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Systematic Review and Meta-analysis

rhBMP in lumber fusion for lumbar spondylolisthesis: A systematic review and meta-analysis

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ABSTRACT

Purpose: To compare the efficacy and safety of recombinant human bone morphogenetic protein (rhBMP) and iliac crest autograft in the fusion treatment of lumbar spondylolisthesis.
Methods: The studies using randomized controlled trials to compare the rhBMP with iliac crest autograft in the treatment of lumbar spondylolisthesis were retrieved from Embase, Pubmed, ProQuest dissertations & theses (PQDT), China national knowledge infrastructure (CNKI), Chinese Biomedical Database, Wanfang Data, Cochrane Library (from March 1998 to March 2018). Postoperative fusion rate, clinical success rate, postoperative intervertebral height, complications, operation time, blood loss and duration of hospitalization were chosen as the outcome indicators. Methodological quality of the trials was critically assessed, and relevant data were extracted. Statistical software Revman 5.3 was used for data-analysis.
Results: Eleven articles were included in the meta-analysis. The results showed that, comparing the efficacy of rhBMP with iliac crest autograft, statistical significance was found in the 24-month fusion rate post operation [95% *CI* (1.38, 24.70), $p = 0.02$] and operation time [95% *CI* (−14.22, −2.08), $p = 0.008$]. There is not sufficient evidence for statistical differences in the remaining indicators.
Conclusion: The current literature shows rhBMP is a safe and effective grafting material in the treatment of lumbar spondylolisthesis. Further evidence is dependent on the emergence of more randomized controlled trials with higher quality and larger sample sizes in the future.

Introduction

Lumbar spondyloisthesis is the luxation or subluxation of one vertebra relative to an adjacent vertebra associated with trauma and regression.[1] The incidence of lumbar spondyloisthesis is 4.7–5% in chinese patients.[2] Post-traumatic lumbar spondylolisthesis is when the violence is directly or indirectly transmitted to the lumbar spine, causing lumbar spine attachments such as pedicles, facet joints, isthmus and other bony structures fracture, resulting in vertebral body slip.[3,4] However, degenerative lumbar spondylolisthesis is the most common type of clinical. Due to long-term sustained lumbar instability, the small joints of the corresponding sports segments are worn and degenerated, and the upper vertebral body gradually moves forward. With the increase of age and the accumulation of fatigue damage, lumbar facet joints, peripheral ligaments and intervertebral disc degeneration gradually increase, coupled with the influence of osteoporosis, and then lumbar spondylolisthesis.[5] Lumbar spondyloisthesis shows no clinical feature in the early stage, with the development of disease, late stage patients could lead to lower limb radiates numbness and intermittent claudication.[6] Posterior lumbar interbody fusion (PLIF) with the use of bone grafts is the most common surgery used to treat a variety of degenerative spinal disorders.[7,8] However, controversy still remains in the use of recombinant human bone morphogenetic protein (rhBMP) and autograft. The aim of the present study was to perform a meta-analysis including all the clinical review articles in the last 20 years to determine whether

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#1 randomized controlled trial
#2 controlled clinical trial
#3 randomized
#4 randomly
#5 trial
#6 groups
#7 OR/#1~#6
#8 Lumbar spondyloisthesis
#9 Autologous bone
#10 AND/#8~#9
#11 OP-1
#12 BMP
#13 #10 AND (#11 OR #12)
#14 #7 AND #13

Fig. 1. Pubmed search strategy.

there were any significant differences in the use of iliac crest autograft vs. rhBMP.

Methods

Search strategy

We searched clinical control trials (CCTs) including randomized controlled trial (RCT) and retrospective case study that compared rhBMP with iliac crest autograft in the treatment of lumbar spondylolisthesis from Embase, Pubmed, ProQuest dissertations & theses (PQDT), China national knowledge infrastructure (CNKI), Chinese Biomedical Database, Wanfang Data, Cochrane Library (from March of 1998–2018). The searched key words were: lumbar spondyloisthesis, osteogenic protein-1 (OP-1), bone morphogenetic protein (BMP), iliac crest autograft, reference lists of relevant studies were hand-searched (Fig. 1). Searches were performed by two reviewers, and the third one was consulted when there was uncertainty reference.

Inclusion criteria

Inclusion criteria for the analysis were (1) articles published after March 1998; (2) Randomized controlled trials (RCTs), prospective studies, retrospective studies, and cohort studies; (3) patients >18 years old and diagnosed with adult lumber spondylolisthesis; (4) patients received lumbar spinal fusion for the treatment of lumber spondylolisthesis; (5) reporting of short- and long-term outcomes, study compared results of rhBMP and iliac crest autograft.

