphoplasty, and examined the efficacy and safety of 2 approaches in patients with OVCF.

1. Methods

This current meta-analysis was carried out in accordance to the PRISMA statement (17) and the recommendations of the Cocharane Collaboration (18).

1.1 Criteria for Considering Studies for the Review

1.1.1 Types of Studies

Randomized controlled trials (RCTs).

1.1.2 Types of Patients

Patients were adults (at least 18 years of age) with chronic back pain caused by OVCF. Patients must have failed previous treatments (pharmacological or exercise therapy) prior to starting diagnostic interventional pain management techniques.

1.1.3 Types of Interventions

The interventions were unilateral and bilateral kyphoplasty performed under fluoroscopic or computed tomography (CT) guidance.

1.1.4 Types of Outcome Measures

- The primary outcome parameter was pain relief.
- The secondary outcome measures were surgery time and cement dosage in operations; recurrent adjacent vertebral fractures and other complications.
- At least 2 authors of this manuscript independently assessed the outcomes measures in an unblinded standardized manner. Any disagreements between reviewers were resolved by a third author and consensus.

1.2 Literature Search

A systematic literature search up to September 2012 of the electronic databases (MEDLINE, EMBASE, OVID, and the Cochrane Central Register of Controlled Trials) revealed a total of 185 potentially eligible publications. The search was limited to clinical trials and included publications without language limitations. The following search terms were used: osteoporosis, osteoporotic vertebral compression fractures, unilateral kyphoplasty, unipedicular approach, single balloon kyphoplasty, one ballon kyphoplasty. A manual search included articles published in *Osteoporosis International*, *Journal of Neurosurgery*, *Journal of Bone and Joint Surgery*, American Volume, and *Journal of Bone and Joint Surgery*, British Volume from 2000 to 2012. The search also included manual reviewing of the articles and abstracts cited in the reference lists of identified RCTs.

1.3 Search Strategy

The search strategy emphasized the treatments and complications of unilateral and bilateral kyphoplasty for OVCF. All studies describing appropriate outcome evaluations with proper statistical evaluations were reviewed. Reports without appropriate diagnosis, book chapters, and case reports were excluded.

Searches were performed by at least 2 authors independently in an unblinded standardized manner. Accuracy was confirmed by a statistician. All searches

were combined to obtain a unified search strategy. A third author and consensus resolved any disagreements between reviewers.

1.4 Study Selection

RCTs were included in the analysis if the following inclusion criteria were met: 1) prospective RTCs and participants were patients with OVCFs; 2) the intervention of unilateral kyphoplasty was compared to bilateral kyphoplasty; 3) the study reported at least one of the following outcomes: surgery time, cement dosage, visual analog score (VAS), restoration rate and loss reduction or height loss rate after the operation, the incidence of the adjacent vertebral fracture, and long-term cement leakage. Studies that included patients with neoplastic etiology (metastasis or myeloma), infection, neural compression, invasive disease, traumatic fracture, neurological deficits, or spinal stenosis were excluded. Other exclusion criteria included severe degenerative disease of the spine and previous surgery at the vertebral body. Studies carried out in cadavers were also excluded. Two reviewers (L-Y Yang and X-L Wang) independently checked all titles, abstracts, and the full text of potentially eligible articles. If the 2 reviewers could not reach a consensus on an article, a third reviewer (L Zhou) made the final decision on whether to include the item in the analysis.

1.5 Data Extraction

Data were extracted independently by 2 reviewers (L-Y Yang & X-L Wang), without blinding to the title and author affiliation. Relevant data included the title, authors, year of publication, sample size, gender, type of intervention, number of vertebral bodies, surgical procedures, duration of the follow-up, industry sponsorship, and financial interest. The primary outcomes included pain, as reflected in a VAS, and incidence of adjacent vertebral fracture and bone cement leakage. Secondary outcomes included surgery time, cement dosage, postoperative kyphosis angle change, the height loss rate, neurological deficits, nerve root irritation, and lung embolism. "Short-term" was defined as within 4 weeks; "long-term" was defined as at least 12 months. The outcomes between 4 weeks and 12 months were not analyzed in this systematic review.

1.6 Methodological Quality and Risk of Bias Assessment

The methodological quality and risk of bias were estimated by 2 authors independently using an unblinded standardized method. A third reviewer was called in if a consensus was not reached. The quality of each article included in the analysis was assessed by Cochrane review criteria (Table 1) (19), and assessment results included "yes," "no, and "unclear." Studies achieving a Cochrane score of 9 or higher were considered as high quality, 6 to 8 were considered as moderate quality, and studies scoring less than 6 were rated as having a "a high risk of bias." Disagreement was resolved by discussion among the authors.

1.7 Clinical Relevance

Clinical relevance was assessed according to the recommendation by the Cochrane Back Review Group (20) using 5 questions (Table 2). At least 3 clinical relevance questions had to be positive for a study to be considered clinically relevant.

1.8 Data Analysis

Separate meta-analyses were undertaken for each outcome. Studies that reported associated complications were identified, and complications were tabulated along with the total number of procedures and patients to obtain the overall complication rates. Differences in cement leak and postoperative adjacent vertebral fracture between the unilateral and bilateral approaches were examined by chi-square analysis. All the meta-analyses were performed with the Review Manager software (RevMan Version 5.1 Cochrane Collaboration). For continuous variables, such as VAS and height loss rate, weighted mean difference (WMD) and 95% confidence interval (95% CI) were calculated. For dichotomous variables such as the incidence of adjacent vertebral compression fractures and cement leakage, relative risk (RR) and 95% CI were calculated. $P < 0.05$ was considered statistically significant. I2 statistic and Q statistic were used to measure heterogeneity of the RCTs. If the I2 value was less than 50%, or $P > 0.1$, a fixed-effects model was used. If the I2 value was 50% or more, or if the P value was 0.1 or less, a random-effects model was used (21).

Funnel plot, as calculated by RevMan Manager software, was used to investigate the potential publication bias (22).

