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Clinical Study

Efficacy of *Escherichia coli*-derived recombinant human bone morphogenetic protein-2 in posterolateral lumbar fusion: an open, active-controlled, randomized, multicenter trial

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Abstract

BACKGROUND CONTEXT: The efficacy and safety of recombinant human bone morphogenetic protein-2 (rhBMP-2) as a bone graft substitute in spinal fusion has been widely researched. However, no study of the efficacy and safety of *Escherichia coli*-derived rhBMP-2 (E.BMP-2) with a hydroxyapatite (HA) carrier has been proposed.

PURPOSE: This study aimed to compare the efficacy and safety of fusion materials between E.BMP-2 and autogenous iliac bone graft in posterolateral fusion (PLF).

STUDY DESIGN/SETTING: An open, active-controlled, randomized, multicenter trial was carried out.

PATIENT SAMPLE: This study included 93 patients who underwent single-level lumbar or lumbosacral PLF.

OUTCOME MEASURES: The primary outcome measure was computed tomography (CT)-based fusion rate at 12 and 24 weeks. Secondary outcome measures were fusion grade by radiographs

FDA device/drug status: Investigational (Novosis, *E. coli*-derived rhBMP-2).

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and CT at 12 and 24 weeks and changes in Oswestry Disability Index (ODI), Short Form-36 (SF-36) Health Survey, and visual analogue scale (VAS).

METHODS: Patients who underwent 1-level PLF (between L1 and S1) for severe spinal stenosis or grade 1 spondylolisthesis were randomized to receive E.BMP-2 with an HA carrier (E.BMP-2 group) or autogenous iliac bone graft (AIBG group). Thin-section CT (<2 mm), VAS, ODI, and SF-36 were obtained pre- and postoperatively at 12 and 24 weeks. Outcome measures were compared between the groups.

RESULTS: A total of 100 patients were enrolled in this trial. Among them, 93 patients underwent planned surgery. Preoperative demographic and clinical data showed no difference between groups. CT-based fusion rates were 100.0% (41/41) for the E.BMP-2 group and 90.2% (46/51) for the AIBG group (p=.062) at 12 weeks and 100.0% (41/41) and 94.1% (48/51) (p=.251) at 24 weeks, respectively. Fusion grade based on radiographs and CT showed non-inferiority of the E.BMP-2 group compared with the AIBG group. All clinical parameters improved postoperatively. However, there was no difference in changes in VAS, ODI, or SF-36 between the groups. No serious adverse event related to E.BMP-2 was found.

CONCLUSIONS: The fusion rate of E.BMP-2 was comparable with that of AIBG following PLF. Good clinical efficacy and safety of E.BMP-2 in spinal fusion were also revealed. It was also suggested that HA shows suitability as a carrier for E.BMP-2. Thus, E.BMP-2 with an HA carrier can be an alternative bone graft material in spinal fusion.

Keywords: Carrier; Clinical trial; *E. coli*; Hydroxyapatite; Iliac bone graft; Lumbar; Posterolateral fusion; rhBMP-2

Introduction

Posterior lumbar interbody fusion or posterolateral fusion (PLF) is a frequently used procedure following wide decompression caused by spinal stenosis or spondylolisthesis. Traditionally, iliac crest bone graft was used to achieve solid bone fusion in spinal surgery. However, there were several problems, such as donor-site morbidity and insufficient volume in cases of osteoporosis or PLF [1]. To avoid the disadvantages of iliac bone graft, various bone graft substitutes, including local bone, allograft, or demineralized bone matrix, have been attempted and studied [2,3].

Recently, recombinant human bone morphogenetic protein-2 (rhBMP-2) has been widely researched as a bone graft substitute, which is known to have an osteoinductive activity [4,5]. Previously, mammalian origin cell lines, such as Chinese Hamster Ovary cells, were used to purify rhBMP-2 [6]. However, this method incurred low yield and high cost for obtaining sufficient amounts of rhBMP-2 because of a post-translational problem [7]. To overcome this problem, *Escherichia coli*-derived rhBMP-2 (E.BMP-2) has been researched as an alternative, and comparable efficacy has been reported [8,9]. Regardless of the economic advantage with large quantity production, the efficacy of E.BMP-2 has been questioned because dimerization does not occur in the final structure. In fact, it was reported that the osteoblastic differentiation by E.BMP-2 in mesenchymal stem cells was inferior to that in Chinese Hamster Ovary cell rhBMP-2 [10]. However, it has been reported that the efficacy of both forms of rhBMP-2 showed no difference for in vivo studies [8,11]. Osteoinductivity of E.BMP-2 has also been reported in many studies [9,11,12]. Furthermore, high purity has been suggested by dimerization through biochemical processing [11,13].