Exclusion criteria

The exclusion criteria were: (1) case report or series; (2) meta-analysis, biomechanical or kinematic studies, review articles, or in vitro studies; (3) study with patient overlap from other qualifying studies or animal studies; (4) patients <18 years old or

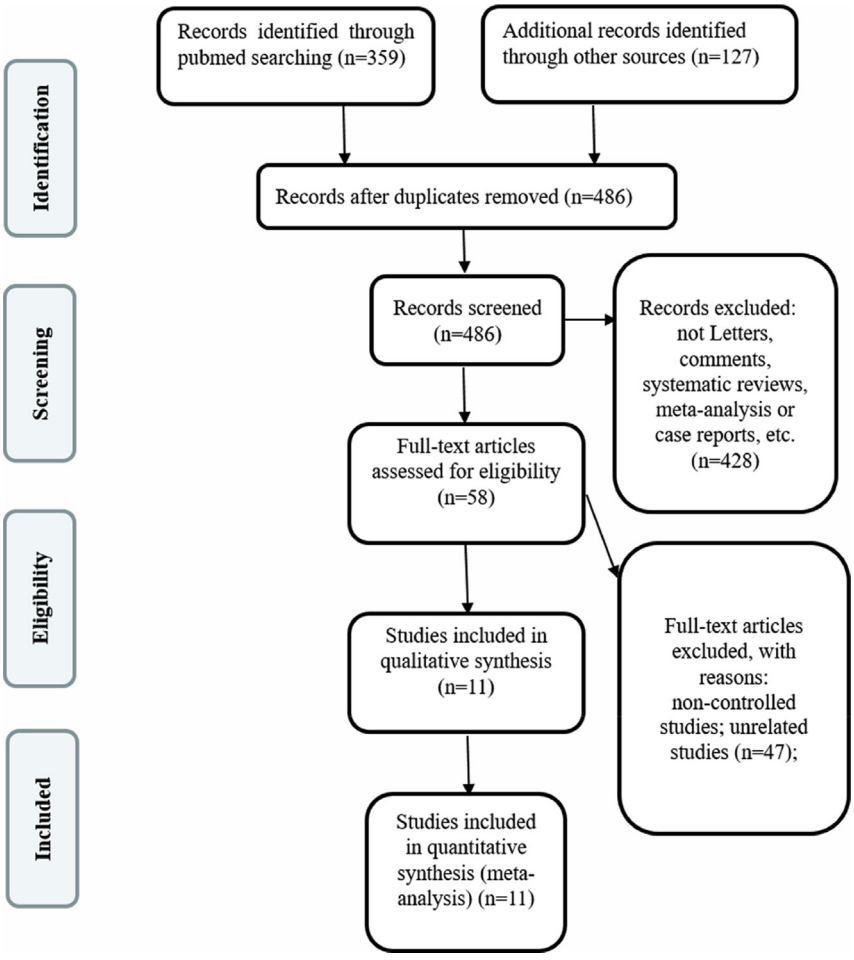

Fig. 2. Flow diagram of the study selection process.

Table 1
General data of the included studies.

Study (year)	Study design	Material	Case No.	Age (years)	Gender (Male/Female)	Months of disease	Outcomes	Follow-up (months)
Lin et al.[9] (2016)	RCT	BMP	32	52.04 ± 17.26	15/17	44.76 ± 18.12	(1) (3) (4)	18
		AB[a]	32	51.26 ± 17.81	17/15	44.52 ± 19.08	(5) (6) (7)	
Delawi et al.[10] (2016)	RCT	BMP	60	54 ± 14	27/33	–	(1) (2) (4)	12
		AB[a]	59	55 ± 13	25/34		(5) (6) (7)	
Yuan et al.[11] (2013)	Retrospective	BMP	38	50.46 ± 14.88	20/18	42.51 ± 17.34	(1) (2)	24
		AB[a]	40	51.26 ± 15.53	19/21	42.75 ± 17.48	(3) (4)	
Fu et al.[12] (2012)	Retrospective	BMP	31	49.23 ± 15.68	–	42.72 ± 111	(1) (2)	24
		AB[a]	31					
Taghavi et al.[13] (2010)	Retrospective	BMP	24	57.3 ± 11.6	11/13	–	(1) (4)	24
		AB[a]	20	55.8 ± 13.2	11/9			
Vaccaro et al.[14] (2008)	RCT	BMP	24	63 (43–80)	13/11	–	(1) (2) (4)	48
		AB[a]	12	67 (51–79)	7/5			
Xiao et al.[15] (2007)	Retrospective	BMP	36	43 (33–58)	14/22	15–180	(1) (2) (3)	12
		AB[a]	42	43 (32–61)	18/24	96–180	(4) (5) (6)	
Kanayama et al.[16] (2006)	RCT	BMP	9	70.3 ± 8.0	5/4	–	(1)	12
		AB[a]	10	58.7 ± 9.0	6/4	–		
Vaccaro et al.[17] (2005)	RCT	BMP	24	63 (43–80)	13/11	–	(1) (2)	24
		AB[a]	12	66 (51–79)	7/5	–	(4) (5)	
Vaccaro et al.[18] (2004)	RCT	BMP	24	63 ± 11.0	13/11	–	(1) (2)	12
		AB[a]	12	66 ± 7.0	7/5	–		
Johnsson et al.[19] (2002)	RCT	BMP	10	42 (23–57)	8/12	–	(1) (4)	12
		AB[a]	10			–		