1.9 Analysis of Evidence

The analysis of the evidence was performed using the United States Preventive Services Task Forces (USPSTF) criteria (23) (Table 3) that has been used in multiple articles of similar type (24-30). The analysis

Table 1. *Cochrave Review Criteria analysis.*

A	1. Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, pre-ordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and pre-ordered list of treatment assignments.Examples of inadequate methods are alternation, birth date, social insurance security number, date in which they are invited to participate in the study, and hospital registration number.	Yes/No/ Unsure
B	2.Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/ Unsure
C	Was knowledge of the allocated interventions adequately prevented during the study?		
	3. Was the patient blinded to the intervention?	This item should be scored "yes' if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes//No/ Unsure
	4.Was the care provider blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/ Unsure
	5. Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for the primary outcomes. This item should be scored"yes"if the success of blinding was tested among the outcome assessors and it was successful or: –for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain,disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes" –for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination –for outcome criteria that do not suppose a contact with participants (e.g., radiography,magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome –for outcome criteria that are clinical or therapeutic events that will be determined by theinteraction between patients and care providers (e.g., co-interventions, hospitalization length,treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes" –for outcome criteria that are assessed from data of the medical forms: the blinding procedureis adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data.	Yes/No/ Unsure
D	Were incomplete outcome data adequately addressed?		
	6.Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored.	Yes/No/ Unsure
	7. Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of non-compliance and co-interventions.	Yes/No/ Unsure
E	8. Are reports of the study free of suggestion of selective outcome reporting?	In order to receive a "yes," the review author determines if all the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/ Unsure
F	Other sources of potential bias:		
	9. Were the groups similar at baseline regarding the most important prognostic indicators?	In order to receive a "yes," the review author determines if all the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make his judgment.	Yes/No/ Unsure
	10. Were co-interventions avoided or similar?	This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.	Yes/No/ Unsure
	11. Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number, and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore, it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/ Unsure
	12. Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/ Unsure

Adapted and Modified: Furlan AD, Pennick V, Bombardier C, van Tulder Ml; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009; 34:1929-1941 (19)

Table 2. Cochrane Clinical relevance questions.

	Y(+)	N(-)	U(unclear)
A) Are the patients described in detail so that you can decide whether they are comparable to those that you see in your practice?			
B) Are the interventions and treatment settings described well enough so that you can provide the same for your patients?			
C) Were all clinically relevant outcomes measured and reported?			
D) Is the size of the effect clinically important?			
E) Are the likely treatment benefits worth the potential harms?			

Scoringadapted and modified from Staal JB, et al. Injection therapy for subacute and chronic low-back pain. Cochrane Database Syst Rev 2008; 3:CD001824 (20).

Table 3. Basic characteristics of included studies.

Study	Sample Size			Vertebral bodies		Gender	Mean age (year)			Follow-up		Follow-up rate (%)
	Group 1	Group 2	Total	Group 1	Group 2		Group 1	Group 2	*P* value	Group 1	Group 2	
Liang et al (31)	24	25	48	55	59	83.67%	70.4	72.4	0.21	31.8 mos.	35.2 mos.	100
Chen et al (32)	27	23	50	31	25	100%	68.37	69.34	0.534	24 mos.	24 mos.	86.21
Chen et al(33)	33	25	58	38	28	100%	67.73	68.52	0.376	2 weeks	2 mos.	100
Hyung et al(34)	24	28	52	NR	NR	94.23%	66.8	68.9	0.16	17.8 mos.	16.6 mos.	100

NR: not reported; Group 1: treatment group; Group 2: Control Group

was conducted using 3 levels of evidence: good, fair, and limited or poor.

At least 2 authors independently analyzed the evidence in an unblinded standardized way. Any disagreements were resolved by a third author and consensus among the reviewers. If there were any conflicts of interest (e.g., with authorship), those reviewers were dismissed from assessment and analysis.

2. Results

2.1 Study Characteristics

The search initially identified 185 potentially eligible publications. After manually screening the titles and abstracts and excluding duplicate reports, 15 studies were identified. Among the 15 publications, 2 case reports (10,11), 4 technical notes without a comparison group (12,31-33), and 4 biochemical studies in cadavers (15,16,34,35) were excluded from the analysis. Further examination of the full text resulted in the exclusion of 2 trials (36,37) for non-prospective design and one trial (38) for the lack of a bipedicular comparison group. The final analysis included 4 studies (39-42) (Fig. 1). Two of the items (40,41) had identical subjects but distinct follow-up periods. Since the 2 reports represented "short-term" vs. the "long-term" follow-up, they were only included in the short-term and long-term analysis but not in the overall analysis.

Demographic and follow-up information are shown in Table 4. The sample size of the 4 RCTs (39-42) is relatively small. All 4 RCTs had more women than men. Two articles by Chen et al (40-41) only included women. The unilateral and bilateral groups had similar age distribution (range: 65-70 years for both groups; $P > 0.05$). The follow-up was 2 weeks in one article (41) and ranged from 16.6 to 35.2 months for the remaining 3 studies. Preoperative radiographic and clinical data (Table 5) did not reveal a significant difference in T value of bone mineral density for 3 articles (40-42). The severity of pain was comparable among the 4 articles.

2.2 Methodological Quality Assessment

The risk of bias assessment is presented in Table 6. The randomization procedure is not adequate in any of the 4 articles. Three articles are rated to be with moderate quality and one has a high risk of substantial bias.

Industry funding and financial interest are shown in Table 6. With the exception of Chung et al (42), there was no industry funding and conflict of financial interest in the other 3 studies (39-42). In Chung's article, there was no information about conflicts of interest, either financially or with authorship. Together with the results of the clinical relevance assessment, the study by Chung et al (42) was deemed as the main cause of