Application of rhBMP-2 requires carriers. Previously, a collagen carrier was frequently used [14]. However, it exhibits poor osteoconductivity and poor affinity for rhBMP2. Subsequently, calcium phosphate-based ceramics were suggested to overcome these disadvantages [15]. Additionally, osteoinductive activity by E.BMP-2 with a hydroxyapatite (HA) carrier was proposed in an animal model [16].

Therefore, we attempted to reveal the efficacy and safety of E.BMP-2 with an HA carrier when applied to lumbar posterolateral fusion. Although there have been several studies comparing clinical outcomes and safety profiles between rhBMP-2 and autogenous iliac bone graft (AIBG) in lumbar fusion surgery, this is the first study to analyze the efficacy and safety of E.BMP-2 with an HA carrier compared with AIBG in spinal fusion. Thus, this study aims to compare clinical efficacy and safety of E.BMP-2 with an HA carrier and AIBG as bone graft substitutes in lumbar PLF.

Materials and methods

Study design

This study was an open, active-controlled, randomized, multicenter trial. Patients were enrolled competitively in eight institutions from March 2013 to March 2016 after approval from the institutional review board at each institution. This trial was registered in ClinicalTrials.gov (NCT01764906) and was conducted following the principles of the Declaration of Helsinki and guidelines of Good Clinical Practice.

Inclusion criteria were as follows: (1) 18–80 years old and (2) patients requiring one-level posterior decompression and L1 and S1 fusion because of severe spinal stenosis, grade 1 spondylolisthesis, or spondylolysis. Exclusion criteria were

EVIDENCE & METHODS

Context
The authors performed an RCT looking at fusion rates and clinical outcomes between E. coli-derived rhBMP-2 in an HA carrier and ICBG for single-level instrumented posterolateral fusions.

Contribution
They found no statistically significant differences in fusion rates, functional and pain outcomes, and complication rates.

Implications
The basic methodology in this study is solid, but caution is worthwhile. Concerns include the short-term follow-up (24 weeks); the ability to accurately assess fusion when HA hasn't yet resorbed; no mention of costs/value (ICBG fused and had equal postop pain—so the older arguments for BMPs that included differences in need for revision and morbidities don't apply); and financial conflicts of interest. Previous studies of rhBMP-2 in posterolateral fusion have shown increased risk of early radicular pain and seroma (which were not directly assessed in this study), and the need for high doses to obtain fusion that likely increase the risk potential.

as follows: (1) average spine T-score <–3.0 on dual-energy X-ray absorptiometry, (2) history of cancer (<5-year disease-free state is confirmed), (3) serum calcium and phosphorous level below –30% of the normal lower limit or above 30% of the normal upper limit, (4) patients who cannot stop anticoagulation therapy, (5) diabetes with serious complications, (6) female patients in their childbearing years who do not agree with contraception during the clinical trial period, and (7) specific conditions including psychological problems, drug intoxication, liver disease, kidney disease, respiratory disease, or metabolic disease.

History, vital signs, and informed consent were obtained during the screening period. Patients were regularly followed up at 2, 12, and 24 weeks postoperatively. Plain radiographs were obtained and laboratory tests were conducted at every visit, and three-dimensional computed tomography (CT, thin cut, <2 mm) was obtained at 12 and 24 weeks postoperatively. Clinical outcomes were evaluated by the visual analogue scale (VAS) concerning back and leg pain, Oswestry Disability Index (ODI), and Short Form-36 (SF-36) Health Survey preoperatively and 12 and 24 weeks postoperatively.

Randomization

Enrolled patients were randomized to two groups in a 1:1 ratio. Randomization was conducted through an interactive web response system. To minimize bias, stratified block randomization by each institution was used. Randomized allocation codes were generated by PROC PLAN procedure using the Statistical Analysis System (SAS Institute Inc, Cary, NC, USA). Surgeons were blinded until the operation day, and could not identify randomization codes for patients in advance.

