MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 3159-3165
DOI: 10.12659/MSM.894656

Received: 2015.05.14
Accepted: 2015.06.07
Published: 2015.10.19

Comparison of rhBMP-2 versus Autogenous Iliac Crest Bone Graft for 2-Level Anterior Cervical Discectomy and Fusion for Cervical Spondylotic Myelopathy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACEF 1 Bingyi Tan
BC 2 Haiyan Wang
DE 1 Jun Dong
BD 1 Zenong Yuan
CD 1 Dachuan Wang
BD 1 Feng Wang

1 Department of Spinal Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, P.R. China
2 Shandong Medical Image Research Institute, Shandong University, Jinan, Shandong, P.R. China

Corresponding Author: Bingyi Tan, e-mail: bingytanjn@163.com
Source of support: Departmental sources

Background: Few studies have examined the efficacy of recombinant human bone morphogenetic protein-2 (rhBMP-2) in 2-level anterior cervical discectomy and fusion (ACDF). The purpose of this study was to compare the outcomes in a series of patients with CSM treated with 2-level ACDF with or without rhBMP-2.

Material/Methods: The retrospective study included a total of 146 patients with CSM. The rhBMP-2 group consisted of 73 patients who underwent 2-level ACDF with rhBMP-2. A total of 73 patients who also received 2-level ACDF with autogenous ICBG alone were included in the matched-pair ICBG group with a ratio of 1:1, based on age, sex, and BMI. All data, including fusion rate and time, VAS, JOA score, operative date, and complications, were assessed.

Results: With respect to the length of hospital stay, operative times, and blood loss, there were no significant difference between the 2 groups. However, the rhBMP-2 group presented a shorter fusion time ($P<0.013$) and higher fusion rate ($P<0.036$) than the ICBG group. In the rhBMP-2 group, 22% required additional treatment for complications compared to 18% of patients in the ICBG group, which showed no significant difference ($P=0.543$).

Conclusions: The application of rhBMP-2 in 2-level ACDF showed higher fusion rates, shorter fusion time, and similar function outcomes compared to those who received ACDF with ICBG alone.

MeSH Keywords: Bone Morphogenetic Protein 2 • Infusions, Spinal • Spinal Cord Compression

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/894656

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Background

As a result of degenerative and congenital changes, cervical spondylotic myelopathy (CSM) is a common spinal cord disorder caused by compromise of spinal canal and the compression of spinal cord, and results in significant spinal cord injury and neurological dysfunction [1–3]. It has been shown to be an age-related degenerative disorder [4,5]. It accounts for approximately 10–15% of cervical spondylosis [3,6], with a hospitalized incidence of 4.04 per 100 000 person every year in China [7]. Currently, it is usually recommended that patients with symptomatic CSM undergo surgery, including anterior cervical corpectomy with fusion (ACCF) [8–10], anterior cervical discectomy with fusion (ACDF) [8,10,11], and ACCF or ACDF, with iliac crest bone graft (ICBG) shown to improve functional outcomes postoperatively [12–14].

In the past 10 years, the application of recombinant human bone morphogenetic protein-2 (rhBMP-2) and an absorbable collagen sponge (ACS) (INFUSE, Medtronic Spinal and Biologics), mainly in anterior lumbar interbody fusion, in patients with degenerative disc disorder has been shown to be efficacious, with favorable outcomes [15–18]. The advantages of rhBMP-2 use include reduction of operating time, less blood loss, shorter hospital stay, proven efficacy for inducing fusion, and decreased morbidity involved in harvest of autograft iliac crest [19–22].

Numerous studies have reported similar complication rates in rhBMP-2 use when used in the posterolateral lumbar spine compared with harvest of autograft iliac crest [23,24]. Although an initial randomized pilot trial sponsored by the FDA showed no increase in complications for rhBMP-2 used in the anterior cervical spine [19], increased complications in postoperative hematoma and soft tissue swelling occasionally associated with airway compromise have been reported in multiple subsequent studies with larger and less contained doses [25–28]. Moreover, other studies [20,29] have demonstrated the use of rhBMP-2 combined with interbody device and lowered doses in the anterior cervical spine can improve safety and efficacy. However, the cost of rhBMP-2 use is higher than traditional procedures. The average cost for the Medtronic Cornerstone PEEK spacer is $990, and the average cost of the Cornerstone bone allograft spacer is $890 [30], but Buttermann [31] reported that the reduction in additional procedure costs in the BMP-allograft group was offset by greater outpatient costs and additional overhead costs to the practitioner.