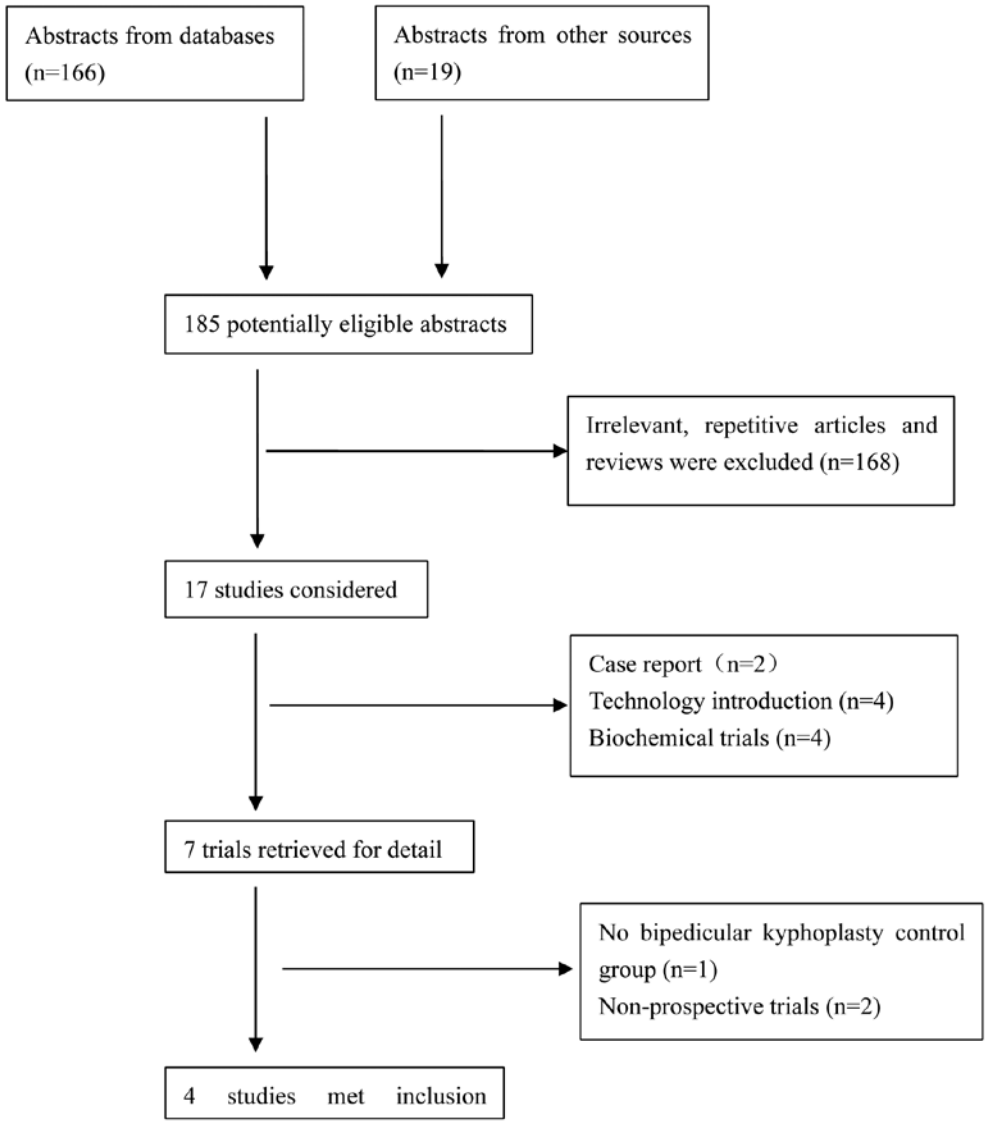

Fig. 1. Flow chart showing the stdy selection process.

the high risk of bias in this systematic review. Chung et al (42) was only used in the meta-analysis of long-term cement leakage rate and vertebral height loss, and not for pain relief. We used a sensitivity analysis to improve the validity of secondary outcomes by excluding this article from the meta-analysis.

2.3 Clinical Relevance

The clinical relevance of the included studies is presented in Table 7. With the exception of Chung et al (42), all articles reached the highest possible score in terms of clinical relevance. Main outcomes and secondary outcomes were recorded sufficiently in an off-standard way.

2.4 Meta-analysis

2.4.1 Surgery Time and Cement Dosage

The overall analysis revealed significantly shorter

Table 4. *Preoperative relevant measurements of patients.*

Study	Mean T value			Mean VAS			Mean kyphotic angle			Outcome relevant
	Group 1	Group II	*P* value	Group 1	Group II	*P* value	Group 1	Group II	*P* value	
Liang et al (31)	NR	NR	—	7.4	7.9	0.52	24.3	27.3	0.39	VAS SF-36 KA
Chen et al (32)	-3.05	-2.84	0.478	7.7	7.4	0.223	NR	NR	—	VAS ODI HLR
Chen et al (33)	-3.08	-2.89	0.473	7.8	7.4	0.164	NR	NR	—	VAS ODI HLR
Hyung et al (34)	-3.55	-3.64	0.89	8.1	7.9	0.54	17.6	18.5	0.37	VAS HLR

Group I: Treatment Group; Group II: Control Group
VAS= Visual Analogue Scale KA= Kyphotic Angle ODI= Oswestry Disability Index
HLR= Height Lost Rate SF-36= Short Form-36 Health Survey NR= Not reported

Table 5. *Preoperative relevant measurements of patients.*

Study	Mean T value			Mean VAS			Mean kyphotic angle			Outcome relevant
	Group 1	Group II	*P* value	Group 1	Group II	*P* value	Group 1	Group II	*P* value	
Liang et al (31)	NR	NR	—	7.4	7.9	0.52	24.3	27.3	0.39	VAS SF-36 KA
Chen et al (32)	-3.05	-2.84	0.478	7.7	7.4	0.223	NR	NR	—	VAS ODI HLR
Chen et al (33)	-3.08	-2.89	0.473	7.8	7.4	0.164	NR	NR	—	VAS ODI HLR
Hyung et al (34)	-3.55	-3.64	0.89	8.1	7.9	0.54	17.6	18.5	0.37	VAS HLR

Group I: Treatment Group; Group II: Control Group

Table 6. *Risk of bias assessment and conflicts of interest of included studies*

Study	Liang et al.(39)	Chen et al. (40)	Chen et al. (41)	Hyung et al. (42)
Randomization adequate	N	U	U	N
Concealed treatment allocation	U	N	N	N
Patient blinded	N	N	N	N
Care provider blinded	N	N	N	N
Outcome assess blinded	Y	Y	N	N
Drop-out rate described	N	Y	Y	N
All randomized participants analyzed in the group	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y
Groups similar at base line regarding most important prognostic indicators	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	U
Time of outcome assessment in all groups similar	Y	Y	Y	Y
Score	7/12	8/12	7/12	5/12
Level of quality or risk of bias	Moderate	Moderate	Moderate	Risk of bias
Industry funds	N	N	N	U
Financial interest	N	N	N	U

Y=yes; N=no; U=unsure

Table 7. *Clinical relevance of included studies*

Study	A)Patient description	B)Description of Intervention and treatment settings	C) Clinically relevant outcomes	D) Clinical importance	E)Benefits versus potential harms	Total criteria met
Liang et al.(31)	+	+	+	+	+	5/5
Chen et al.(32)	+	+	+	+	+	5/5
Chen et al.(33)	+	+	+	+	+	5/5
Hyung et al.(34)	+	+	-	+	+	4/5

+=positive; -=negative

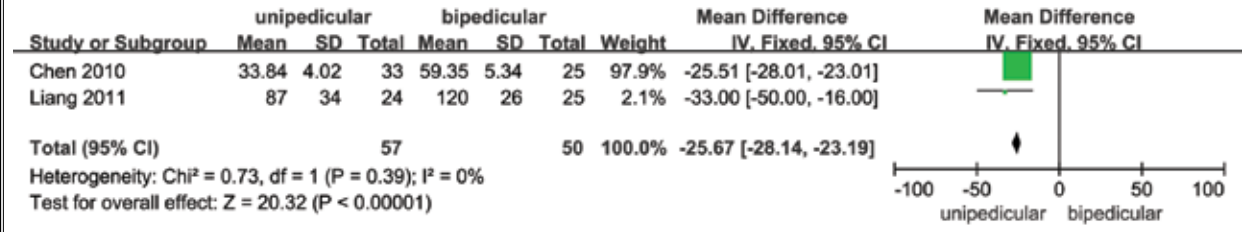

Fig. 2. Forest plot of surgery time.