Intervention

Lumbar PLF was performed as a routine matter. After posterior midline approach, decompression with laminectomy and flavectomy was performed. Pedicle screw fixation in the involved level and assigned bone graft materials were applied between two transverse processes. In the E.BMP-2 group, we used Novosis (Bioalpha Inc, Gyeonggi-do, Korea), which was *E. coli*-derived rhBMP-2 with an HA carrier. About 3 g (8 cc) of HA was soaked with 1 vial (3.0 mg) of E.BMP-2 and applied in the intertransverse space with caution to avoid leaking into the neural structure. This process was repeated in the contralateral side. In the AIBG group, about 8 cc of iliac bone graft was used in each side. The bone graft from laminectomy was not used in both groups. Then, wound closure was performed after applying suction drainage.

Outcome measures

The primary outcome measure was CT-based fusion rate at 12 and 24 weeks. The fusion status was assessed by bone bridging in coronal reconstruction images of CT scans. Secondary outcome measures were fusion grade by radiographs and CT at 12 and 24 weeks, and percent change from baseline of ODI, SF-36, and VAS. Fusion grade was defined as follows: grade 1—no fusion; grade 2—partial or limited unilateral; grade 3—partial or limited bilateral; grade 4—solid unilateral; grade 5—solid bilateral [17]. Fusion grades 2, 3, 4, and 5 were defined as "fusion." Radiological outcomes were assessed twice at a one-month interval by two independent radiologists who were not involved with any other aspects of the study.

Percent change from baseline of ODI, SF-36, and VAS was calculated as (ODI, SF-36, and VAS at each visit – Baseline)/Baseline × 100 (%). In case of SF-36, mean score was used in the calculation after converting the score of each item to a scale of 0–100.

Safety evaluation

Safety of E.BMP-2 was evaluated by occurrence and severity of all adverse events. Treatment-emergent adverse events were analyzed by each group and each part of the body. Each event was assessed for a relationship with E.BMP-2.

Statistical analysis

Sample size was estimated using the study of Glassman et al. [17]. In this study, fusion grades at 24 weeks were 4.35±1.11 and 3.16±1.44 in the rhBMP-2 group and AIBG group, respectively. In this regard, the limit of non-inferiority

was established as 1.1. The null hypothesis was that the inferiority of E.BMP-2 to autogenous iliac bone graft, based on CT-based fusion grade at 24 weeks, would be greater than the non-inferiority limit (fusion grade in the E.BMP group – fusion grade in the AIBG group >−1.1). To obtain a power of 90% with an alpha of 0.05, 40 patients were required for each group with a 1:1 randomization ratio. Finally, 50 patients were to be enrolled in each group in anticipation of a 20% follow-up loss.

Demographic data were analyzed descriptively. Comparative analysis between the groups was performed using the two-sample *t* test or Wilcoxon rank sum test for continuous variables and chi-square test or Fischer exact test for categorical variables. Intraobserver and interobserver agreements were assessed by calculating intraclass correlation coefficients (ICCs), with ICCs of 0.8 to 1.0, 0.6–0.79, and <0.6 defined as good, moderate, and poor, respectively. All statistical analyses were performed using the Statistical Analysis System (SAS Institute Inc). p-Values <.05 were considered statistically significant.

Results

Patients

Among the 103 patients screened, 100 patients were randomized into the two groups. After exclusion (5 withdrawal, 1 violation of the protocol, and 1 incompatibility judged by the investigator), the intention-to-treat analysis of the outcomes was based on 93 patients (42 for the BMP-2 group and 51 for the AIBG group). Enrollment, allocation, and exclusion are summarized in Fig. 1. Per-protocol analysis was based on 87 patients after excluding a further six patients who violated the protocols during follow-up. Six violations of protocols were as follows: 2 absence of 24-week CT scans, and 4 uses of prohibited drugs or therapies.

Demographic and baseline characteristics did not differ between the E.BMP-2 and AIBG groups (Table 1). Operation time (168 minutes vs. 180 minutes, p=.148), degree of transfusion (484 mL vs. 558 mL, p=.376), and hospitalization period (10.2 vs. 10.4 days, p=.553) did not differ between the groups.