Outcomes: (1) Postoperative fusion rate; (2) Clinical success rate; (3) postoperative intervertebral height; (4) Complications; (5) Operation time; (6) Blood loss; (7) Length of Length of hospital stay.
[a] AB: iliac crest autograft; BMP: bone morphogenetic protein; RCT: randomized controlled trial.

inclusion of patients with spinal deformities, tumors, or infections; (5) study objective or intervention measures failed to meet the inclusion criteria; (6) original documents of experimental design being not precise; (7) no non-rhBMP control group or studied with incomplete data.

Data extraction and quality assessment

Inclusion decisions were made independently by two reviewers participated according to the pre-stated eligible criteria. Disagreement between the two reviewers was resolved by discussion or consulting to a third reviewer if necessary. The risk-of-bias assessment tool outlined in Cochrane Handbook was used to measure the methodological quality of RCTs. Six domains are evaluated: random sequence generation, allocation concealment, blinding of patients and personal, blinding of outcome assessment, incomplete outcome data, and selective reporting risk. The modified Jadad scale was used to assess the quality of cohort studies. Relevant data were recorded in this analysis, including: first author's name, published year, sample size of rhBMP and iliac crest autograft in the treatment of lumbar spondylolisthesis, duration of follow-up, postoperative fusion rate, clinical success rate, postoperative intervertebral height, complications, operation time, blood loss and duration of hospitalization.

Statistical analysis

Data was independently entered into Revman 5.3 software by two reviewers. Dichotomous outcomes were expressed in terms of odds ratio (OR) and the weighted mean difference (WMD) was used for continuous outcomes, both with 95% confidence intervals (95% *CI*). Heterogeneity was tested using both the chi-square test and I^2 test. A fixed-effects model was chosen when there was no statistical evidence of heterogeneity ($I^2 < 50\%$) and random-effects model was adopted if significant heterogeneity was found. If the heterogeneity was found, we checked the study population, treatment, outcome and methodologies to determine the source of heterogeneity. If it could not be quantitatively synthesized or the event rate was too low to measure, we used qualitative evaluation. A funnel plot was applied to assess the presence of publication bias.

Results

A total of 486 potentially relevant articles were identified. After screening all the titles and abstracts, 428 studies were excluded. After reading all the full-text of 58 studies, 11 studies including 565 patients met all the inclusion criteria were found (Fig. 2). Quality was assessed by modified Jadad scale. The total score is 7 points. Above 4 is considered as high quality paper, and below 3 is

Table 2
Types of lumbar spondylolisthesis, rhBMP and surgical methods.

Study (year)	Lumbar spondylolisthesis	rhBMP type	Surgical methods
Lin et al.[9] (2016)	–	rhBMP combined with local bone	–
Delawi et al.[10] (2016)	Degenerative/Isthmic spondylolisthesis	rhBMP-7 combined with local bone	Single-level fusion
Yuan et al.[11] (2013)	–	rhBMP combined with local bone	–
Fu et al.[12] (2012)	Degenerative/Post-traumatic spondylolisthesis	rhBMP combined with local bone	–
Taghavi et al.[13] (2010)	–	rhBMP-2 putty	Single/multi-level fusion
Vaccaro et al.[14] (2008)	Degenerative spondylolisthesis	rhBMP-7 putty	Single-level fusion
Xiao et al.[15] (2007)	–	rhBMP combined with local bone	Single-level fusion
Kanayama et al.[16] (2006)	Degenerative spondylolisthesis	rhBMP-7 putty	Single-level fusion
Vaccaro et al.[17] (2005)	Degenerative spondylolisthesis	rhBMP-7 putty	Single-level fusion
Vaccaro et al.[18] (2004)	Degenerative spondylolisthesis	rhBMP-7 putty	Single-level fusion
Johnsson et al.[19] (2002)	–	rhBMP-7 putty	Single-level fusion