Table 8. *Operative details of included studies*

Study	Mean time from injury to surgery			Surgery time (min)			Mean PMMA used in operations (ml)		
	Group 1	Group II	*P* value	Group 1	Group II	*P* value	Group 1	Group II	*P* value
Liang et al (31)	4.3 weeks	5.1 weeks	—	87	120	<0.05	3.9	5.5	<0.05
Chen et al (32)	10.11 mos	11.35 mos	0.131	34.12	57.33	<0.001	4.11	5.82	<0.001
Chen et al (33)	10.39 mos	11.04 mos	0.396	33.84	59.39	<0.001	NR	NR	—
Hyung et al (34)	3.44 weeks	3.68 weeks	—	NR	NR	—	3.44	6.43	<0.001

Group I: Treatment Group; Group II: Control Group ; PMMA= Polymethyl methacrylat; NR= Not reported

time for the unilateral approach (WMD = -25.67 vs. bilateral surgery, 95% CI = -28.14, -23.19, $P < 0.00001$) (Fig. 2), with no significant heterogeneity (I2 = 0%, = 0.39). Cement leakage could not be calculated without standard differences of the recorded dose even though the relevant data in each article is statistically significant (less cement for unilateral approach; $P < 0.05$ in 3 studies; Table 8).

2.4.2 Pain Relief

All 4 studies evaluated pain using the VAS after unilateral and bilateral kyphoplasty. The results seem to indicate that the duration of postoperative rehabilitation did not affect the degree of pain relief. The short-term analysis that included 2 studies (39,41) revealed no significant difference in pain relief between the 2 approaches (WMD = 0.12, 95% CI = -0.40, 0.63, $P = 0.65$) (Fig.3). Similar results were obtained in the long-term analysis (39,40) (WMD = 0.11, 95% CI = -0.44, 0.66, $P = 0.69$) (Fig.4). There was no significant heterogeneity (short-term: I2 = 0%, $P = 0.62$; long-term: I2 = 0%, $P = 0.61$).

2.4.3 Adjacent Vertebral Fracture

Two out of the 4 studies (a total of 99 patients) reported adjacent vertebral fracture during long-term follow-up (39,40). The analysis did not reveal a significant difference (7.84% for the unilateral approach and 8.33% for the bilateral approach). The relative risk ranged from 0.25 to 3.26, with no significant difference ($P = 0.88$). There was no significant difference in the long-term adjacent vertebral fracture rate in either study (Fig. 5) The result of heterogeneity test was not statistically significant (P = 0.22; I2 value of 34%), indicating that the pooling is valid.

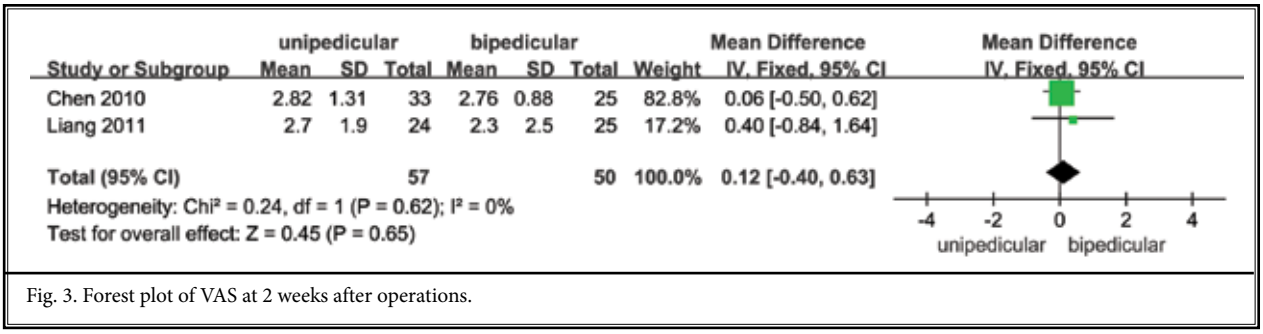

Fig. 3. Forest plot of VAS at 2 weeks after operations.

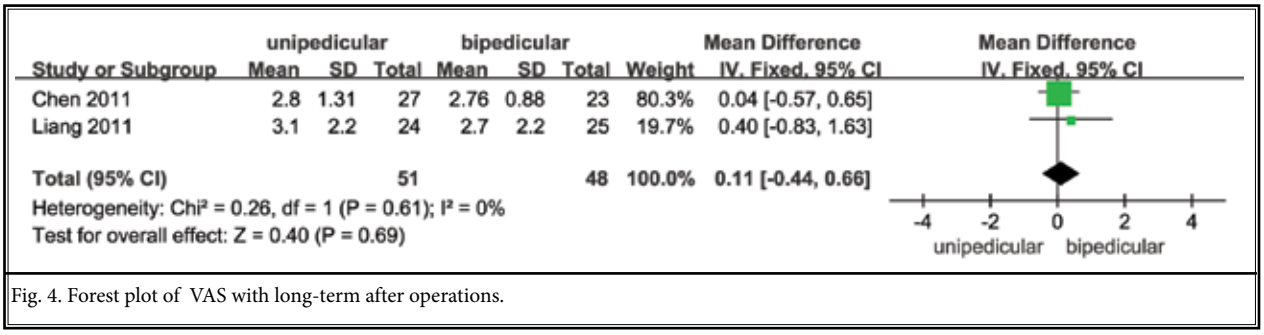

Fig. 4. Forest plot of VAS with long-term after operations.

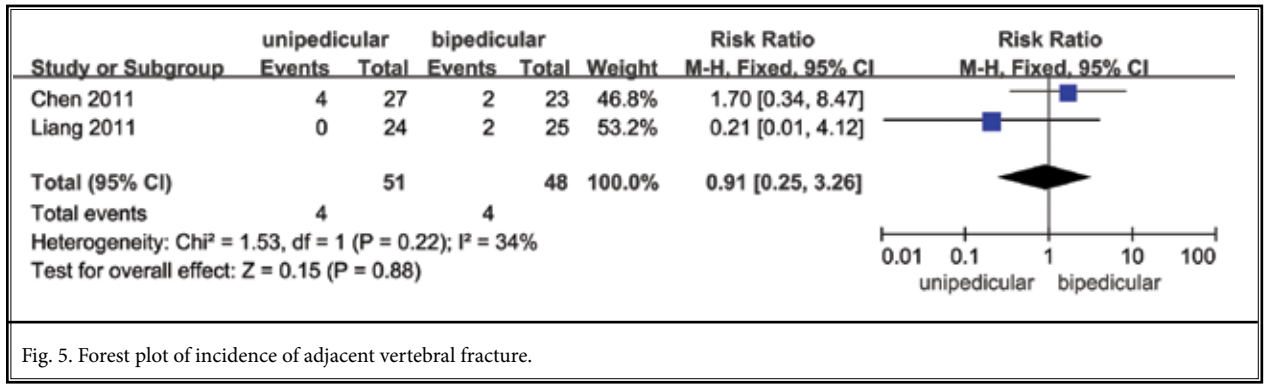

Fig. 5. Forest plot of incidence of adjacent vertebral fracture.