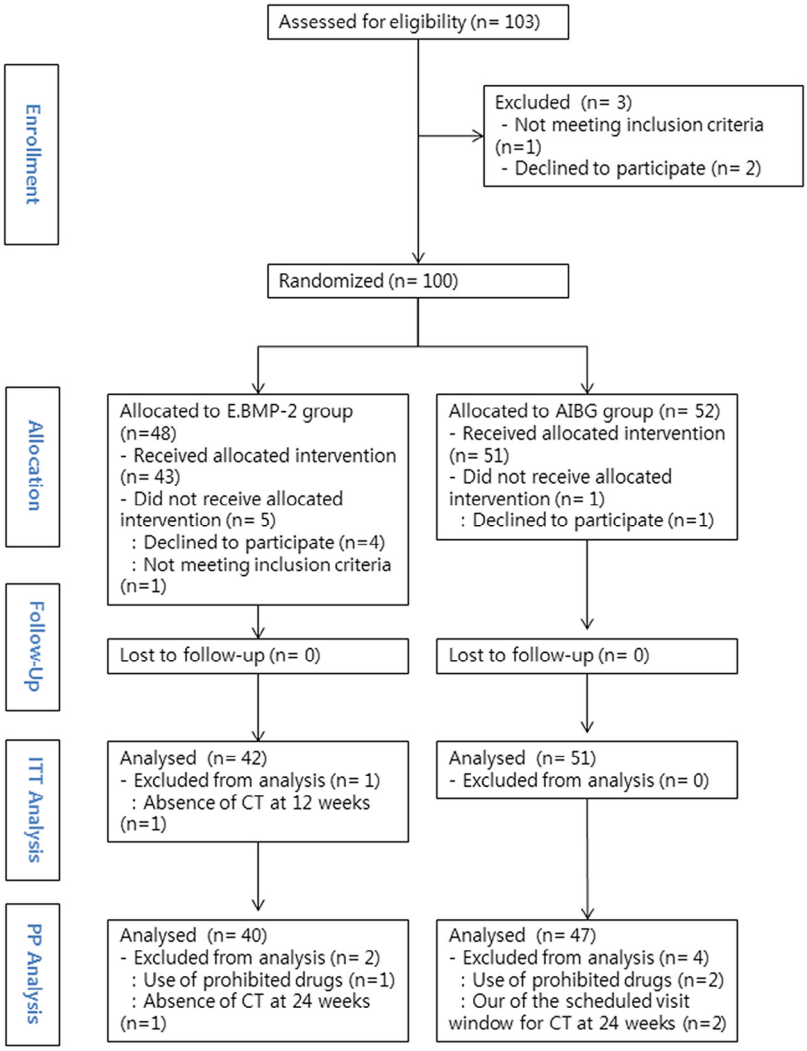

Fig. 1. Flow diagram showing the process of enrollment, allocation, follow-up, and analysis.

Table 1
Demographic and baseline characteristics

	E.BMP-2 group (n=42)	AIBG group (n=51)	p-Value
Age (y)	64.9±8.4	62.0±9.2	.121
Gender			.533
Male	20 (47.6%)	21 (41.2%)	
Female	22 (52.8%)	30 (58.8%)	
Height (cm)	160.4±9.2	160.1±9.0	.982
Weight (kg)	64.4±9.6	66.4±10.8	.354
BMI (kg/m^2)	25.0±3.1	25.9±3.3	.214
Smoking			.345
Current smoker	4 (9.5%)	6 (11.8%)	
Ex-smoker	6 (14.3%)	13 (25.5%)	
Non-smoker	32 (76.2%)	32 (62.7%)	
Drinking			1.000
Current drinker	13 (40.0%)	17 (33.4%)	
Ex-drinker	4 (9.5%)	4 (7.8%)	
Non-drinker	25 (59.5%)	30 (58.8%)	
BMD (T-score)	–0.4±1.5	–0.2±1.7	.555
Radiological findings			
Grade 1 spondylolisthesis	22 (52.4%)	25 (49.0%)	
Spinal stenosis	31 (73.8%)	43 (84.3%)	
Spondylolysis	0	2 (3.9%)	
Herniated intervertebral disc	7 (16.7%)	14 (27.5%)	

E.BMP-2, *Escherichia coli*-derived recombinant human bone morphogenetic protein-2; AIBG, autogenous iliac bone graft; BMI, body mass index; BMD, bone mineral density.

Primary outcome measure

CT-based fusion rates showed no difference between the groups. Fusion rates at 12 weeks were 100.0% (42/42) in the E.BMP-2 group and 90.2% (46/51) in the AIBG group (p=.062). Fusion rates at 24 weeks were 100.0% (41/41) in the E.BMP-2 group and 94.1% (48/51) in the AIBG group (p=.251).

Characteristics of fusion in CT images were slightly different between the groups. Although fusion mass was detected in both groups, HA carriers remained without resorption in the E.BMP-2 group. However, continuity of fused mass was more uniformly observed in the AIBG group than the E.BMP-2 group (Fig. 2).