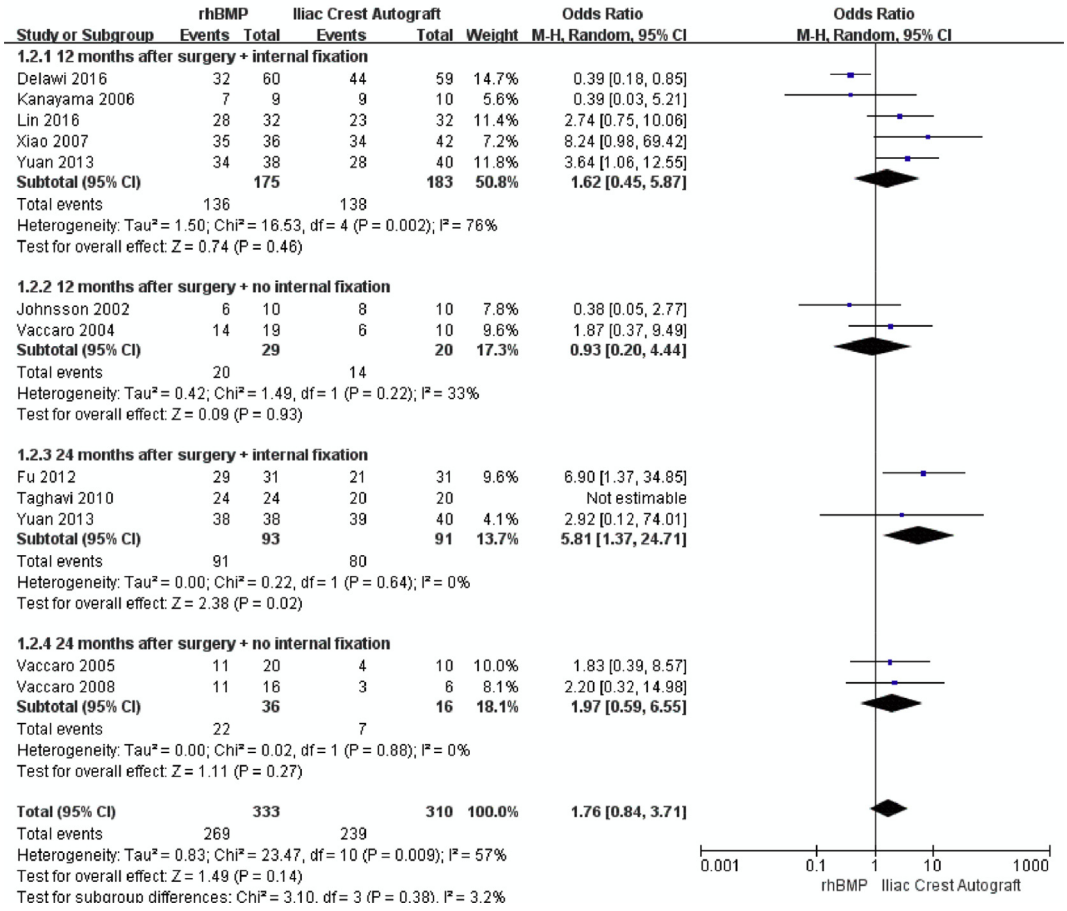

Fig. 3. Forest plot to assess rate of postoperative fusion between two materials.

regarded as medium quality paper. Among them, there were 8 high quality papers and 3 medium quality papers (Tables 1 and 2).

Postoperative fusion rate

In the eleven trials included, the follow-up of lumbar fusion rate was performed at 12 months/24 months after surgery and the use of internal fixation was split into 4 subgroups for comparison. Because the results of studies were heterogeneous (I^2 = 57%, $p < 0.05$). Therefore, a random effect model was used for meta-analysis. The results showed that there was a statistically significant difference in lumbar fusion rate in the subgroup of internal fixation at 24 months postoperatively [95% *CI* (1.37, 24.71), $p = 0.02$]. Total fusion rate [95% *CI* (0.84, 3.71), $p = 0.14$] were not statistically significant (Fig. 3).