2.4.4 Cement Leakage

Cement leakage was reported in 3 studies (39,41,42), with a total 10 cases in 159 patients. The risk of cement leakage did not differ between the 2 approaches (7.41% in unilateral and 5.18% in bilateral; P = 0.56, RR = 1.39, 95% CI = 0.46-4.26) (Fig. 6). No apparent heterogeneity was found (I2 = 28%, P = 0.25).

2.4.5 Vertebral Height Loss

Vertebral height loss was reported in 2 articles (40,42), and calculated at the final follow-up as: (each time point vertebral height -restored vertebral height) / restored vertebral height. No severe reduction occurred in either group with a similar rate of height loss (Fig. 7). The Chung et al study (42) indicated a higher rate of vertebral height loss in the unilateral group in a 2-year follow-up (P = 0.0001 vs. bilateral). The heterogeneity test showed a P value of 0.08 and I2 value of 68%. An analysis using a random-effects model failed to reveal a statistically significant difference in vertebral height loss rate (P = 0.10, RR = 2.08, 95% CI = -0.39-4.54).

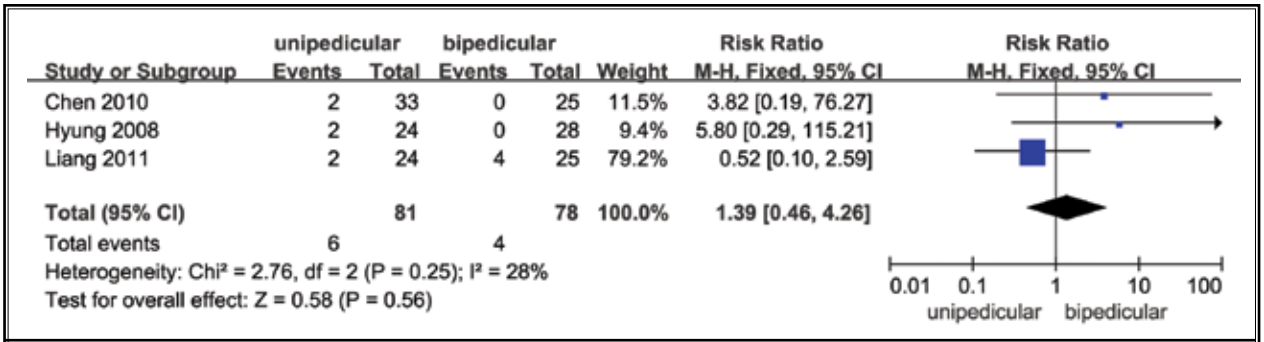

Fig. 6. Forest plot of rate of cement leakage.

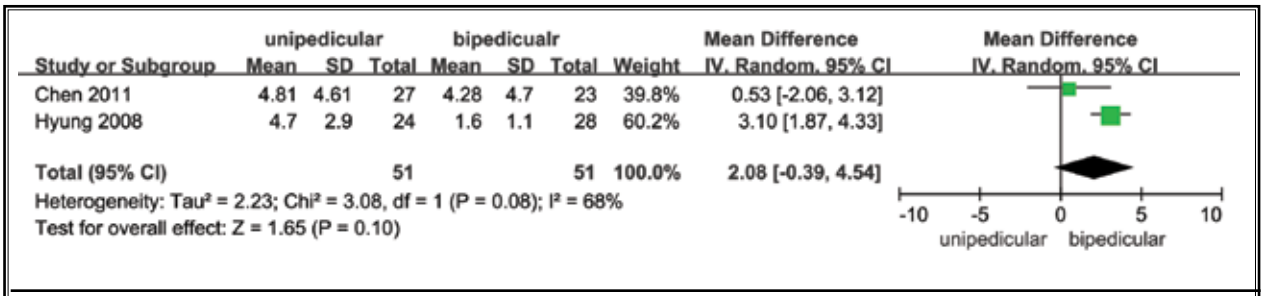

Fig. 7. Forest plot of the vertebral height loss rate.

2.4.6 Sensitivity Analysis

Sensitivity analysis by excluding the study of Chung et al (42) revealed a RR of cement leakage at 0.94 (95% CI = 0.26-3.42), with no significant difference from previously reported RR (RR = 1.39, 95% CI = 0.46-4.26). The results indicated no difference between unilateral and bilateral kyphoplasty in terms of cement leakage. The results also showed that the risk of bias caused by the study of Chung et al (42) does not affect the outcome of the meta-analysis of cement leakage. For vertebral height loss, a sensitivity analysis was not conducted since only 2 studies were included in the meta-analysis of vertebral height loss.

2.5 Publication Bias

The funnel plot of long-term vertebral height loss rate (Fig. 8) is asymmetrical, indicating the presence of significant publication bias. We speculate that the heterogeneity is due to the lack of blinding of vertebral height measurement and high bias risk of one included article (42). In addition, the small sample size tends to generate a larger difference and exaggerate the potential difference. As a result, we believe it is premature to conclude that unilateral kyphoplasty could achieve the same degree of loss of reduction as the bilateral kyphoplasty. More RCTs of larger sample sizes are necessary.

2.6 Analysis of Evidence and Validity

Based on the USPSTF criteria, the evidence is considered at 3 levels – good, fair, and limited or poor. Analysis of evidence and validity is limited since only 3 moderate quality studies were included and one of these had high risk of bias. In spite of this, assessments were attempted using standards commonly adopted by systematic reviews (24,25).

3. Discussion

Osteoporosis is caused by an imbalance between bone formation and resorption (43). A diagnosis is made when the bone mineral density (BMD) T-score is lower than -2.5 standard deviation (SD). All studies included in this study met the T-score criteria.