Secondary outcome measures and adverse events

Fusion grade based on radiographs and CT at 12 and 24 weeks are compared in Table 2. In all analyses, lower limit of the 95% confidence interval was greater than the non-inferiority limit (–1.1). Intraobserver agreements were good (ICC=0.836 for rater 1 and 0.802 for rater 2). Interobserver agreements were moderate (ICC=0.785 for the first rating and 0.748 for the second rating). Clinical parameters showed improvement postoperatively in both groups. VAS (lumbar, right leg, and left leg), ODI, and SF-36 at baseline, 12 weeks, and 24 weeks are described in Fig. 3. No differences for each clinical parameter were observed between the groups at baseline, 12 weeks, and 24 weeks. In addition, percent change from

Table 2
Fusion grade based on radiographs and CT scans at 12 and 24 weeks

	E.BMP-2 group (n=42)	AIBG group (n=51)	p-Value
Fusion grade by radiographs (12 wk)	4.86±0.47	4.20±1.00	<.001
Mean difference (95% CI)		0.66 (0.33, 0.99)	
Fusion grade by radiographs (24 wk)	4.98±0.16	4.04±1.09	<.001
Mean difference (95% CI)		0.93 (0.60, 1.27)	
Fusion grade by CT (12 wk)	4.48±0.83	4.02±0.93	.013
Mean difference (95% CI)		0.46 (0.09, 0.82)	
Fusion grade by CT (24 wk)	4.56±0.81	3.98±0.94	<.001
Mean difference (95% CI)		0.61 (0.25, 0.97)	

E.BMP-2, *Escherichia coli*-derived recombinant human bone morphogenetic protein-2; AIBG, autogenous iliac bone graft; CT, computed tomography; CI, confidence interval.

baseline of VAS, ODI, and SF-36 showed no difference at 12 and 24 weeks between the groups (Table 3).

The most frequently observed adverse events were constipation (11 patients in the E.BMP-2 group and 10 patients in the AIBG group) and pyrexia (9 patients in the E.BMP-2 group and 13 patients in the AIBG group). However, there was no difference for overall adverse events between the groups (p=.975). Serious treatment-emergent adverse events were detected in 9 patients (10 cases): two for the E.BMP-2 group and eight for the AIBG group (Table 4, p=.173). However, no events were related to the medical device. No deaths or serious complications leading to trial termination

}Table 3
Percent changes from baseline of VAS, ODI, and SF-36

	E.BMP-2 group (n=42)	AIBG group (n=51)	p-Value
VAS (lumbar) at 12 wk	–66.4±33.3	–37.8±97.7	.288
Mean difference (95% CI)		–28.62 (–59.42, 2.18)	
VAS (lumbar) at 24 wk	–56.4±37.9	–42.4±88.3	.814
Mean difference (95% CI)		–14.08 (–42.91, 14.75)	
VAS (left leg) at 12 wk	–70.1±43.5	–47.0±106.3	.819
Mean difference (95% CI)		–23.08 (–57.78, 11.62)	
VAS (left leg) at 24 wk	–67.3±40.9	–56.1±77.8	.247
Mean difference (95% CI)		–11.17 (–37.92, 15.59)	
VAS (right leg) at 12 wk	–47.6±124.5	–68.4±46.7	.651
Mean difference (95% CI)		20.75 (–22.72, 64.22)	
VAS (right leg) at 24 wk	–38.4±142.6	–64.3±81.2	.404
Mean difference (95% CI)		25.83 (–27.46, 79.12)	
ODI at 12 wk	–29.8±48.7	–36.1±44.8	.480
Mean difference (95% CI)		6.35 (–12.92, 25.62)	
ODI at 24 wk	–39.1±44.6	–38.3±43.6	.960
Mean difference (95% CI)		–0.79 (–19.13, 17.56)	
SF-36 at 12 wk	50.2±62.8	50.3±87.1	.881
Mean difference (95% CI)		–0.10 (–31.05, 30.86)	
SF-36 at 24 wk	60.3±74.3	60.0±87.4	.684
Mean difference (95% CI)		0.29 (–33.82, 34.40)	

E.BMP-2, *Escherichia coli*-derived recombinant human bone morphogenetic protein-2; AIBG, autogenous iliac bone graft; VAS, visual analogue scale; ODI, Oswestry Disability Index; SF-36, Short Form-36 Health Survey; CI, confidence interval.

