Journal of Orthopaedic Translation 24 (2020) 166–174

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Original Article

Exploratory meta-analysis on dose-related efficacy and complications of rhBMP-2 in anterior cervical discectomy and fusion: 1,539,021 cases from 2003 to 2017 studies

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ARTICLE INFO

Keywords:
Anterior cervical discectomy and fusion
Efficacy and complications
Infuse® bone graft
Meta-analysis
Recombinant human bone morphogenetic protein-2
Spinal fusion

ABSTRACTS

Background/Objective: Anterior cervical discectomy and fusion (ACDF), commonly using autogenous iliac bone graft may be limited by donor site availability, donor-site morbidity, lower fusion rate among specific patients and longer surgical time. Surgeons used rhBMP-2 as an alternative in order to fill these clinical needs. However, studies comparing with and without rhBMP-2 in ACDF have reported conflicting results on efficacy and complications. Therefore, the purpose of this article was to evaluate efficacy and complications through dose-related rhBMP-2 and surgical level-dependence in ACDF.

Methods: We comprehensively searched PubMed and the Cochrane Library and performed a systematic review and cumulative meta-analysis of all randomized controlled trials (RCTs), prospective and retrospective comparative studies assessing with and without rhBMP-2 treatments.

Results: 1 RCTs, 4 prospective studies and 24 retrospective studies including a total of 1,539,021 cases were identified. Patients in ACDF with rhBMP-2 might benefit from significantly higher fusion rates than that in non-rhBMP-2, not only total value but also in 3 tiers of rhBMP-2 doses. It is worth noting that the low dose of rhBMP-2 (<0.7 mg/level) showed highest fusion rate among all rhBMP-2 doses. Patients in rhBMP-2 also experienced higher complication rate, dysphagia and wound infections than that in non-rhBMP-2. In 2-level ACDF, the fusion rate was significantly better in rhBMP-2 than non-rhBMP-2 but not for complication rate. Surgery operative time, lengths of hospital stay and neurologic symptoms did not differ significantly between two treatments.

Conclusions: rhBMP-2 chosen in ACDF offered higher fusion, but also higher complication rate with more dysphagia and wound infections than non-rhBMP-2. To gain the efficacy and safety, rhBMP-2 dosing recommendations for ACDF would be better < 0.7 mg/level. Moreover, rhBMP-2 may be an option to improve nonunion in high risk of multi-level ACDF.

The translational potential of this article: This article indicated that the product development of facilities used in ACDF, the dose of rhBMP-2 may be lower than 0.7 mg/level was enough to gain the good fusion rates. However, the complications were higher in patients used rhBMP-2, therefore the manufacturers should pay attention to mitigate such side effects.

Introduction

Anterior cervical discectomy and fusion (ACDF), a common surgical procedure, has been used for decades in patients suffering from neck pain and/or neurological deficits without response to conservative managements [1–3]. The procedure of ACDF includes the removal of the herniated or degenerative disc, followed by insertion of an interbody graft to fuse together the bones above and below the disc [4–6]. Iliac crest bone

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https://doi.org/10.1016/j.jot.2020.01.002
Received 11 August 2019; Received in revised form 4 January 2020; Accepted 13 January 2020
Available online 18 February 2020

graft (ICBG), the gold-standard graft material, presents its superior osteoconductive, osteoinductive and osteogenic properties [4]. However, autogenous iliac bone graft also possesses several disadvantages, including increased procedure time, limited donor site availability and donor site morbidity [7], including pain, wound infection, haematoma or lateral femoral cutaneous nerve injury [8]. Donor site complication rates caused from autologous bone grafts were reported to be from 9.4 to 50% [9]. These limitations and nontrivial incidence of nonunion have stimulated surgeons and researchers to find potential alternatives to bone matrix, including recombinant human bone morphogenetic proteins (rhBMPs).

rhBMPs, the cytokines with osteoinductive activity, belong to the transforming growth factor β (TGF-β) superfamily, showing better bone healing with the proposal of less morbidity compared to the usual methods of bone graft harvest [10]. Currently, recombinant human bone morphogenetic protein-2 (rhBMP-2) is recognised as the only bone inducer with level I of clinical evidence [10]. Additionally, Chau et al. compared all the bone graft alternatives in ACDF, showing that rhBMPs possessed the best fusion rates, highest osteoinduction and the most effective adjuvant graft without donor site morbidity [11].

However, some independent studies reported complications after rhBMP-2 use in the ACDF, including dysphagia, dysphonia, cervical swelling, readmission, wound complications and ossification [12]. All of the recent research controversies make it difficult for surgeons to understand the proper use of rhBMP-2 in a clinical practice. The intent of exploring this potential alternative to bone matrix was to improve the success of ACDF and the patients' quality of life. What if patients have difficulties to collect autogenous iliac bone graft or high risks of nonunion rate? Is it possible to use lower dose of rhBMP-2 to avoid adverse events? Does rhBMP-2 show the same efficacy and safety issues in single- and multi-level ACDF? Therefore, we have undertaken a meta-analysis and systematic review that examines the evidence for and against rhBMP-2 at the dose and surgical level, so that it provides insights into new researches in a better effort to provide surgeons with a working framework in which rhBMP-2 could be applied in their clinical practices.

Evidence acquisition

A prospective protocol of objectives, literature-search strategies, inclusion and exclusion criteria, outcome measurements and methods of statistical analysis was prepared *a priori* according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis of Observational Studies in Epidemiology recommendations for study reporting [13,14].

Literature-search strategy

A literature search was performed in October 2018 without restriction to regions, publication types or languages. The primary sources were the electronic databases of PubMed and the Cochrane Library. The following medical subject headings (MeSH) terms and their combinations were searched in [Title/Abstract]: anterior cervical discectomy and fusion, cervical spine surgery, anterior cervical fusion, anterior cervical spine, cervical revision fusion, spinal fusion, cervical fusion, recombinant human bone morphogenetic protein-2, bone morphogenetic protein, rhBMP-2 and rhBMP, except animal, rat, rabbit and mouse. The Related Articles function was also used to broaden the search, and the computer search was supplemented with manual searches of the reference lists of all retrieved studies, review articles and conference abstracts. When multiple reports describing the same population were published, the most recent or complete report was used.