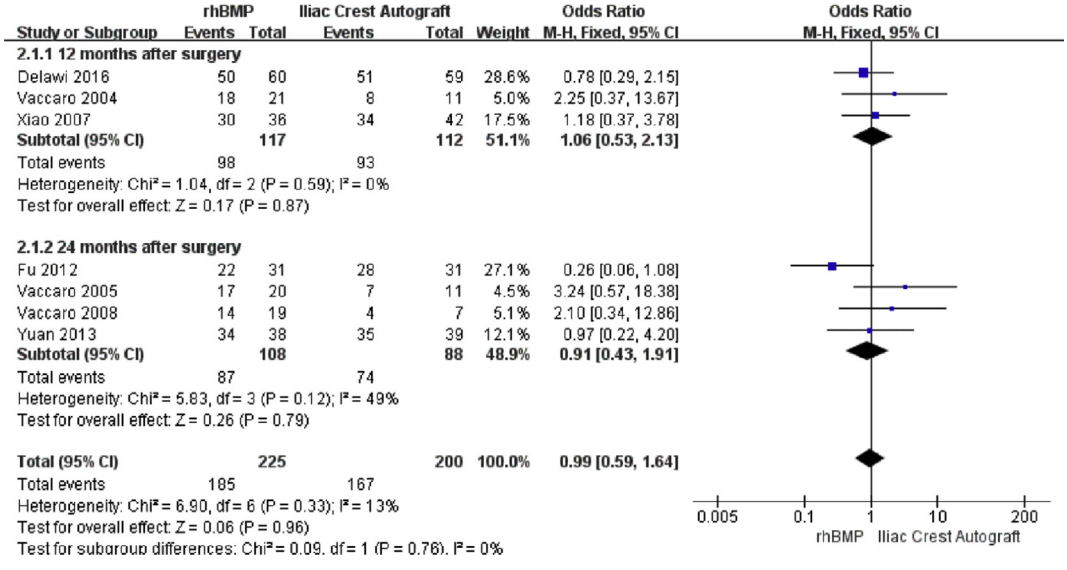

Fig. 4. Forest plot to assess clinical success between two materials.

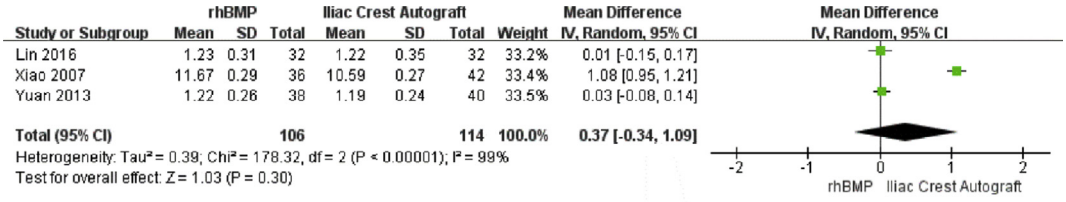

Fig. 5. Forest plot to postoperative intervertebral height between two materials.

Clinical success rate

Seven Trials compared the rate of clinical success (function improvement) after surgery. Results showed that there was a low evidence of heterogeneity among all these studies ($I^2 = 0\%$, $p > 0.05$), and the fixed model was performed. There was no statistical difference between two material groups [95% *CI* (0.59, 1.64), $p = 0.96$] (Fig. 4).

Postoperative intervertebral height

Three trials reported the intervertebral height 12 months after surgery. Results showed that there was a high evidence of heterogeneity across all these studies ($I^2 = 99\%$, $p < 0.05$), and the random model was performed. There was no statistical difference between two material groups [95% *CI* (−0.34, 1.09), $p = 0.30$] (Fig. 5).

Complications

Eight trials reported the complications and revision surgery in detail. Results showed that there was no evidence for heterogeneity among all these studies ($I^2 = 42.3\%$, $p > 0.05$), and the fixed model was performed. The pooled effects for overall complications and revision surgery from these eight relevant studies did not reveal significant differences between the two groups [95% *CI* (0.49, 1.27), p = 0.32] (Fig. 6).

Operation time

Four trials applied the operation time in detail. Results showed that there was no evidence for heterogeneity across all these studies ($I^2 = 0\%$, $p > 0.05$), and the fixed model was performed. The operation time of rhBMP group was less than that of iliac crest autograft group. There was statistical difference between two material groups [95% *CI* (−14.22, −2.08), p = 0.008] (Fig. 7).

Blood loss

Three trials compared the blood loss in operation. Results showed that there was no evidence for heterogeneity among all these studies ($I^2 = 0\%$, $p > 0.05$), and the fixed model was performed. There was no statistical difference between two material groups [95% *CI* (−14.20, 4.78), p = 0.33] (Fig. 8).