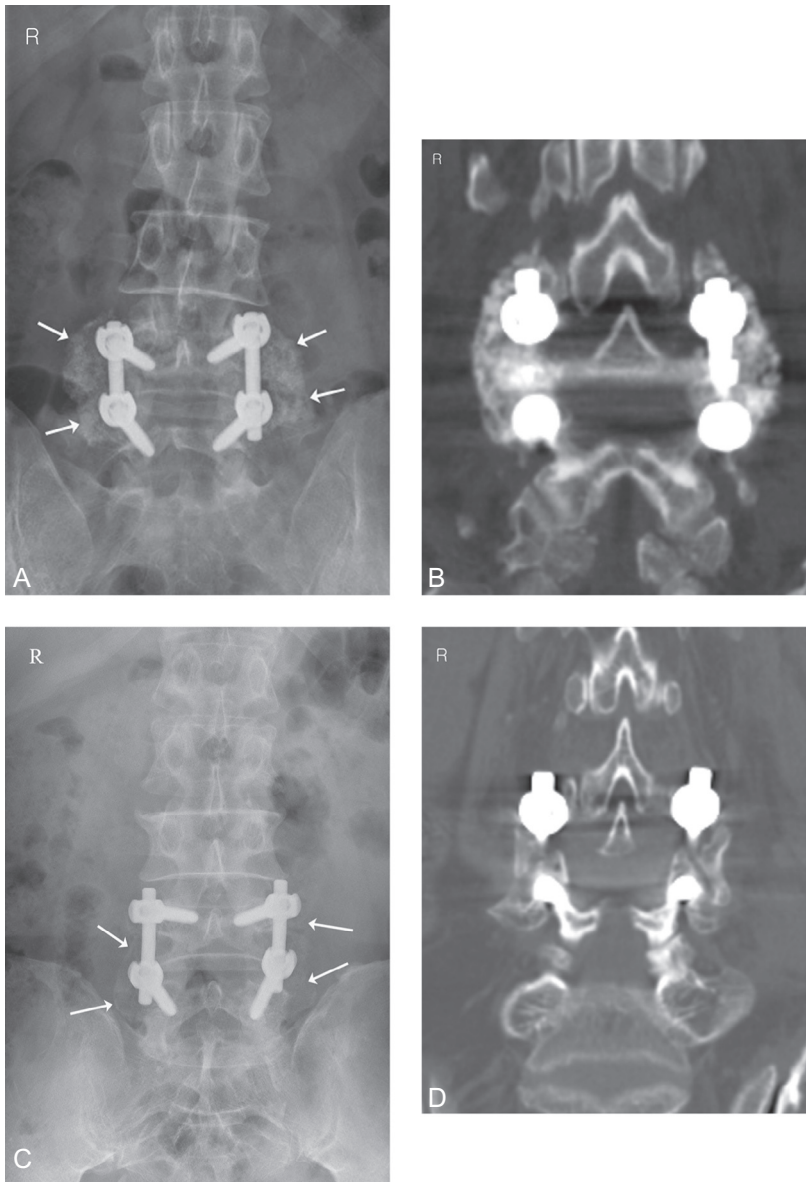

Fig. 2. Characteristics of fusion mass taken in postoperative 12 weeks. (A) Fusion mass in a radiograph in the E.BMP-2 group (arrows). (B) Remaining HA carrier without resorption in the E.BMP-2 group. (C) Fusion mass in a radiograph in the AIBG group (arrows) (D) Continuously fused mass in the AIBG group. AIBG, autogenous iliac bone graft; E.BMP-2, *Escherichia coli*-derived recombinant human bone morphogenetic protein-2; HA, hydroxyapatite.

were found. In addition, no difference of laboratory tests was found between two groups.

Discussion

The efficacy of rhBMP-2 in spinal surgery has been widely researched. Many studies revealed comparable fusion rates and clinical outcomes for rhBMP-2 as a bone graft substitute in different types of spinal fusion. More rapid incorporation and formation of fusion mass was suggested when rhBMP-2 was used as a bone graft substitute in PLF [17]. In another multicenter trial, the fusion rate was higher in the rhBMP-2 group than in the autograft group (94% vs. 69%, p=.007), although clinical outcomes were not different [18]. The efficacy of E.BMP-2 as an alternative to mammalian cell origin rhBMP-2 was also suggested in animal studies [19,20]. Additionally, osteoinductivity of E.BMP-2 was comparable with that of mammalian cell BMP-2 [21,22]. Based on our study, efficacy of E.BMP-2 with an HA carrier in spinal fusion was comparable with that of an autograft. Moreover, there was a trend of early fusion in the E.BMP-2 group compared with the AIBG group (100.0% vs. 90.2%, at 3 months), although it did not reach statistical significance (p=.062). This difference disappeared 6 months postoperatively (p=.251). This means that more rapid fusion might be induced by E.BMP-2. Osteoinductive activity to induce rapid fusion will be critical for patients with specific conditions, such as osteoporosis. This activity could be