Inclusion and exclusion criteria

All available randomised controlled trials (RCTs) and retrospective comparative studies (cohort or case-control studies) that evaluated ACDF with rhBMP-2 in all age groups and that had at least one of the quantitative outcomes mentioned in the next section of this paper were included. Editorials, letters to the editor, review articles, case reports and animal experimental studies were excluded.

Data extraction and outcomes of interest

Data from the included studies were extracted and summarised independently by two of the authors (Wen and Shi). Any disagreement was resolved by the adjudicating senior authors (Jiang and Yang). The primary outcomes were fusion rate, complication rate, dysphagia, wound infections and neurologic symptoms. If sufficient data were available, postoperative fusion rate, complications and dysphagia were subdivided by dose of rhBMP-2 and the number of surgical level (ACDF). The secondary outcomes were surgery operative time and lengths of hospital stay.

Quality assessment and statistical analysis

Studies were rated for the level of evidence provided according to the criteria by the Centre for Evidence-Based Medicine in Oxford, UK [15]. The methodological quality of RCTs was assessed by the Cochrane risk of bias tool [16]. The methodological quality of retrospective studies was assessed by the modified Newcastle–Ottawa scale [17], which consists of three factors: patient selection, comparability of the study groups and assessment of outcome. A score of 0–9 (allocated as stars) was allocated to each study except RCTs. RCTs and observational studies achieving six or more stars were considered to be of high quality. All the meta-analyses were performed using Review Manager 5.0 (Cochrane Collaboration, Oxford, UK). The weighted mean difference (WMD) and odds ratio (OR) were used to compare continuous and dichotomous variables, respectively. All results were reported with 95% confidence intervals (CIs). For studies that presented continuous data as means and range values, the standard deviations were calculated using the technique described by Hozo et al. [18]. Statistical heterogeneity between studies was assessed using the chi-squared test with significance set at $p < 0.10$, and heterogeneity was quantified using the I^2 statistic. The random-effects model was used if there was heterogeneity between studies; otherwise, the fixed-effects model was used [16]. Sensitivity analyses were performed for high quality studies. Funnel plots were used for potential publication bias.

Evidence synthesis

In the final analysis, 29 studies including a total of 1,539,021 cases fulfilled the predefined inclusion criteria and were included (Figure 1). These publications were full-text articles [19–48]. Examination of the references listed for these studies did not yield any further studies for evaluation. Agreement between the two reviewers was 97% for study selection and 93% for quality assessment of trials.

Characteristics of eligible studies

The characteristics of included studies are shown in Table 1. Among the included studies, there was 1 small sampled RCT without clarified confidence interval and <80% follow-up (level of evidence: 2b) [39]; 2 prospective nonrandomised, historically controlled trials (level of evidence: 2b) [24,32]; 2 prospective therapeutic cohort studies (level of evidence: 2b) [35,38]; 1 prospective study that collected data prospectively without controls (level of evidence: 4) [44]; 14 retrospective studies comparing contemporary series of patients (level of evidence: 3b) [22,23,25,26,28–31,33,34,37,42,45–47]; 2 retrospective studies using historical series as controls (level of evidence: 4) [36,41] and remaining 7 retrospective studies without controls (level of evidence: 4) [19–21,27,40,43,48]. The primary exposure or intervention was rhBMP-2. As for the control groups, there were 4 studies choosing ICBG, 16 studies using non-rhBMP-2, including β-tricalcium phosphate, allograft/demineralised bone matrix, autologous osteophyte, allograft or unstated in control groups, and 9 studies without controls.

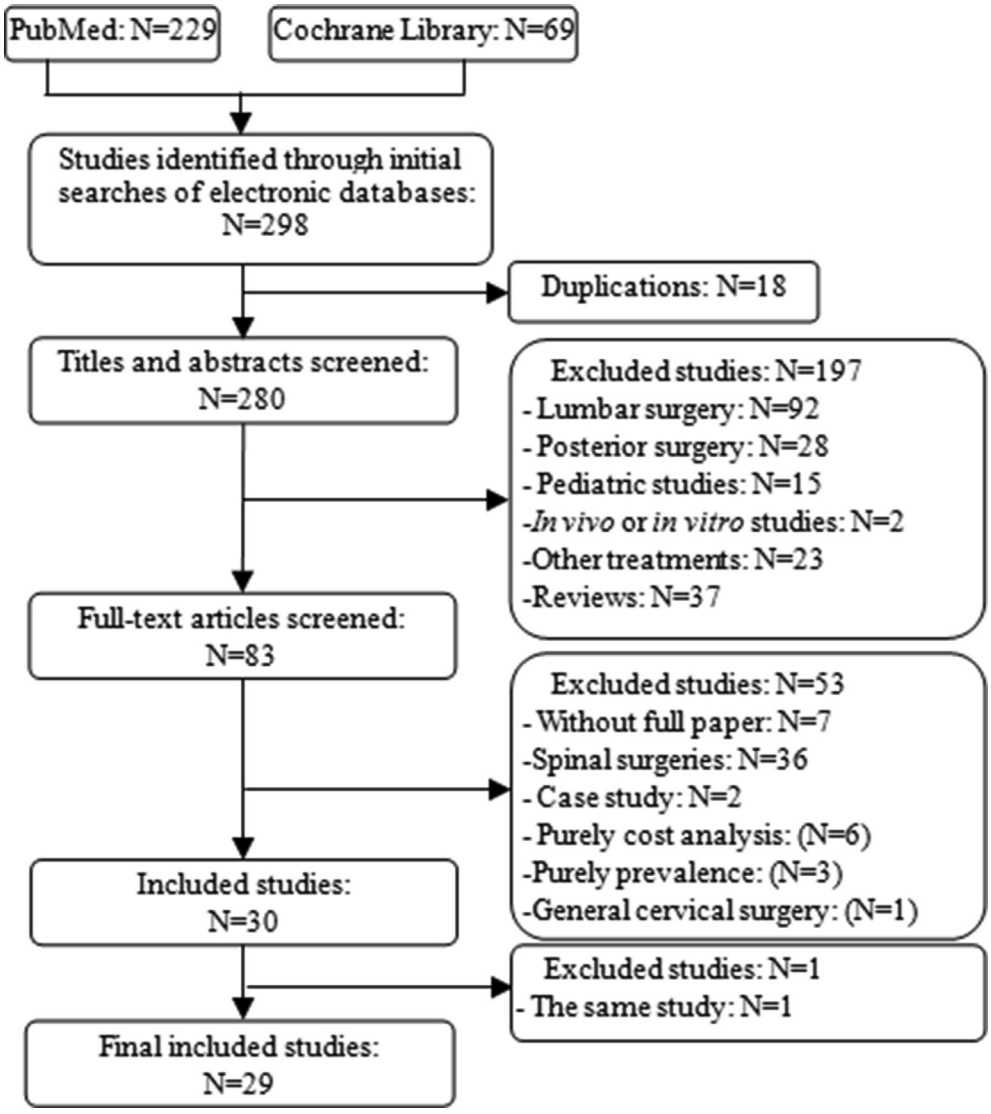

Figure 1. Flow diagram of studies identified, included and excluded.