Duration of hospitalization

Three trials reported the duration of hospitalization. Results showed that there was no evidence for heterogeneity among all

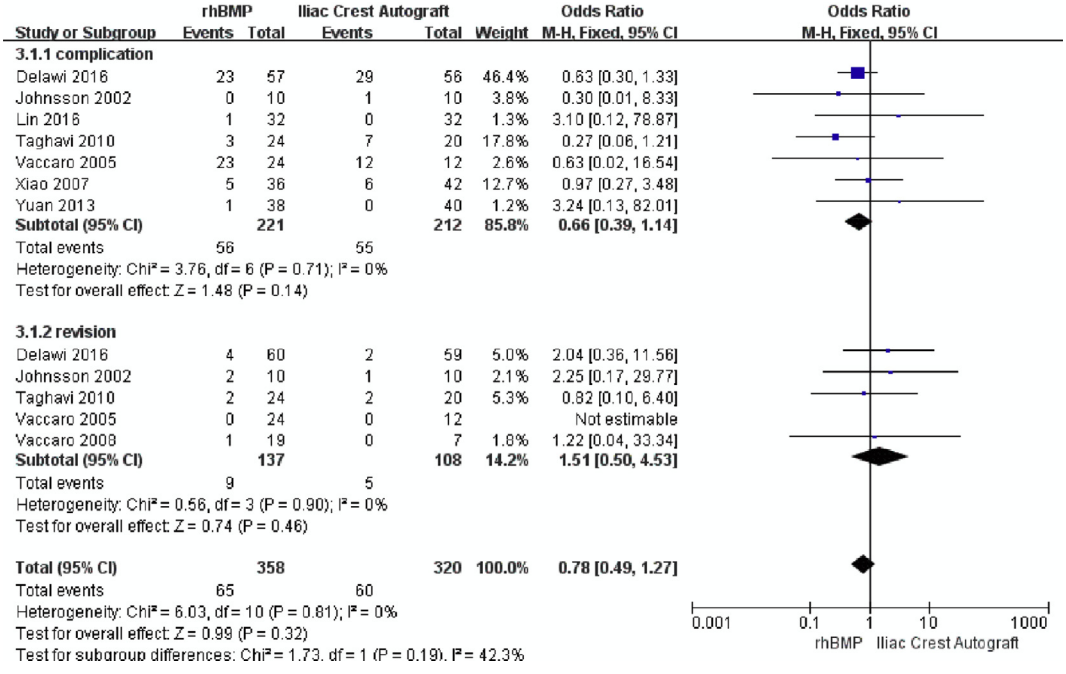

Fig. 6. Forest plot to complications and revisions between two materials.

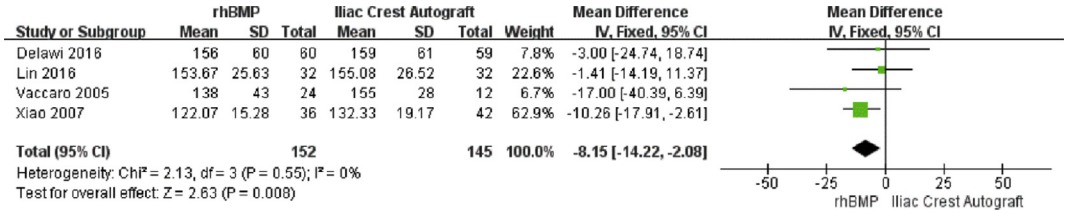

Fig. 7. Forest plot to operation time between two materials.

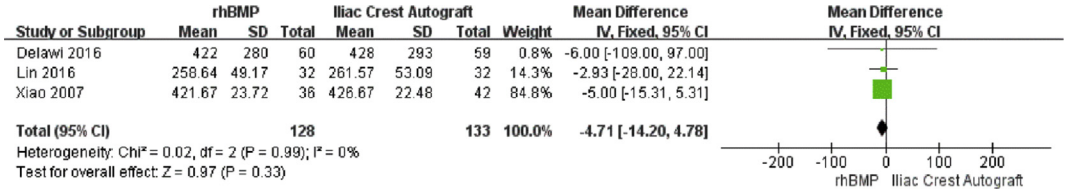

Fig. 8. Forest plot to blood loss between two materials.

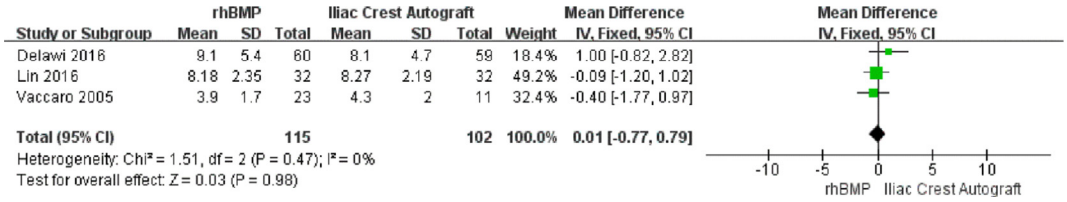

Fig. 9. Forest plot to duration of hospitalization between two materials.

these studies ($I^2 = 0\%$, $p > 0.05$), and the fixed model was performed. There was no statistical difference between two material groups [95% *CI* (−0.77, 0.79), p = 0.98] (Fig. 9).