To the best of our knowledge, although several previous studies [30,32,33] have reported on 2-level ACDF with versus without rhBMP-2, they failed to adequately distinguish between single-level and multi-level cases, which might influence the assessment of results, and these studies had different findings. Moreover, a meta-analysis published by Simmonds et al. [34] reported that rhBMP-2 use increased fusion rates and reduced pain compared with ICBG; however, a meta-analysis by Fu et al. [35] demonstrated that rhBMP-2 had no clinical advantage over ICBG and might be associated with increased risk of wound complications and dysphagia. Therefore, further studies on the comparison of rhBMP-2 use with ICBG in the treatment of CSM are urgently required. The purpose of this study was to compare postoperative outcomes in a series of patients with CSM treated with 2-level ACDF with or without rhBMP-2.

Material and Methods

This study was approved by the Institutional Review Board of Shandong Provincial Hospital. Written informed consent was obtained from all subjects included in this study.

Between January 2007 and October 2011, medical records of a total of 83 consecutive patients diagnosed with CSM and who underwent a 2-level (2 or more levels) ACDF with ICBG plus rhBMP-2/ACS (0.9 mg of rhBMP-2 per level) along with plate fixation in our hospital were retrospectively reviewed. Patients were included when they had the following criteria: 1) age 60–70 years; 2) follow-up of more than 24 months; and 3) complete data of the patients for pre- and post-operative assessment could be obtained from medical records and questionnaires. We excluded patients with active infection, trauma, tumor, metabolic disease, severe chronic disease, severe osteoporosis, or symptomatic vascular disease, and those who underwent previous cervical surgery. During the same time, 73 patients who received 2-level ACDF only with ICBG were included in a matched-pair control group at a ratio of 1:1 based upon surgical levels, age, sex, body mass index (BMI), and smoking status. Preoperative therapy was similar for all patients.

The clinical and radiographic records of all subjects were reviewed. All demographics, including patient characteristics, examination results, and operative data, were collected from hospital records or questionnaires. The radiographic data were assessed by 2 independent experienced specialists. All subjects received a 2-year follow-up postoperatively.

All surgeries were carried out by 1 of 2 fellowship-trained and experienced spine surgeons. All patients were placed in the supine position on the operating room table, and underwent ACDF with autogenous ICBG as described by Smith and Robinson [36], which mainly consisted of complete discectomy and burring down of the uncinate processes. For the patients in the control group, a small incision was made at the lateral of the iliac crest, and blunt dissection was conducted to expose the crest. For the patients in the case group, rhBMP-2 was reconstituted according to the manufacturer's instructions

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Table 1. Patient demographics and preoperative data.

Parameter	rhBMP-2 group	ICBA group	*P* value
Sample size (n)	73	73	–
Age (mean ±SD, years)	64.4±11.2	65.1±10.8	0.702
Gender (M/F)	42/31	44/29	0.823
BMI (kg/m^2)	23.9±3.6	24.1±3.2	0.437
Smokers	25	23	0.725
Follow-up (mo)	26.8±15.4	27.5±17.4	0.898
Preoperative VAS	8.4±3.45	8.8±3.29	0.794
Preoperative NDI score	35.1±3.34	34.4±3.75	0.543
Preoperative JOA score	7.9±2.42	8.1±2.59	0.589

rhBMP-2 – recombinant human bone morphogenetic protein-2; ICBG – iliac crest bone graft; SD – standard deviation; BMI – body mass index; VAS – visual analog scale; NDI – neck disability index; JOA – Japanese Orthopedic Association.

and combined with local autograft. The same screw rod implant system was used in all subjects.

All patients were managed by a standard pre- and postoperative protocol. Deep and superficial drains were routinely placed for 48 h postoperatively and antibiotics were given during the perioperative period until the drains were removed.