Methodological quality of included studies

The quality of included studies is shown in Table 1. True randomisation was used in one RCT. Two prospective nonrandomised trials adopted historical records as controls. None of the retrospective studies adopted an appropriate protocol for treatment assignment, with allocation usually at the discretion of the physician. No studies provided information about allocation concealment or the blinding method. The study-conducting year, dose of rhBMP-2 and level(s) of ACDF were revealed in most studies, benefiting our stratified evaluation. Matching criteria between the groups were variable. Most of studies provided the duration of follow-up. Methods for handling missing data and intention-to-treat analyses were not adequately described in the majority of studies.

Efficacy

The key efficacy outcome, fusion rate, was evaluated in 17 studies, which contained 11 two-arm studies [22–26,29,31,35,36,38,39] and 6 one-arm studies [20,21,43,44,46,48]. To investigate the superiority of fusion rates between rhBMP-2 and non-rhBMP-2 in ACDF, 11 studies comparing the two treatments showed that groups choosing rhBMP-2 had significantly higher fusion rate in ACDF than non-rhBMP-2, 98.28% and 95.17%, respectively (OR:7.01, 95% CI: 3.90–12.60, $p < 0.00001$). To evaluate the influence of doses of rhBMP-2, the index of fusion rate was further divided by low (<0.7 mg/level), middle (0.7–1.1 mg/level) and high (>1.1 mg/level) dose of rhBMP-2, showing higher fusion rate in rhBMP-2 than non-rhBMP-2 (OR: 4.38, 95% CI: 0.21–90.11, $p = 0.34$; OR: 6.06, 95% CI: 3.19–11.51, $p < 0.00001$; OR: 3.92, 95% CI: 0.66–23.19, $p = 0.13$), shown in Figure 2A. The average of fusion rate extracted from 17 studies was 98.34% in patients with rhBMP-2, 95.17% in patients without rhBMP-2, 98.8% in low dose of rhBMP-2, 98.22% in middle dose of rhbmp-2 and 95.29% in high dose of rhBMP-2, as shown in Table 2. A further RCT study using rhBMP-2 in low dose (0.5 mg/level) was being performed by us, showing consistent results (data were not shown).

Complications

First, pooling the data from nine studies that assessed complication rate in 395,106 patients showed a significant higher complication rate in the rhBMP-2 group than that in the non-rhBMP-2 group, 7.94% and 6.38%, respectively (OR: 1.52, 95% CI: 1.38–1.67, $p < 0.00001$). Among the nine studies, three studies with 0.7–1.1 mg/level of rhBMP-2 showed higher but nonsignificant change in complication rate between the

Table 1
Characteristics of included studies.

Year	Study	Level of evidence	Design	Patients (no.)	Dose of rhBMP-2	Level of ACDF	Treatments	Follow-up (months)	Quality score
1999–2000	Baskin (2003)	2b	RCT	33	0.6 mg/level	1-,2-	rhBMP-2 vs. ICBG	24	RCT
2002–2003	Boakye (2005)	4	R	24	0.7 mg/level	1-,2-,3-	rhBMP-2 vs. none	13.0	★★★★
2011–2013	Lovasik (2017)	3b	R	191	NA	1-,2-,3-,4-	rhBMP-2 vs. bTCP	12	★★★★★★
2007–2009	Burkus (2017)	2b	P	710	0.6–1.05 mg/level	1-	rhBMP-2 vs. non-BMP	24	★★★★★★★★
2007–2011	Arnold (2016)	2b	P	710	0.6–1.05 mg/level	1-	rhBMP-2 vs. allograft	24	★★★★★★★★
2007–2011	Tan (2015)	3b	R	146	0.9 mg/level	2-	rhBMP-2 vs. ICBG	26.8 vs. 27.5	★★★★★★★★★
2009–2011	Guppy (2014)	3b	R	2327	NA	NA	BMP vs. non-BMP	7–24	★★★★★★★
1997–2012	Frenkel (2013)	3b	R	45	0.26–2.1 mg/level	2-,3-,4-	BMP vs. non-BMP	35 vs. 54	★★★★★★★★★
NA	Vaidya (2007)	2b	P	23	1 mg/level	≥1	rhBMP-2 vs. demineralised bone matrix	24	★★★★★★
NA	Buttermann (2008)	2b	P	66	0.9 mg/level	1-,2-,3-	BMP vs. ICBG	>24	★★★★★★
2007–2012	Khajavi (2014)	4	P	72	0.5–0.7 mg/level	2-,3-,4-	rhBMP-2 vs. none	13.8	★★★★★★
2002–2006	Tumialan (2008)	4	R	200	0.7 or 1.05 or 2.2 mg/level	1-,2-,3-,4-	rhBMP-2 vs. none	16.7	★★★★★
2008–2011	Pourtaheri (2015)	4	R	37	0.26–0.35 mg/ level	3-	rhBMP-2 vs. none	48	★★★★★★
NA	Klimo (2009)	4	R	22	1.1–2.1 mg/level	1-,2-,3-	rhBMP-2 vs. none	14.5	★★★★
2011–2012	Xu (2014)	3b	R	40	2.1 mg/level	1-,2-	rhBMP-2 vs. autologous osteophyte	12	★★★★★★★
2003–2004	Shields (2006)	4	R	151	2.1 mg/level	1-,2-,3-,4-	rhBMP-2 vs. none	>8	★★★
2006–2008	Stachniak (2011)	4	R	30	0.6 mg/level	2-,3-	rhBMP-2 vs. none	9	★★★
2002–2004	Vaidya (2007)	3b	R	46	1 mg/level	1-,2-,3-	rhBMP-2 vs. demineralised bone matrix	28.03 vs. 23.6	★★★★★★
2007–2012	Kukreja (2015)	4	R	197	0.7 mg/level	1-,2-,3-,4-	rhBMP-2 vs. none	24	★★★★★
2002–2009	Goode (2014)	3b	R	57,484	NA	2-,3-,4-	BMP vs. non-BMP	12	★★★★★★
2004–2007	Williams (2011)	3b	R	5184	NA	NA	BMP vs. non-BMP	NA	★★★★★
2002–2009	Fineberg (2013)	3b	R	213,421	NA	NA	BMP vs. non-BMP	NA	★★★★★
2002–2004	Smucker (2006)	3b	R	234	NA	≥1	rhBMP-2 vs. non-BMP	1.5	★★★★★★
2002–2007	Lu (2013)	4	R	150	0.7–2 mg/level	≥2	rhBMP-2 vs. allograft	35 vs. 25	★★★★★★★★★
2002–2006	Cahill (2009)	3b	R	27,067	NA	NA	BMP vs. non-BMP	NA	★★★★★
NA	Shen (2010)	4	R	127	4 mg (total)	3-,4-,5-	rhBMP-2 vs. none	24	★★★★★
1996–2012	Riederman (2017)	4	R	400	0.7 mg/level	1-,2-,3-,4-	rhBMP-2 vs. ICBG	NA	★★★★
2003–2010	Jain (2014)	3b	R	924,004	NA	NA	rhBMP vs. non-BMP	NA	★★★★★
2005–2011	Lord (2017)	3b	R	215,047	NA	NA	BMP vs. non-BMP	3	★★★★★
2006–2010	Cole (2014)	3b	R	91,543	NA	≥1	rhBMP-2 vs. non-rhBMP	>19	★★★★★★