Publication bias

All the 11 studies included in this meta-analysis had gone through a strict quality assessment. Seven of them were RCTs, 4 CCTs, and the possibility of a bias was low. But the funnel figure showed that there was a small bias, which may be associated with the incomplete collection of relevant literature, insufficient sample size and the different level of clinical physicians. Sensitivity analysis showed a good overall result (Figs. 10 and 11).

Discussion

Lumbar spondylolisthesis is caused by congenital dysplasia, trauma, strain and other causes of abnormal skeletal connection of the adjacent vertebral body.[20] Because the degrees of degeneration and trauma were different, the symptoms of lumbar spondylolisthesis can be progressive exacerbation, such as low back muscles pain with lower limb radioactivity numbness pain and intermittent behavior, etc.[21,22] Thus many surgeons tend to prefer operative treatment for lumbar spondylolisthesis.[23] PLIF with the use of bone grafts is the most common surgery employed to treat a variety of traumatic or degenerative spinal disorders.[24,25] The ultimate goal of PLIF is achieving stable spinal fusion.[26] At present, the bone graft materials used in the fusion surgery reported in the literature include autologous bone, allograft bone, xenogenesis bone and artificial bone materials.[27,28] Autograft bone is believed to have superior osteoconductive, osteoinductive, and osteogenic properties as compared to alternatives. However, it is reported to be associated with a high rate of postoperative pain, second surgical site, and limited amount.[29,30] rhBMP (rhBMP-2, rhBMP-7, etc.) is an alternation as iliac crest autograft for PLIF recent years.[31,32] rhBMP has shown the induction of intramembranous ossification and endochondral ossification, generating good fusion rate. It is reported in the literature that benefits of rhBMP are ready availability and osteoconductive properties, while its cost is greater than iliac crest autograft.[33] Which graft material is more effective and safe for lumbar spondylolisthesis fusion surgery remains controversial. Thus, the purpose of this study was to do a systematic review comparing the clinical outcomes of vertebral fusion with rhBMP vs. iliac crest autograft.

Meta-analysis is a commonly used evidence-based medical tool in clinical practice. It can analyze the results of multiple independent clinical trials and draw more definite conclusions. The selected articles of this study were subjected to more rigorous screening. All trails were case-control studies, including 4 retrospective and 7 randomized controlled studies. A total of 565 patients were included, including 270 iliac crest autograft and 295 rhBMP composite bones. The two groups of patients were compared from cases of postoperative fusion, cases of clinical success, postoperative intervertebral height, complications, operation time, blood loss and duration of hospitalization. From the results of the meta-analysis, the difference for the cases of fusion in the internal fixation subgroup at 24 months after surgery [95% *CI* (1.38, 24.70), $p = 0.02$], and the operative time [95% *CI* (−14.22, −2.08), $p = 0.008$] between two groups was statistically significant. rhBMP appear to yield higher fusion rates in instrumented lumbar fusion procedures and comparable fusion rates in the noninstrumented group, it could also reduce the operation time. rhBMP is an acidic glycoprotein widely present in bone matrix.[34] It is a multifunctional growth factor and has a biological role in inducing osteogenesis. The

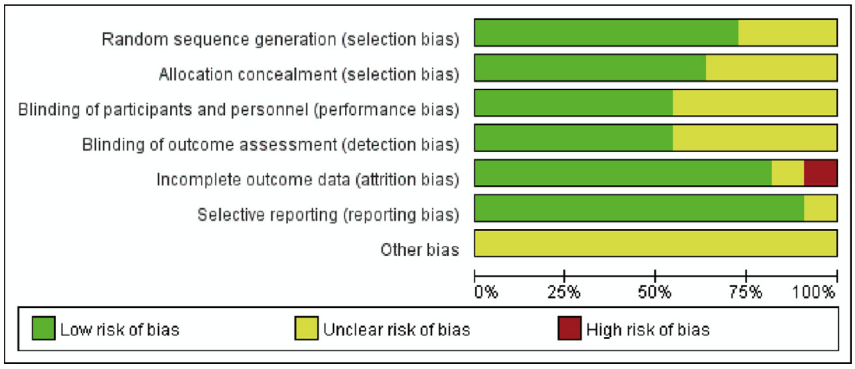

Fig. 10. Risk of bias graph. Each risk of bias item is presented as a percentage across all included studies and indicates the proportional level for each risk of bias item.

rhBMPs currently found to have osteogenic differentiation ability are mainly rhBMP-2, -4, -6, -7, -9, of which rhBMP-2 and -7 are considered to be the most active factor that can induce bone formation together.[35,36] Singh et al.[37] reported that rhBMP (39 cases) and iliac crest autograft (11 cases) combined with pedicle screw fixation for posterolateral lumbar fusion, follow-up 2 years, the total fusion rate was 97% in the rhBMP group and 77% in iliac crest autograft group. The results of this study are consistent with our analysis. Moreover, the reason for the shorter operation time in the rhBMP group may be no second surgical procedure (iliac crest autografting) during fusion surgery.