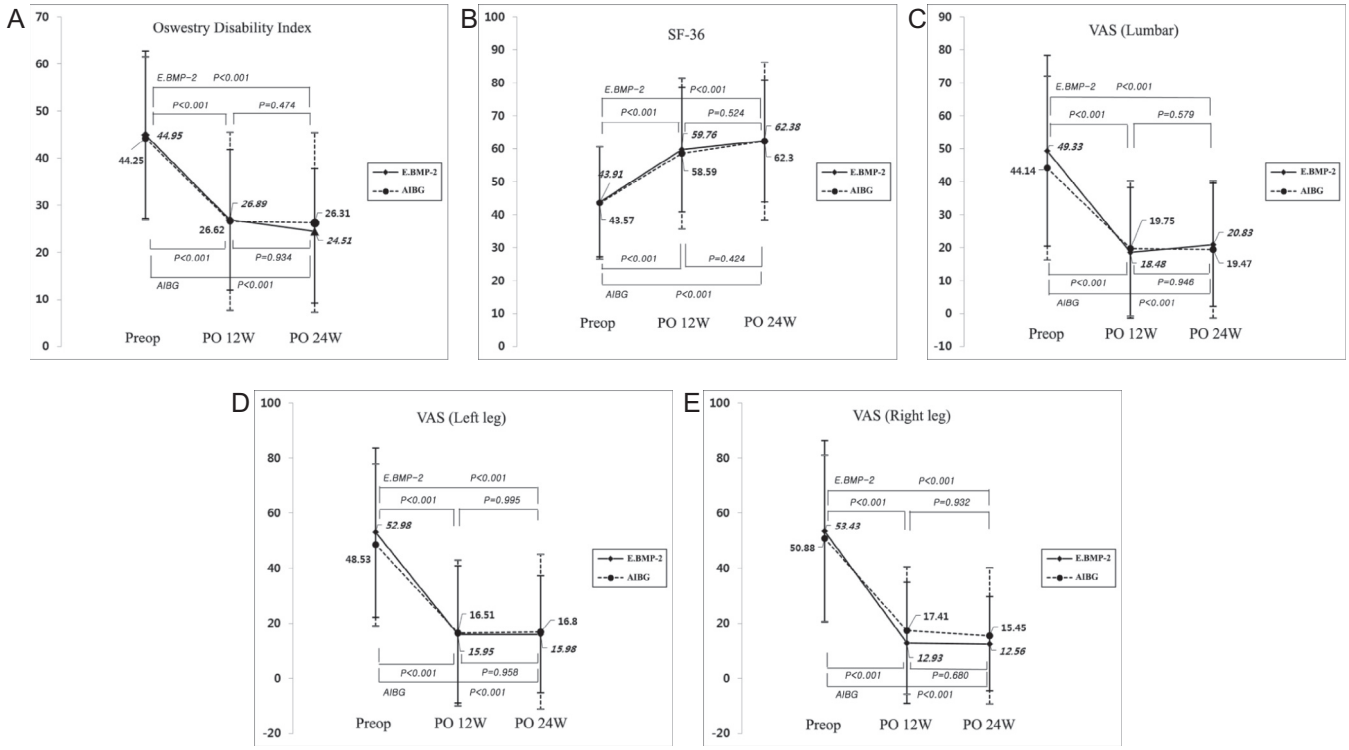

Fig. 3. Comparison of clinical parameters between the groups. (A) Oswestry Disability Index (ODI), (B) Short Form-36 (SF-36), (C) Visual analogue scale (VAS) (lumbar), (D) VAS (left leg), (E) VAS (right leg). AIBG, autogenous iliac bone graft; E.BMP-2, *Escherichia coli*-derived recombinant human bone morphogenetic protein-2.

increased by a higher dosage of E.BMP-2, which was supported by previous studies [16,19].