As the density of central cancellous bone mass decreases, mechanical load starts to be dispersed onto cortical bone, thus predisposing a person to increased

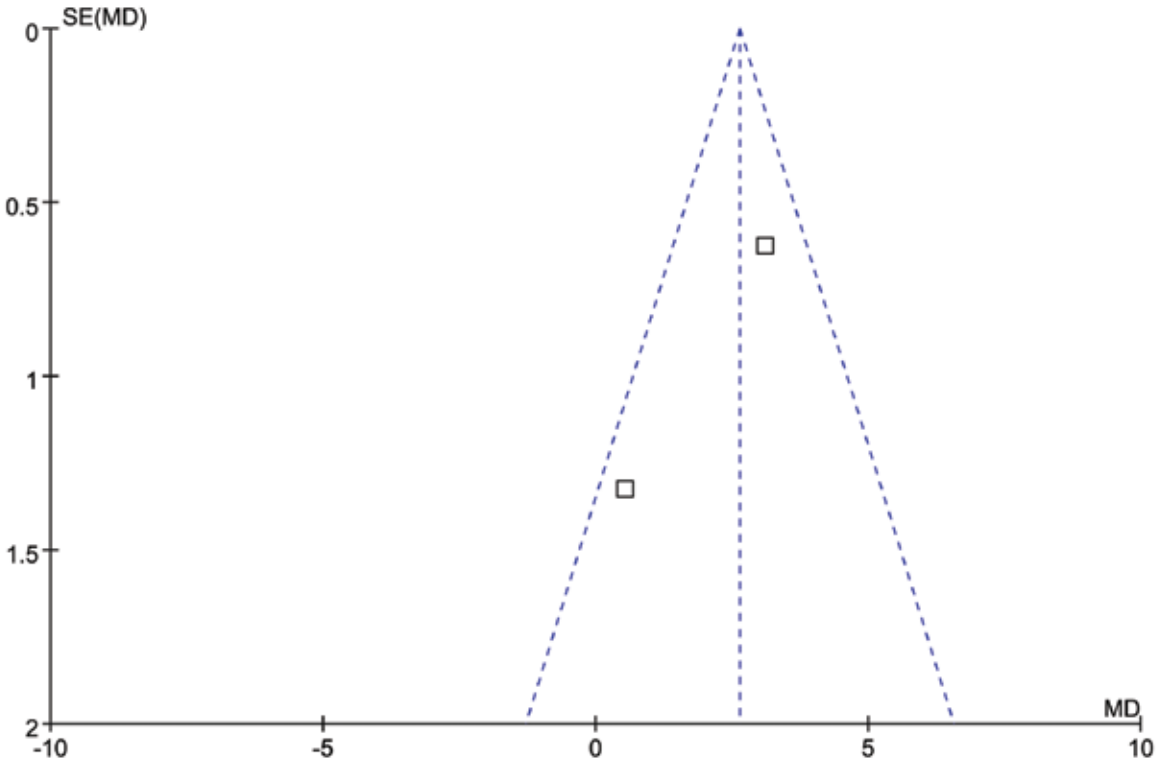

Fig. 8. Funnel plot on the vertebral height loss rate..

risk of fracture (44). OVCFs often occur in mid/low thoracic and high lumbar areas, and particularly in the thoracolumbar junction (45,46). Treatment should provide lasting symptom relief and restore the normal anatomy. Earlier studies (47,48) have demonstrated that kyphoplasty is an optimal treatment for OVCFs due to rapid pain relief and stabilization of the vertebral body.

All the studies included in the current study are RCTs. However, the description of randomization protocol is not sufficient in all 4 trials. Also, allocation concealment is poor in all 4 trials. In only 2 studies (39,40), were outcome assessments carried out by staffs who should be blinded to the information of patients. Blinding of the patients and surgeons was not carried out in any of studies. Three of the RCTs have moderate quality and one has a high risk of bias. Additional heterogeneity may be due to different surgical technologies, number and position of vertebra treated, gender difference, pre-surgical medical status, follow-up duration, differing vertebral height of osteoporotic compression fractures, and the duration between injury and surgery.

Theoretically, pain relief in the bilateral group should be more effective due to larger amount of cement and higher stability. However, our analysis did not reveal a significant difference between the 2 groups (39-42). Biochemical analysis in cadavers also failed to show statistical differences between unipedicular and bipedicular kyphoplasty on the restoration of fractured vertebra (15,49). However, a previous clinical study of balloon kyphoplasty showed that the pain relief is not always positively correlated with the restoration of height and amount of PMMA (50).

Excessive cement is a substantial risk factor for complications in kyphoplasty, such as adjacent vertebral fracture and cement leakage. Our analysis clearly indicated that more cement is used in the bilateral group. However, we failed to observe an increased incidence of adjacent-level vertebral fracture and cement leakage in bilateral kyphoplasty.

Cement leakage did not differ between the 2 groups. Also, cement leakage apparently did not result in severe clinical consequences in any of the cases: no

patient with cement leaksge developed neurologic symptoms. This finding is confounded by substantial assessment bias. Heini et al (51) reported an increased rate of cement leakage using CT as compared to standard x-ray imaging. Additionally, different radiologists may have used different criteria for the diagonsis in the included studies.

Liebschner et al (52) demonstrated that greater filling results in a substantial increase in stiffness beyond the maximum of intact level using a finite-element model of elderly L1 vertebral body. Injected cement transfers a proportion of the load through the central augmented trabeculae structure and alters the load distribution onto the adjacent-level. In addition to the pressure of daily life produced by excess motion, the stiffening of the treated vertebra could put adjacent vertebrae at higher risk of subsequent fracture or degenerative change. The Liebschner et al (52) study indicated that filling 15% of the vertebral body is sufficient for restoration to the same stiffness of pre-fractured level. The key point for cement injection is symmetrical dispersion on the 2 sides of the mid-line of vertebra, and not the dose. Berlemann et al (53) suggested that the stiffness restoration of fracture level could decrease the maximum load of adjacent level to 70%. Belkoff et al (54) believed that 2 mL of PMMA cement is sufficient to restore the strength of a compression vertebral body. For stiffness of vertebral bodies at thoracic and lumbar vertebra, 4 mL and 6 mL are sufficient. The distribution of cement in the vertebral body is an important factor related to postoperative re-fractures (34). Bipedicular kyphoplasty creates uniform stiffness across the 2 sides of the vertebra, whereas unipedicular kyphoplasty creates a biomechanical balance (34). But after adjusting the distribution of cement across the mid-line, there is no statistical difference in vertebral height and restoration between the unilateral vs. bilateral approaches (15).

Chung et al (42) showed that bilateral kyphoplasty has an advantage in the reduction of kyphosis and the loss of reduction in comparison to unilateral approach. Another study (39), however, failed to show a difference between the 2 approaches. When we combined the results of height loss rate in the 2 studies, no statistically significant difference was found, but the I2 value at 68% suggested a high risk of bias. The height loss rate is similar in the unilateral and bilateral groups at 6 months and 2 years after surgery (42). Importantly, pain relief did not differ between the 2 groups in either short-term or long-term follow-up as shown in this meta-analysis (Figs. 3 and 4).

The instruments used in and procedural consideration for unilateral vs. bilateral kyphoplasty are identical. The amount of cement is a major difference. Unilateral kyphoplasty is increasingly used. The advantages and potential drawbacks of the unilateral approach need to be investigated due to a lack of information from studies of large sample size and long-term follow-up and number of patients. The current study showed similar results in pain relief as well as incidence of major complications. The relative value unit (RVU) did not differ between 2 approaches.