All patients received clinical and radiographic assessment preoperatively and postoperatively, and were asked to return for follow-up at 6 weeks, and then at 3, 6, 12, and 24 months postoperatively. Perioperative clinical parameters, including operative time, blood loss, and length of hospital stay, were obtained from medical records. The clinical outcome measures included Japanese Orthopedic Association (JOA) score, neck disability index (NDI) score, visual analog scale (VAS), patient satisfaction questionnaires, and the incidence of operative complications. Radiographic assessment was performed using dynamic X-rays. Fusion was evaluated by flexion-extension lateral radiographs introduced by Cervical Guidelines [37]. The incidence of dysphagia was retrospectively assessed with the Dysphagia Short Questionnaire developed by Skeppholm et al. [38]. Patients were classified as smokers if they had continuously smoked for at least 1 year pre- and postoperatively.

All statistical analyses were performed using SPSS version 17.0 software. The differences of dichotomous variables between the 2 groups were determined using the chi-square test. The outcomes between 2 groups were compared using a paired *t* test. Continuous variables presented as mean ± standard deviation (SD) were analyzed using the unpaired *t* test. A *P* value less than 0.05 was considered significant.

Results

In this study, a total of 146 patients who underwent an ACDF procedure were included, 73 out of which received rhBMP-2 and were included in the rhBMP-2 group with an average follow-up of 26.8 months, and the remaining with ICBG alone were included in the ICBG group with an average follow-up of 27.5 months. There were 25 smokers in the rhBMP-2 group and 23 smokers in the ICBG group. Smoking status was unrelated to outcomes scores. No significant differences were found between the 2 groups in preoperative VAS, ODI, or JOA score (Table 1).

Table 2 displays the clinical outcomes for the 2 groups. With respect to the length of hospital stay, operative times, and blood loss, there were no significant difference between the 2 groups. However, the rhBMP-2 group had a shorter fusion time ($P<0.013$) and higher fusion rate ($P<0.036$) than the ICBG group (Figure 1). No significant differences were observed between the 2 groups in functional outcomes, including VAS, ODI, or JOA score.

Regarding complications rate, 21.6% of patients in the rhBMP-2 group and 17.8% of patients in the ICBG group required extra treatment for complications, which showed no significant difference ($P=0.543$). In the rhBMP-2 group, 4 patients had deep wound infection, 4 with prolonged wound drainage, 2 with cardiac infection, 2 with gastrointestinal infection, 3 with urinary tract infection, 1 with deep vein thrombosis, and 1 with iliac crest site deep infection. In the ICBG group, 2 patients had deep wound infection, 3 with prolonged wound drainage, 3 with cardiac infection, 1 with gastrointestinal infection, 1 with urinary tract infection, 1 with deep vein thrombosis, and 1 with iliac crest site deep infection.

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Table 2. Clinical and functional outcomes for the two groups.

	rhBMP-2 group	ICBA group	*P* value
Hospital stay (d)	12.1±3.6	12.4±3.2	0.610
Operative time (min)	189.3±53.8	172.6±51.6	0.057
Blood loss (mL)	419±87.5	394±85.3	0.082
Fusion time, d	82.6±28.4	93.2±22.6	0.013*
Fusion rate (%)	64 (87.7%)	54 (74.0%)	0.036*
VAS (mean ±SD)	1.8±1.12	2.1±1.29	0.162
NDI (mean ±SD)	14.6±4.2	13.2±3.7	0.336
JOA (mean ±SD)	13.4±2.71	12.9±3.01	0.558

* *P* value was significant.