*The follow-up months in rh-BMP-2 versus non-rhBMP-2.

rhBMP-2 group and non-rhBMP-2 group, 30.56% and 19.70%, respectively (OR: 1.84, 95% CI: 0.94–3.62, $p = 0.08$). Additionally, two studies that conducted ACDF using high dose (>1.1 mg/level) of rhBMP-2 also showed higher but nonsignificant change in complication rate between two groups, 24.14% and 11.90%, respectively (OR: 4.03, 95% CI: 0.99–16.47, $p = 0.06$), as shown in Figure 3A. Taking together with one-arm studies, the complication rates of three tiers of rhBMP-2 dose between two groups are shown in Table 2.

Second, the most severe and doctor-concerning complication was dysphagia, which was reported in 15 studies in 1,530,323 patients, showing significant more patients with dysphagia in the rhBMP-2 group than in the non-rhBMP-2 group, 2.29% and 1.72%, respectively (OR: 1.58, 95% CI: 1.37–1.82, $p < 0.00001$), as shown in Figure 3B. Five studies choosing middle dose (0.7–1.1 mg/level) rhBMP-2 reported significantly higher incidence of dysphagia than non-rhBMP-2 patients (OR: 3.35, 95% CI: 1.86–6.12, $p < 0.0001$). Other studies choosing low or high dose did not reveal the incidence of dysphagia. Therefore, our meta-analysis did not indicate a correlation between rhBMP-2 dose and incidence of dysphagia.

Third, other complications included wound infections and neurologic symptoms. Seven studies in 609,812 patients showed that there were more wound infections in patients treated with rhBMP-2 compared with patients treated without rhBMP-2, 0.93% and 0.83%, respectively (OR: 1.49, 95% CI: 1.10–2.01, $p = 0.010$). Regarding neurological symptoms, four studies in 577,495 patients reported nonsignificantly adverse symptoms in the group of rhBMP-2 than non-rhBMP-2 (OR: 1.22, 95% CI: 0.91–1.64, $p = 0.18$), as shown in Figure. 3C and D.

Influences of rhBMP-2 on the levels of ACDF

The impacts of rhBMP-2 on the levels of ACDF were divided by the number of ACDF level. But only one study researched influences of rhBMP-2 in 1-level ACDF, which reported fusion rates in postoperative 24 months to be 99.4% versus 87.2%, dysphagia rate 16.4% versus 7.3%, pseudoarthrosis rate 0.4% versus 8.2% and ossification rate 78.6% versus 59.2% (rhBMP-2 group versus non-rhBMP-2) [24]. In 2-level ACDF, fusion rate influenced by rhBMP-2 from three studies was significantly higher in the rhBMP-2 group than in the non-rhBMP-2 group, 93.3% and 77.6% (OR: 3.24, 95% CI: 1.49–7.04, $p = 0.003$), respectively; complication rate influenced by rhBMP-2 from two studies did not generate significant difference, 17.4% and 13% (OR: 1.66, 95% CI: 0.78–3.54, $p = 0.19$) in the rhBMP-2 group and non-rhBMP-2 group, respectively. This part of meta-analysis is shown in Fig. 4A and B. Lastly, there is one study conducting one-arm trial to investigate rhBMP-2