In summary, the appropriate amount and proper distribution of cement are necessary for optimal treatment efficacy and minimizing the side effects. With sufficient surgical training, surgeons could achieve the same biochemical property and clinical effects by using unilateral kyphoplasty. For elderly patients with severe osteoporosis but with a moderate degree of vertebral compression fracture and pain, unilateral kyphoplasty is more appropriate. Risks associated with anesthesia, operation time, and cost would also be reduced. For patients with acute pain and severe vertebral height loss, with relatively healthy bone mineral density, bilateral kyphoplasty should be considered.

4. Limitations

Only 4 studies of relatively small sample size were included. Also, publication bias was apparent. The quality of 3 out of the 4 included studies was moderate and one study has a high risk of bias. As a result, the conclusion should be interpreted with care. More high-quality RCTs with long-term follow-up that address both efficacy and complications are needed.

5. Conclusion

Unilateral and bilateral kyphoplasty are both efficacious and safe for OVCFs. The 2 approaches are practically equal in short-term and long-term pain relief. Incidence of complications also did not differ significantly between the 2 approaches. Selections of unilateral versus bilateral kyphoplasty should be based on the overall assessment of the fracture severity, bone density, and the general condition of the patient.

References

1. Jun Z, Xin M, Xuesong Z, Qin S, Huilin Y. The long-term incidence of subsequent vertebral body fracture after vertebral augmentation therapy: A systemic review and meta-analysis. *Pain Physician* 2012; 15:515-522.
2. Fritzell P, Ohlin A, Borgström F. Cost-effectiveness of balloon kyphoplasty versus standard medical treatment in patients with osteoporotic vertebral compression fracture: A Swedish multicenter randomized controlled trial with 2-year follow-up. *Spine* 2011; 36:2243-2251.
3. Yan D, Duan L, Li J, Soo C, Zhu H, Zhang Z. Comparative study of percutaneous vertebroplasty and kyphoplasty in the treatment of osteoporotic vertebral compression fractures. *Arch Orthop Trauma Surg* 2011; 131:645-650.
4. Lim BG, Lee JY, Lee MK, Lee DK, Kim JS, Choi SS. Kyphoplasty for the treatment of vertebral compression fractures in a cancer patient with neurological deficits and anterior vertebral wall destruction. *Pain Physician* 2011; 14:539-544.
5. Goz V, Koehler SM, Egorova NN, Moskowitz AJ, Guillerme SA, Hecht AC, Qureshi SA. Kyphoplasty and vertebroplasty: Trends in use in ambulatory and inpatient settings. *Spine J* 2011; 11:737-744.
6. Wardlaw D, Cummings SR, Van Meirhaeghe J, Bastian L, Tillman JB, Ranstam J, Eastell R, Shabe P, Talmadge K, Boonen S. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture: A randomized controlled trial. *Lancet* 2009; 373:1016-1024.
7. McGirt MJ, Parker SL, Wolinsky JP, Witham TF, Bydon A, Gokaslan ZL. Vertebroplasty and kyphoplasty for the treatment of vertebral compression fractures: An evidenced-based review of the literature. *Spine J* 2009; 9:501-508.
8. Garfin SR, Buckly RA, Ledlie J. Balloon kyphoplasty for symptomatic vertebral body compression fractures results in rapid, significant, and sustained improvements in back pain, function, and quality of life for elderly patients. *Spine* 2006; 31:2213-2220.
9. Yohan R, Christoph EH, Peter F, Claes O. Kyphoplasty in osteoporotic vertebral compression fractures - guidelines and technical considerations. *J Orthop Surg Res* 2011; 6:43.
10. Hu MM, Eskey CJ, Tong SC, Nogueira RG, Pomerantz SR, Rabinov JD, Pryor JC, Hirsch JA. Kyphoplasty for vertebral compression fracture via a uni-pedicular approach. *Pain Physician* 2005; 8:363-367.
11. Hoh BL, Rabinov JD, Pryor JC, Hirsch JA. Balloon kyphoplasty for vertebral compression fracture using a unilateral balloon tamp via a uni-pedicular approach: Technical note. *Pain Physician* 2004; 7:111-114.
12. Papadopoulos EC, Edobor-Osula F, Gardner MJ, Shindle MK, Lane JM. Unipedicular balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures: Early results. *J Spinal Disord Tech* 2008; 21:589-596.
13. Lee SB, Cho KS, Huh PW, Yoo DS, Kang SG, Kim DS, Park CK. Clinical and radiographic results of unilateral transpedicular balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures. *Acta Neurochir Suppl* 2008; 101:157-160.
14. Mudano AS, Bian J, Cope JU, Curtis JR, Gross TP, Allison JJ, Kim Y, Briggs D, Melton ME, Xi J, Saag KG. Vertebroplasty and kyphoplasty are associated with an increased risk of secondary vertebral compression fractures: A population-based cohort study. *Osteoporos Int* 2009; 20:819-826.
15. Steinmann J, Tingey CT, Gruz G, Dai Q. Biomechanical comparison of unipedicular versus bipedicular kyphoplasty. *Spine* 2005; 30:201-205.
16. Tohmeh AG, Mathis JM, Fenton DC, Levine AM, Belkoff SM. Biomechanical efficacy of unipedicular versus bipedicular vertebroplasty for the management of osteoporotic compression fractures. *Spine* 1999; 24:1772-1776.
17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ* 2009; 339:2535.
18. Bero L, Rennie D. The Cochrane Collaboration. Preparing, maintaining, and disseminating systematic reviews of the effects of health care. *JAMA* 1995; 274: 1935-1938.
19. Furlan AD, Pennick V, Bombardier C, van Tulder M; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 2009; 34:1929-1941.
20. Staal JB, de Bie R, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low-back pain. *Cochrane Database Syst Rev* 2008; 3:CD001824.
21. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2.* The Cochrane Collaboration, 2009.
22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629-634.
23. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D. Methods Work Group, Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force. *Am J Prevent Med* 2001; 20:21-35.
24. Benyamin RM, Manchikanti L, Parr AT, Diwan S, Singh V, Falco FJ, Datta S, Abdi S, Hirsch JA. The effectiveness of lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain. *Pain Physician* 2012; 15:E363-404.
25. Helm I S, Benyamin RM, Chopra P, Deer TR, Justiz R. Percutaneous adhesiolysis in the management of chronic low back pain in post lumbar surgery syndrome and spinal stenosis: A systematic review. *Pain Physician* 2012; 15:E435-462.
26. Benyamin RM, Wang VC, Vallejo R, Singh V, Helm Ii S. A systematic evaluation of thoracic interlaminar epidural injections. *Pain Physician* 2012; 15:E497-514.
27. Simopoulos TT, Manchikanti L, Singh V, Gupta S, Hameed H, Diwan S, Cohen SP. A systematic evaluation of prevalence and diagnostic accuracy of sacroiliac joint interventions. *Pain Physician* 2012; 15:E305-E344.
28. Falco FJE, Manchikanti L, Datta S, Sehgal N, Geffert S, Onyewu O, Singh V, Bryce DA, Benyamin RM, Simopoulos TT, Vallejo R, Gupta S, Ward SP, Hirsch JA. An update of systematic assessment of diagnostic accuracy of lumbar facet joint nerve blocks. *Pain Physician* 2012; 15:E869-E908.
29. Singh V, Manchikanti L, Onyewu O, Benyamin RM, Datta S, Geffert S, Parr AT, Falco FJE. An update of appraisal of accuracy of thoracic discography as a diagnostic test for chronic spinal pain. *Pain Physician* 2012; 15:E757-E775.
30. Atluri S, Singh V, Datta S, Geffert S, Sehgal N, Falco FJE. Diagnostic accuracy of thoracic facet joint nerve blocks: An update of the assessment of evidence. *Pain Physician* 2012; 15:E483-E496.