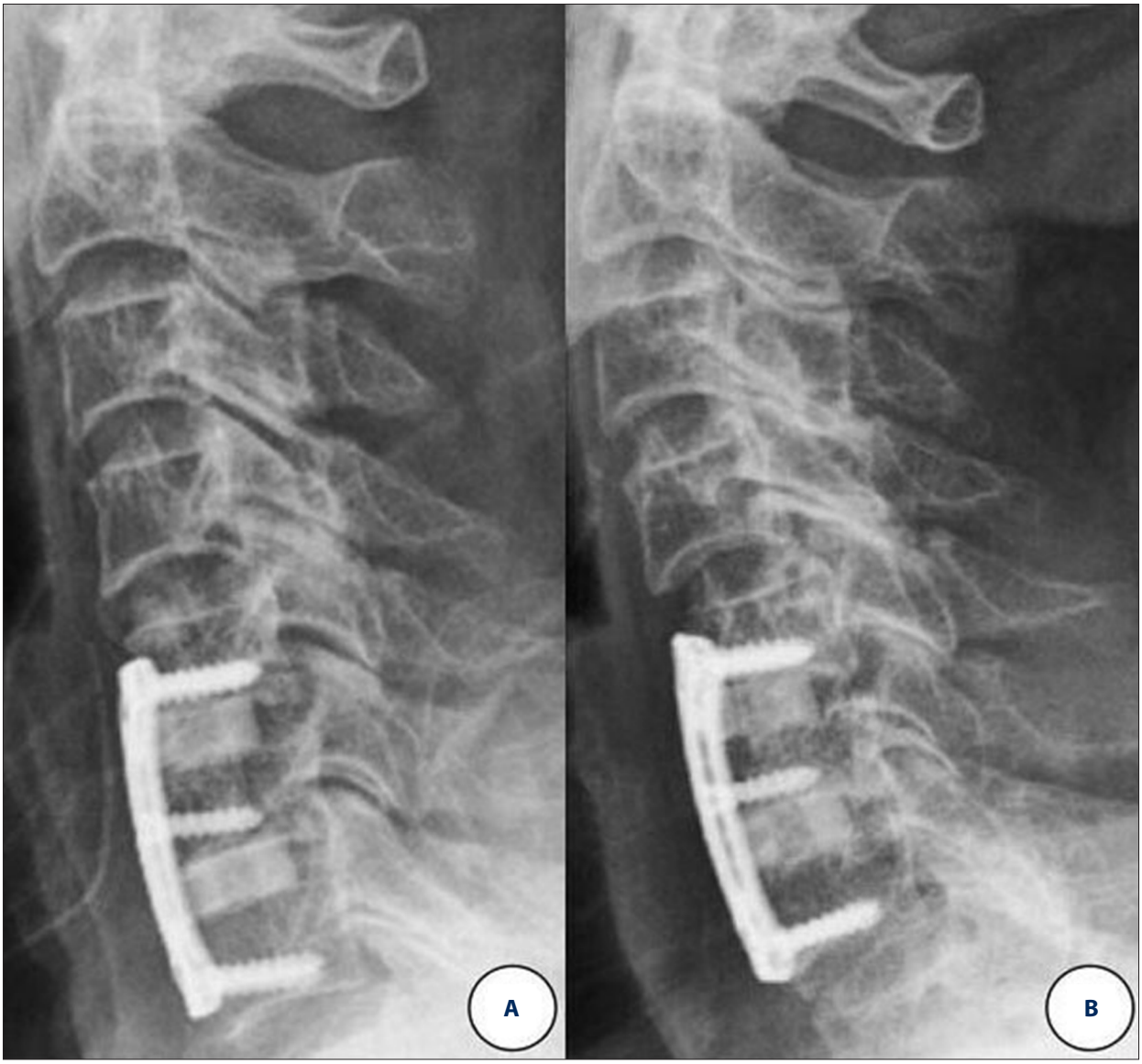

Figure 1. Lateral X-ray film at 2 weeks (**A**) and at 5 months (**B**) postoperatively in a patient who had a 2-level ACDF using rhBMP-2.

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Table 3. Complications.

Complication	rhBMP-2 group	ICBA group	*P* value
Deep wound infection	4	2	–
Prolonged wound drainage	4	3	–
Cardiac infection	2	3	–
Gastrointestinal infection	2	1	–
Urinary tract infection	3	1	–
Deep vein thrombosis	1	1	–
Iliac crest site deep infection	1	1	–
Total	16	13	0.543

All infections were completely controlled by intravenous antibiotics and daily dressing (Table 3).