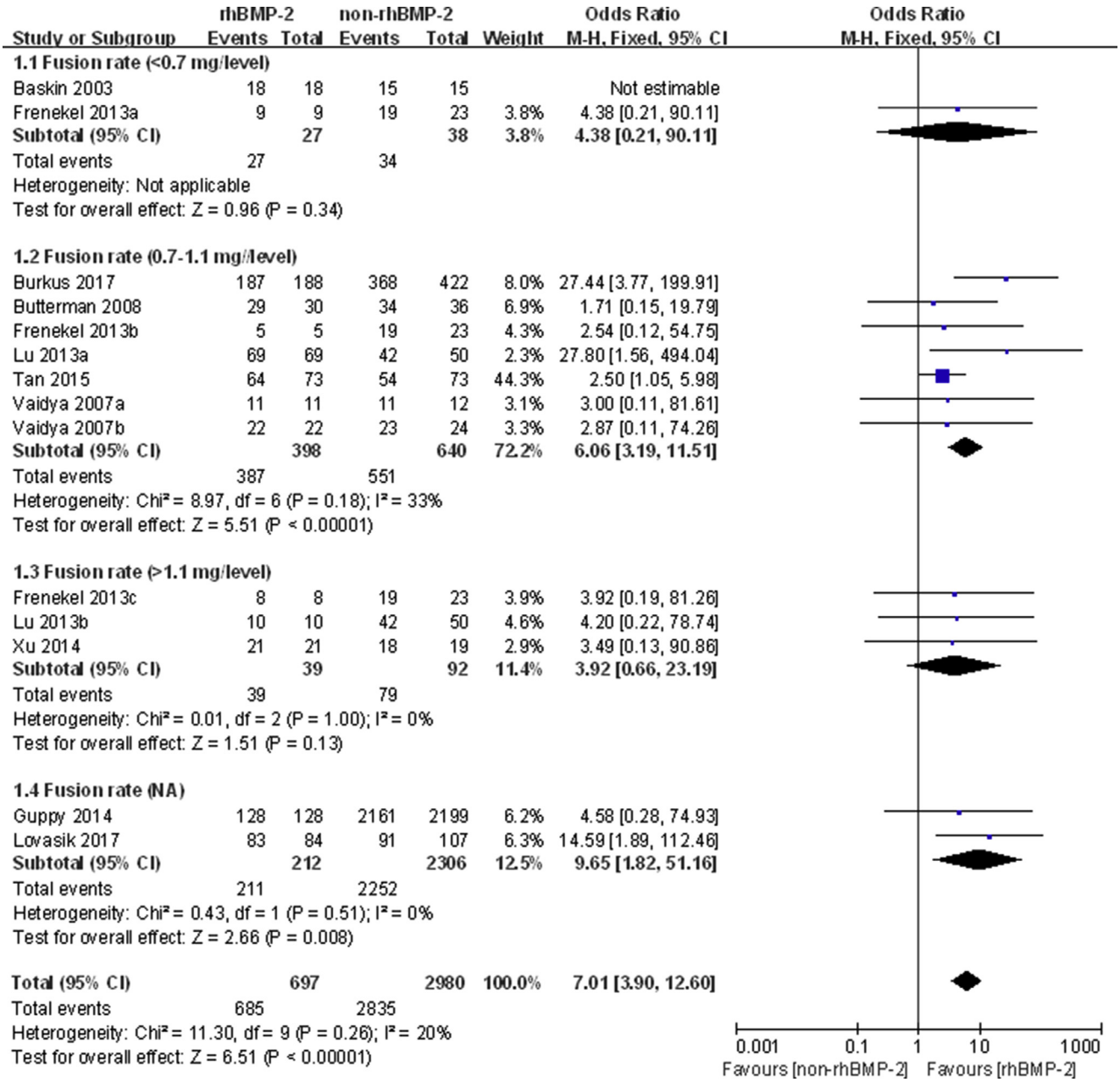

Figure 2. Forest plot and meta-analysis of fusion rate. rhBMP-2 = recombinant human bone morphogenetic protein; CI = confidence interval.

effects on 3-level ACDF, which reported one patient who was undertaking an anterior cervical plate removal due to dysphagia among 37 patients; others reached fusion at six months after surgery so that the total fusion rate was 97.3% [46]. Other 27 studies conducting multi-level ACDF did not separate the data according to the level of ACDF. Therefore, our meta-analysis showed that rhBMP-2 increased fusion rate and no significant difference of complication rate on 2-level ACDF. However, current data did not generate the influence of rhBMP-2 on different levels of ACDF.

Table 2
Fusion rate and complication rate with or without rhBMP-2.

	rhBMP-2				non-rhBMP-2
	low	middle	high	total	total
Fusion rate	98.80%	98.22%	95.29%	98.34%	95.17%
Complication rate	0%	15.26%	24.14%	7.94%	6.38%

The score improvements of pain and disability were not extracted to meta-analyse because some papers only revealed the mean values without SD values.

Second outcomes

Three studies with 816 patients reported relative lower but nonsignificant operation time in patients adopting rhBMP-2 than that of non-rhBMP-2 (OR: −10.12, 95% CI: −27.88–7.65, $p = 0.26$). Other three studies with 214,197 patients revealed similar lengths of hospital stay between patients taken ACDF with rhBMP-2 and without rhBMP-2 (OR: −0.08, 95% CI: −0.34 – 0.18, $p = 0.55$), as shown in Fig. 5A and B.

Sensitivity analysis and publication bias

One RCT and 28 perspective and retrospective studies that scored six or more stars on the modified Newcastle—Ottawa scale were included in