31. Ryu KS, Park CK, Kim MK, Kim DH. Single balloon kyphoplasty using far-lateral extrapedicular approach: Technical note and preliminary results. *J Spinal Disord Tech* 2007; 20:392-398.
32. Ryu KS, Huh HY, Jun SC, Park CK. Single-balloon kyphoplasty in osteoporotic vertebral compression fractures: Far-lateral extrapedicular approach. *J Korean Neurosurg Soc* 2009; 45:122-126.
33. Lee SB, Cho KS, Huh PW, Yoo DS, Kang SG, Kim DS, Park CK. Clinical and radiographic results of unilateral transpedicular balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures. *Acta Neurochir Suppl* 2008; 101:157-160.
34. Chen B, Li Y, Xie D, Yang X, Zheng Z. Comparison of unipedicular and bipedicular kyphoplasty on the stiffness and biomechanical balance of compression fractured vertebrae. *Eur Spine J* 2011; 20:1272-1280.
35. Higgins KB, Harten RD, Langrana NA, Reiter MF. Biomechanical effects of unipedicular vertebroplasty on intact vertebrae. *Spine* 2003; 28:1540-1547.
36. Song BK, Eun JP, Oh YM. Clinical and radiological comparison of unipedicular versus bipedicular balloon kyphoplasty for the treatment of vertebral compression fractures. *Osteoporos Int* 2009; 20:1717-1723.
37. Wang Z, Wang G, Yang H. Comparison of unilateral versus bilateral balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures. *Journal of Clinical Neuroscience* 2012; 19:723-726.
38. Endres S, Badura A. Shield kyphoplasty through a unipedicular approach compared to vertebroplasty and balloon kyphoplasty in osteoporotic thoracolumbar fracture: A prospective randomized study. *Orthop Traumatol Surg Res* 2012; 98:334-340.
39. Chen L, Yang H, Tang T. Unilateral versus bilateral balloon kyphoplasty for multilevel osteoporotic vertebral compression fractures. *Spine* 2011; 36:534-540.
40. Chen C, Wei H, Zhang W, Gu Y, Tang G, Dong R, Xu Y, Chen L. Comparative study of kyphoplasty for chronic painful osteoporotic vertebral compression fractures via unipedicular versus bipedicular approach. *J Spinal Disord Tech* 2011; 24:62-65.
41. Chen C, Chen L, Gu Y, Xu Y, Liu Y, Bai X, Zhu X, Yang H. Kyphoplasty for chronic painful osteoporotic vertebral compression fractures via unipedicular versus bipedicular approachment: A comparative study in early stage. *Injury* 2010; 41:356-359.
42. Chung HJ, Chung KJ, Yoon HS, Kwon IH. Comparative study of balloon kyphoplasty with unilateral versus bilateral approach in osteoporotic vertebral compression fractures. *International Orthopaedics* 2008; 32:817-820.
43. Burston B, McNally DS, Nicholson HD. Determination of a standard site for the measurement of bone mineral density of the human calcaneus. *J Anat* 1998; 193:449-456.
44. Kayanja MM, Ferrara LA, Lieberman IH. Distribution of anterior cortical shear strain after a thoracic wedge compression fracture. *Spine J* 2004; 4:76-87.
45. Lee YL, Yip KM. The osteoporotic spine. *Clin Orthop Relat Res* 1996; 323:91-97.
46. Ledlie JT, Renfro M. Balloon kyphoplasty: One-year outcomes in vertebral body height restoration, chronic pain and activity levels. *J Neurosurg Spine* 2003; 98:36-42.
47. Lieberman IH, Dudeney S, Reinhardt MK, Bell G. Initial outcome and efficacy of "kyphoplasty" in the treatment of painful osteoporotic vertebral compression fractures. *Spine* 2001; 26:1631-1638.
48. Garfin SR, Yuan HA, Reiley MA. New technologies in spine: Kyphoplasty and vertebroplasty for the treatment of painful osteoporotic compression fractures. *Spine* 2001; 26:1511-1515.
49. Silverman SL. The clinical consequences of vertebral compression fracture. *Bone* 1992; 13:27-31.
50. Kasperk C, Hillmeier J, Nöldge G, Grafe IA, Dafonseca K, Raupp D, Bardenheuer H, Libicher M, Liegibel UM, Sommer U, Hilscher U, Pyerin W, Vetter M, Meinzer HP, Meeder PJ, Taylor RS, Nawroth P. Treatment of painful vertebral fractures by kyphoplasty in patients with primary osteoporosis: A prospective nonrandomized controlled study. *J Bone Miner Res* 2005; 20:604-612.
51. Heini PF, Walchli B, Berlemann U. Percutaneous transpedicular vertebroplasty with PMMA: Operative technique and early results. A prospective study for the treatment of osteoporotic compression fractures. *Eur Spine J* 2000; 9:445-450.
52. Liebschner MA, Rosenberg WS, Keaveny TM. Effects of bone cement volume and distribution on vertebral stiffness after vertebroplasty. *Spine* 2001; 26:1547-1554.
53. Berlemann U, Ferguson SJ, Nolte LP, Heini PF. Adjacent vertebral failure after vertebroplasty. A biomechanical investigation. *J Bone Joint Surg Br* 2002; 84:748-752.
54. Belkoff SM, Mathis JM, Jasper LE, Deramond H. The biomechanics of vertebroplasty. The effect of cement volume on mechanical behavior. *Spine* 2001; 26:1537-1541.