Discussion

Recombinant human bone morphogenetic protein-2 is an osteoinductive growth factor that stimulates stem cells to differentiate into bone-producing cells [39]. RhBMP-2, used as an ICBG replacement in conjunction with lordotic tapered cages for anterior lumbar interbody fusion, was approved by the FDA in 2002. Since then, rhBMP-2/ACS has been widely used, but the initial application has been considered off-label in transforaminal lumbar interbody fusion or posterolateral spinal fusion [24,40,41]. A number of animal and human studies have thoroughly evaluated whether this substance could effectively promote spinal fusion; in many case-control reports, the success rate and quality or quantity of the fusion mass have been superior to autograft [42,43].

Primary reports have been favorable. A study of 98 patients using rhBMP-2 on a compression-resistant matrix (CRM) *vs.* ICBG for single-level posterolateral lumbar fusion with 2-year follow-up published by Dimar et al. [27] demonstrated significant clinical improvements in both groups at all time intervals, but there were no statistically significant differences between groups. RhBMP-2 achieved significantly higher success rates of fusion, shorter operative times, less blood loss, and similar complications rates compared to ICBG alone. Boden et al. [44] carried out a prospective, randomized pilot study to compared rhBMP-2 with 60% hydroxyapatite and 40% tricalcium phosphate granules with autogenous ICBG. They found rhBMP-2 still achieved better fusion rates clinical outcomes despite the relatively high concentration of rhBMP-2 used. However, the relatively small sample size of their study might influence reliability of the results. Despite constant expansion of rhBMP-2 use in spinal fusion surgery to increase spinal fusion rates and avoid donor-site complications, to the best of our knowledge the present study is the first to compare ICBG plus rhBMP-2/ACS with ICBG alone for anterior 2-level fusion. In our study, the fusion rate for iliac crest in ACDF was 74%. However, Yoon et al. [45] reported a fusion rate of 97% for multi-level ACDF. The low fusion rate in our study might be due to status of patients or experience of surgeons, especially the difference in radiographic methods of assessment.

ACDF with autogenous ICBG is an effective treatment in the management of CSM. In the present study the case group received rhBMP-2 together with autograft bone, which can avoid the risk of transmission associated with the use of allograft bone [46]. The most notable complication reported in previous studies regarding rhBMP-2 use in ACDF is dysphagia caused by retropharyngeal cervical soft-tissue swelling [21,47]. However, those ACDF procedures without rhBMP-2 in multilevel fusion had an inherent risk of dysphagia associated with cervical swelling [48]. The present study revealed ACDF with rhBMP-2 is as effective as ICBG alone in terms of fusion times and rates, and has the same risk of complications and similar functional scores.

A previous study reported a possible correlation between the total rhBMP-2 dose and the incidence of dysphagia [30], which suggests the impact of the total dose of rhBMP-2 used on the severity of dysphagia. However, Buttermann [31] used 0.9 mg for a single-level ACDF of up to 2.7 mg of BMP for a 3-level ACDF, with no dose relationship observed with neck swelling. In this study, we observed no difference in dysphagia incidence between the 2 groups. Therefore, further studies still are needed.

Although the economics of rhBMP-2 use is not the focus of this paper, it is a subject that deserves more attention. Depending on the price of rhBMP-2, there is an approximate $900 difference in instrumentation/substrate cost between cases with and without rhBMP-2. Lu et al. reported an increased cost of approximately $22 000 with this procedure. However, the

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contribution to higher implantation costs by bone graft alternatives may be offset by higher fusion rates, lower revision rates, and improved clinical outcomes. Therefore, the overall long-term costs in both groups are similar.

Several limitations of the present study should be considered. First, some subjects were not randomized into groups, which weakens the comparison. Second, the relatively small number of patients in each group might preclude detection of any true differences between them. Third, clinicians develop their own criteria for the choice of surgical procedure for individual cases. Finally, the follow-up period was too short to evaluate the long-term results or any long-term differences in clinical outcomes of the 2 groups. Spine surgeons must continue to balance the inherent risks of surgical intervention with the expected benefits. Studies are needed to determine the optimal carrier, placement, and dosing in the anterior cervical spine.

Conclusions

In summary, the use of rhBMP-2 in 2-level ACDF showed higher fusion rates, shorter fusion time, and similar function outcomes compared to ACDF with ICBG alone. However, in consideration of several weaknesses of our study, further studies with larger sample sizes and better experimental designs are needed.

Competing interests

The authors declare that they have no competing interests.

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