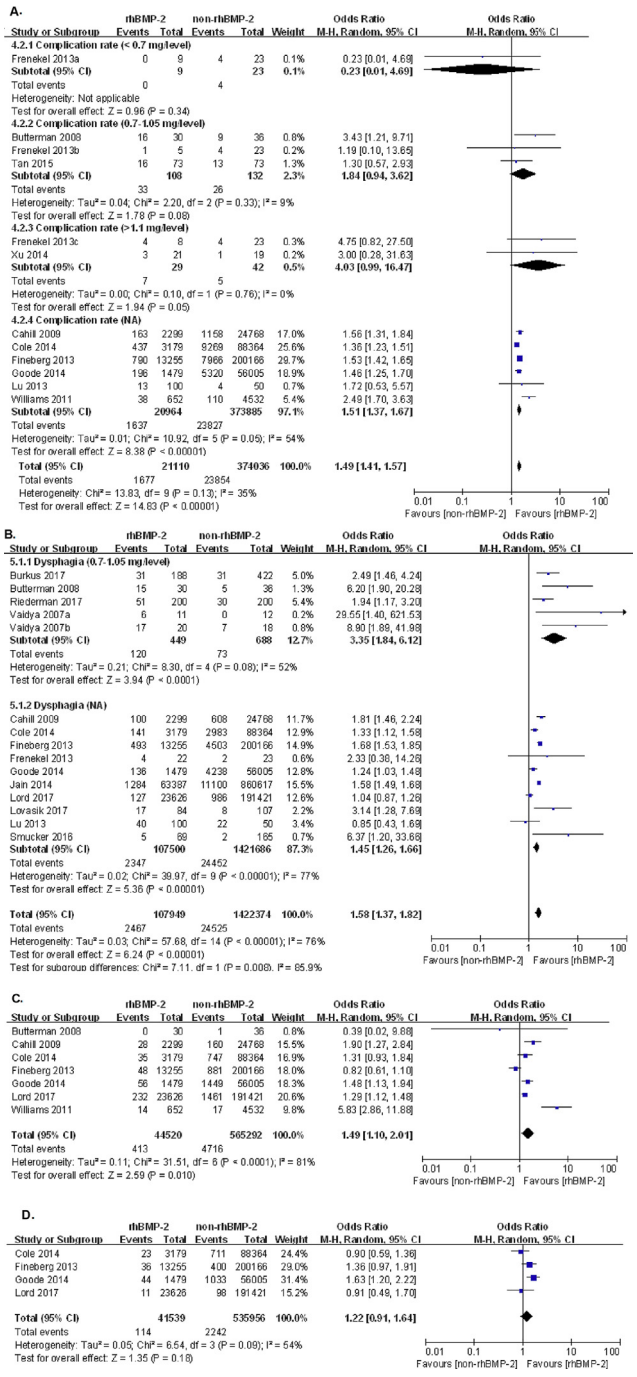

Figure 3. (A) Forest plot and meta-analysis of complication rate; (B) dysphagia; (C) wound infections; (D) neurologic symptoms. rhBMP-2 = recombinant human bone morphogenetic protein; CI = confidence interval.

sensitivity analysis, shown in Table 3. There was a slight change among these outcomes, but the significance of these outcomes was still in the same range. The degree of between-study heterogeneity decreased dramatically for "length of hospital stay", "complication rate" and "wound infections" and slightly for "dysphagia". Between-study heterogeneity remained statistically significant for "operative time" and "dysphagia".

Fig. 6 shows the funnel plot of the studies included in our meta-analysis that reported fusion rates. All recruited studies lied inside the 95% CIs, with an even distribution around the vertical, indicating no obvious publication bias.

Discussion

As the multi-functional growth factors, rhBMPs were introduced to several medical scenarios to promote the bone-healing rate with the proposal of less morbidity [10]. Presently, there are two rhBMPs, rhBMP-2 and rhBMP-7 (OP-1, Stryker Biotech, Hopkinton, MA), approved by FDA to treat a variety of bone-related conditions including delayed union and nonunion [49], bringing alternatives to autologous bone graft with significant donor site morbidity. rhBMP-2 was received with the FDA approval in July of 2002 on single-level anterior lumbar interbody fusion from vertebral L2-S1 for the treatments of degenerative disc disease, Grade I spondylolisthesis, and/or retrolisthesis with the lumbar tapered fusion device LT-CAGE (Medtronic Sofamor Danek) [4]. rhBMP-2 has been rapidly used off-label for anterior cervical fusion, but the postoperative complications of soft tissue swelling, dysphagia and respiratory complications raised FDA attentions to release a Public Health Notification at July 2008 [50]. Therefore, 29 studies using rhBMP-2 in ACDF were aggregated to find some clues that dose of rhBMP-2 or levels of ACDF affected the relevant efficacy and safety outcomes.

The rhBMP-2 minimum dose used for single- or multi-level ACDF was nearly 1/10 of maximum dose between studies, which was 0.26 mg/level compared to 2.1 mg/level. To reveal the influence of dose of rhBMP-2 on efficacy and risks, we stratified the data according to the dose of rhBMP-2 to three tiers: high dose (>1.1 mg/level), middle dose (0.7–1.1 mg/level) and low dose (<0.7 mg/level).

The fusion rate was higher in rhBMP-2 groups than in the non-rhBMP-2 group, regardless of the dose of rhBMP-2. Additionally, the fusion rates were associated with the dose of rhBMP-2: higher dose of rhBMP-2, lower fusion rate. These findings indicate surgeons that low dose of rhBMP-2 is enough for the improvement of fusion rate in the ACDF. Another meta-analysis of rhBMP in spinal arthrodesis surgery by Hofstetter et al. reported 100% fusion rate in different doses of BMP in ACDF except 98.88% fusion rate in 0.7–2.1 mg/level, which did not showed the dose-dependent change on postoperative fusion rate [4]. This may be resulted in the only seven publications included, compared to our meta-analysis with 29 studies. Therefore, from better fusion rate, rhBMP-2 was recommended to ACDF, even in the dose of <0.7 mg/level. It is noteworthy that this dose of rhBMP-2 is much lower than the manufacturer's recommendation that was recommended by FDA from 4.2 mg to 12 mg rhBMP-2 per level [4].

High doses of rhBMP-2 were associated with increased complication rates in lumbar interbody fusion, which were consistent with our findings [4]. The included studies using low dose of rhBMP-2 (<0.7 mg/level) did not report the complication rate, while studies using middle and high doses of rhBMP-2 reported higher complication rate than low dose group and non-rhBMP-2 treatment. Frenkel et al. reported that patients had no complication in rhBMP-2 low dosage (<0.5 mg/level), but reported 12.5% (1 patient) in middle dose (0.5–1.1 mg/level) and 50% (4 patients) in high dose (1.4–2.1 mg/level), showing the increasing dose-dependent complication rate. Tumialan et al. also realised that changes of the complication rate may be brought by doses of rhBMP-2 on complication rate, reporting three times dose reduction of rhBMP-2 from 2.1 to 1.05 to 0.7 mg/level to avoid asymptomatic excess interbody bone formation and potential dysphagia [43]. Taking together with peers' studies, our analysis showed that although rhBMP-2 could improve fusion, rhBMP-2 may induce higher complication rates compared to that in non-rhBMP-2, especially at high and middle doses of rhBMP-2 (>0.7 mg/level).

The most observed complication syndromes, including dysphagia, wound infections and neurologic symptoms, showed higher incidence in the rhBMP-2 group than in the non-rhBMP-2 group. Regarding the dose of rhBMP-2 in these ACDF studies, one RCT that utilised low dose of rhBMP-2 (0.6 mg/level) did not report dysphagia case in its own publication [39], but it was revealed in two Yale Open Data Access (YODA) studies [51,52] that there was 1 dysphagia case from 18 patients in the rhBMP-2 group (5.56%) and 2 from 15 in the ICBG group (13.33%),