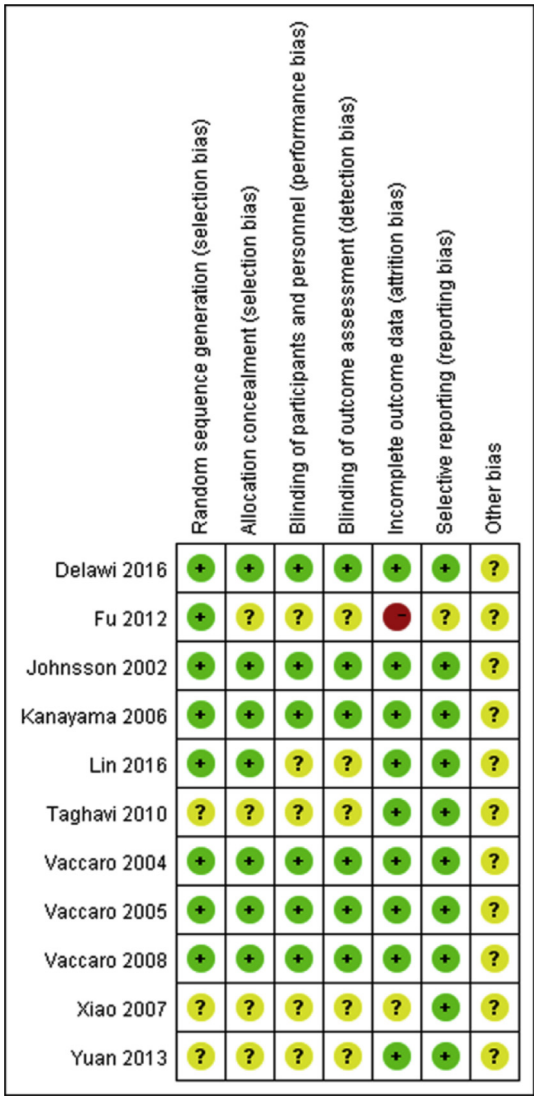

Fig. 11. Risk of bias summary. Methodological quality of the included studies. This risk of bias tool incorporates assessment of randomization (sequence generation and allocation concealment), blinding (participants, personnel and outcome assessors), completeness of outcome data, selection of outcomes reported and other sources of bias. The items were scored with "yes", "no", or "unclear".

In 2002, the US Food and Drug Administration approved the rhBMP-2/absorbable collagen sponge (ACS)/vertebral fusion device for anterior lumbar fusion.[38] Slosar et al.[39] reported that rhBMP-2 composite allogeneic bone was used in 45 patients with anterior lumbar interbody fusion for 2 years, there were no complications in the rhBMP group, no revision surgery, and 4 patients in the control group underwent revision surgery. Therefore, we analyzed the adverse effects across two groups. Our data showed no statistical difference in overall complication rates and revision rates [95%CI (0.49, 1.27), $p = 0.32$] between the use of iliac crest autograft and the use of rhBMP.

In conclusion, rhBMP has good osteoinductivity, and it is should be applied for the treatment of lumbar spondylolisthesis. The clinical effect of rhBMP is satisfactory, which has higher fusion rate and fewer complications. If you do not consider its costs, it is a good alternative to autologous iliac bone grafting.

This systematic review included 11 articles, and the methodological quality evaluation results were not all high. Four studies were case-control studies, 7 RCTs. Therefore, there are several limitations that should be noted. The patient's informed consent, the choice of surgical approaches, the different rhBMP carriers, the medical ethical issues, and the other inevitable biases also potentially limited the reliability of the outcomes. In the same outcome measurements system, we include into the maximum of 11 articles least of three and this may be the cause of heterogeneity increasing between groups. The small number of studies and enrolled patients might not provide sufficient statistical power. Therefore, the above conclusions still need to further verify depends on the emergence of more randomized controlled trials with higher quality and larger sample sizes in the future. Finally, rhBMP putty is expensive, further studies that include cost–benefit analyses will be valuable.

Funding

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Ethical statement

Not applicable; as this is a systematic review.

Conflicts of interest

There are no conflicts of interest associated with this article.

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