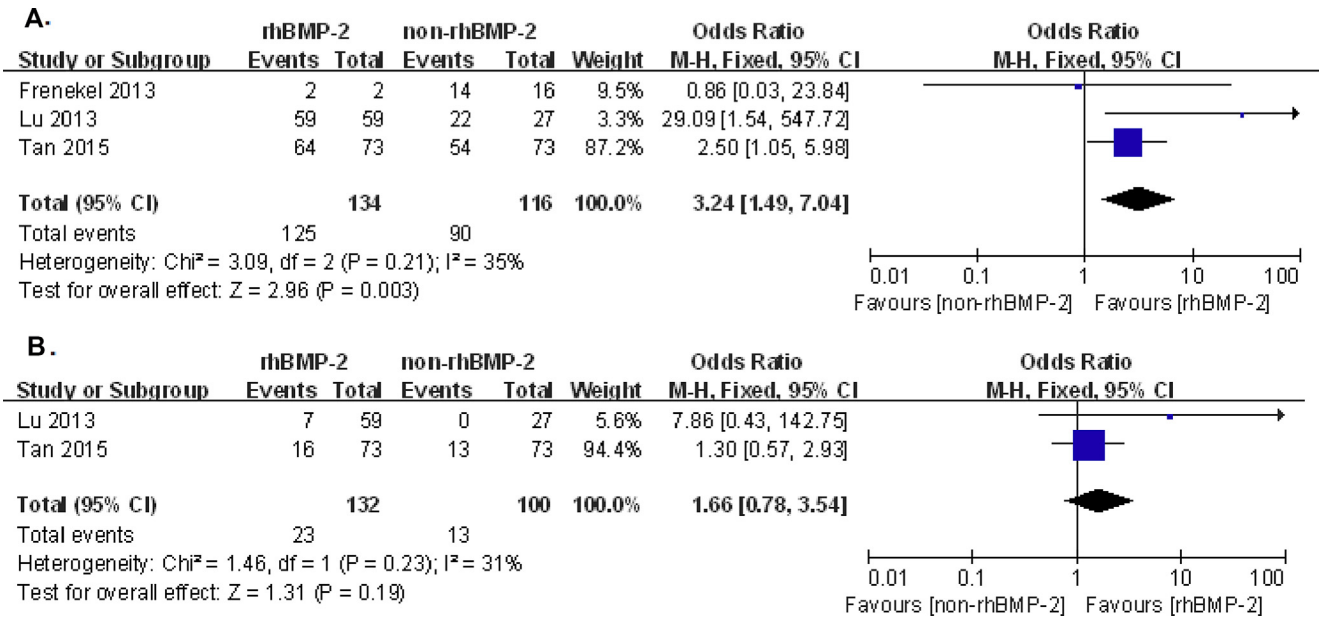

Figure 4. Forest plot and meta-analysis of influences of rhBMP-2 on the level of ACDF. (A) fusion rate; (B) complication rate in 2-level ACDF. rhBMP-2 = recombinant human bone morphogenetic protein; CI = confidence interval.

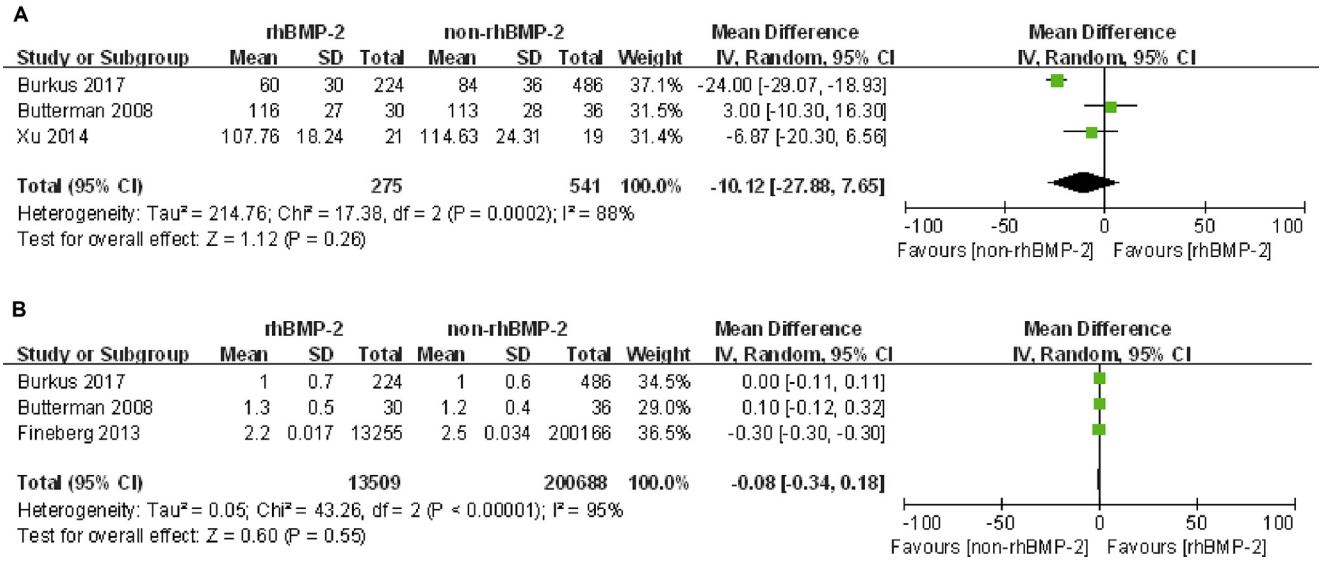

Figure 5. (A) Forest plot and meta-analysis of operation item; (B) length of hospital stay. rhBMP-2 = recombinant human bone morphogenetic protein; SD = standard deviation; IV = inverse variance method; CI = confidence interval.

showing fewer cases of dysphagia in low-dose rhBMP-2. Other two one-arm studies using ultra-low-dose (0.26–0.35 mg/level) [46] and low-dose (0.5–0.7 mg/level) [44] rhBMP-2 reported 2 of 72 (2.78%) and 4 of 37 (11%) incidence of dysphagia, respectively. However, it was hard to meta-analyse dysphagia caused by low-dose rhBMP-2 through the above three studies because of lacking contemporary non-rhBMP-2 series. Additionally, dysphagia incidence could be influenced by female gender, multi-level surgery and surgical site at C3/4 [53]; the wound infections were only considered the wounds in the cervical spine site due to no bone graft collection site in the rhBMP-2 group. We expected that these confounding factors affecting the judges of rhBMP-2 could be eliminated in future well-designed blinded RCTs. Based on our findings of complication rate and symptoms, we recommended that, when spine surgeons consider rhBMP-2 in polyetheretherketone (PEEK), the dose of rhBMP-2 would be better lower than 0.7 mg/level in ACDF for the safety concern.

The quality of life was related to neurological syndromes and pain. Neurological syndromes showed nonsignificantly adverse symptoms in the group of rhBMP-2 than non-rhBMP-2 in our meta-analysis. Regarding pain, the recruited papers applied mean value of pain score without SD, so that the meta-analysis of pain was hard to calculate. However, Basin et al. reported higher improvement of neck pain and arm pain in ACDF with the rhBMP-2 group not in ACDF without rhBMP-2 [39]. Burkus et al. reported no significant difference of neck pain and arm pain between rhBMP-2 and non-rhBMP-2 [24]. These two papers used 20-point numeric rating scale to evaluate pain, and other two recruited papers used VAS to evaluate pain, which also found no difference between the two groups [26,38]. Therefore, although these

Table 3
Sensitivity analysis comparison of rhBMP-2 and non-rhBMP-2.

Outcomes of interest	Study no.	rhBMP-2 no.	non-rhBMP-2 no.	WMD/OR (95% CI)	*p* value	Study heterogeneity			
						$\chi 2$	*df*	*I2*, %	*p* value
Total fusion rate	11	697	2980	6.96 [3.87, 12.52]	<0.00001	11.19	9	20	0.26
Operative time	3	275	541	−10.12 [27.88, 7.65]	0.26	17.38	2	88	0.0002
Hospital stay	2	254	522	0.02 [-0.08,0.11]	0.7	0.64	1	0	0.42
Complication rate	7	4904	144,570	1.40 [1.29, 1.52]	<0.00001	3.55	6	0	0.68
Dysphagia	10	5182	145,202	1.96 [1.39, 2.75]	0.0001	30.77	9	71	0.0003
Wound infections	3	3808	80,809	1.58 [1.26, 1.98]	<0.0001	1.72	2	0	0.42
Neurological symptoms	2	4658	144,369	1.23 [0.68, 2.22]	0.49	5.21	1	81	0.02
Fusion rate in 2-level ACDF	3	134	116	3.24 [1.49, 7.04]	0.003	3.09	2	35	0.21
Complication rate in 2-level ACDF	2	132	100	1.66 [0.78, 3.54]	0.19	1.46	1	31	0.23

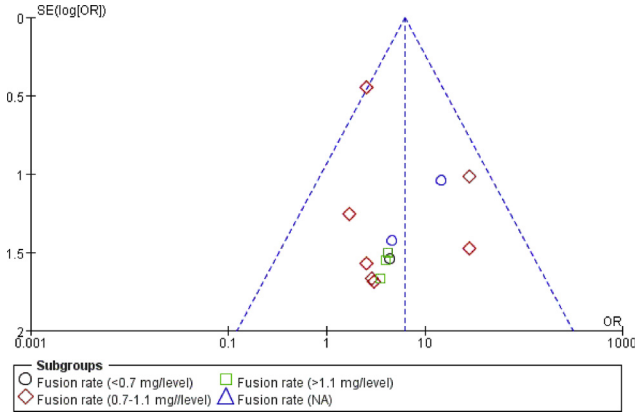

Figure 6. Funnel plot illustrating meta-analysis of fusion rate. SE = standard error; OR = odds ratio.

recruited papers could not generate the meta-analysis of pain, they showed no difference or better improvement of pain in rhBMP-2 not in non-rhBMP-2. From the two aspects—neurological syndromes and pain, ACDF with rhBMP-2 did not influence patients' quality of life, compared to ACDF without rhBMP-2.

Most studies of rhBMP-2 on ACDF did not separate the efficacy and safety data according to the levels of ACDF. Based on limited data, the trend of effects of rhBMP-2 was not obvious based on the levels of ACDF. In collected papers, one 1-level ACDF study showed fusion rates were 99.4% versus 87.2% in rhBMP-2 and non-rhBMP-2 groups [24]; our meta-analysis of 2-level ACDF showed 93.3% and 77.6%, respectively. Lu et al. analysed their data based on the levels of ACDF, showing stable 100% fusion rate but also increased complication rate and dysphagia on level-dependence in the rhBMP-2 group; these indices did not change on level-dependence in the non-rhBMP-2 group. Meanwhile, Hofstetter et al. reported the decreased fusion rate when fused levels of ACDF increased in the control group, but the fusion rate remained at 98.88–100% even in 4-level ACDF in rhBMP-2 groups, indicating the rhBMP-2 has a high osteoinduction and improved fusion in multilevel ACDF [4]. Based on the data from 29 studies and our meta-analysis, rhBMP-2 improved fusion rate especially in multi-level ACDF, but the influence did not show any level dependence. Therefore, when an ACDF due to the multi-level has a high risk of nonunion, rhBMP-2 may be an option of increasing the fusion.

The current meta-analysis is limited by only one RCT; others are prospective and retrospective nonrandomised studies. Without randomisation and double blind, the data generated may be influenced by confounding factors, like levels of ACDF, other medical conditions and surgeons' techniques. We well designed and were performing a RCT using low dose (0.5 mg/level) of rhBMP-2 in ACDF under the management of the patient and investigator variables. The data will reveal more associations of efficacy and risks of this osteoinductive cytokine in ACDF soon.

Conclusion

The rhBMP-2 doses used for single- or multi-level ACDF in 29 studies differed greatly from 0.26 to 2.1 mg/level. It is encouraging that lowest dose of rhBMP-2 was enough to achieve the best fusion rate compared to other doses of rhBMP-2. However, it is accompanied by higher complication rate with more dysphagia and wound infections in ACDF with rhBMP-2, compared to that in ACDF without rhBMP-2. Based on the meta-analysis, the lowest dose of rhBMP-2, which gained both the higher bone union and minimum complications, was 0.7 mg/level. Furthermore, considering the higher risk of nonunion in multi-level of ACDF, rhBMP-2 may be an option of increasing the fusion. Even so, healthcare practitioners should weigh the benefits of increasing union and potential risks of dysphagia and other complications drawn by this growth factor before the procedure of ACDF. Therefore, the optimal dose of rhBMP-2 in ACDF is necessary to be redefined by manufacturers in further large-volume, well-designed RCTs with extensive follow-up to achieve association from multiple dimensions.

Conflict of Interest

The authors have no conflicts of interest to disclose in relation to this article.

Acknowledgements

This work was supported by China International Exchanges and Talents Programs of CUS-RF [205458] and China Postdoctoral Science Foundation Grant [2018M643015].

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