However, the toxicity of E.BMP-2 can be a problem with higher dosage. No observed adverse effects occurred with the intravenous administration of 0.5 mg/kg E.BMP-2 in rats [23]. It was also suggested that the lethal dose of E.BMP-2 would be higher than 7.0 mg/kg in rats [24]. These studies showed relative safety of E.BMP-2. We used 3 mg of E.BMP-2 bilaterally. If we assume that the mean weight of patients is 60 kg, then 0.1 mg/kg is the corresponding dose used herein. This is thought to be a safe dose based on previous toxicology studies. In fact, no E.BMP-2-related complications were observed during this trial.

Table 4
Incidence of serious treatment-emergent adverse events

	E.BMP-2 group (n=42)	AIBG group (n=51)	p-Value
Overall	2 (4.8%)	8 (15.7%)	.107
Pyrexia	1 (2.4%)	1 (2.0%)	
Pneumonia	0	1 (2.0%)	
Urinary tract infection	0	1 (2.0%)	
Postoperative hematoma	0	1 (2.0%)	
Wound dehiscence	0	1 (2.0%)	
Abdominal pain	1 (2.4%)	0	
Muscular weakness	0	1 (2.0%)	
Normal pressure hydrocephalus	0	1 (2.0%)	
Deep vein thrombosis	0	1 (2.0%)	

E.BMP-2, *Escherichia coli*-derived recombinant human bone morphogenetic protein-2; AIBG, autogenous iliac bone graft.

Conversely, there have been several reports expressing concern because of high complication rates. High subsidence rate and end plate resorption were frequently reported, although their clinical significance was not clearly revealed [25–29]. Painful seroma formation, which required revision surgery, was reported in 4.6% of the patients [30]. Soft tissue swelling can be a life-threatening complication, especially in cervical anterior surgery [31]. This critical safety issue prevented widespread use of rhBMP-2, especially in the cervical spine [32,33]. In addition, retrograde ejaculation [34–36], direct neural toxicity [37,38], and foraminal ossification were suggested by many studies [39].

Nevertheless, there is also support for the safety of rhBMP-2 [40,41]. However, it would be prudent to judge the risk of complications based on the recent meta-analysis [36]. They demonstrated a higher rate of general complications as well as retrograde ejaculation, heterotopic ossification, and cervical tissue swelling. In our study, the incidence of general complications as well as serious adverse events did not differ between the groups. Because degrees of improvement in clinical outcomes did not differ between the groups, it was inferred that the risk of neuritis or symptomatic seroma formation did not increase. However, because the trial period of this study was 24 weeks from the surgery, only short-term complications could be detected. In fact, one of the concerns of using rhBMP-2 was the risk of cancer development. This concern

resulted from the possible activation of BMP receptors in various cancer types. However, the risk of developing a new cancer was not likely to be higher than expected. In one retrospective cohort study of 527 patients, the standardized incidence ratio for cancer was 0.84 [0.56–1.21] [42]. In addition, no correlation was reported between the use of rhBMP-2 and development of cancer (hazard ratio=0.99 [0.95–1.02]) in another large-scale retrospective cohort study [43].

The applicability of rhBMP-2 is another important issue. Stable carriers with high osteoconductive activity and good affinity for rhBMP-2 are required to enhance the osteoinductive activity of rhBMP-2. Although collagen carriers were frequently used in the past, HA has been suggested as an alternative. The HA granules existed in CT images 6 months postoperatively without resorption, which means stability of HA as a carrier. Its higher affinity with E.BMP-2 has been proposed by several studies [20,44]. The suitability of HA as a carrier for E.BMP-2 was also confirmed in this study.

This study has a few limitations. First, drop-out rate (13%) due to the violation of the protocol or withdrawal was not low, even though follow-up loss was absent. This was mainly caused by the strict regulation protocol. Second, the number of enrolled patients were not equal among the institutions because enrollment was conducted in a competitive manner. However, no differences of outcomes were found among the institutions. Third, quality of bone fusion was not assessed. In a previous study, quality of bone fusion by rhBMP-2 was reported to be inferior to that of AIBG in anterior lumbar interbody fusion [45]. We did not assess the quality of bone fusion due to remaining HA granules in the E.BMP-2 group, while continuous bone fusion mass was obviously found for the AIBG group in CT images. Fourth, the follow-up period was not adequate to evaluate long-term clinical outcomes and safety. Regardless of the above limitations, this prospective randomized controlled trial is thought to be worthy of notice based on the solid study design with reliable sample size estimation and strict study protocol. However, this is the first study to compare the efficacy and safety of bone graft substitutes between E.BMP-2 with an HA carrier and AIBG in PLF.

In conclusion, the fusion rate with E.BMP-2 was comparable with AIBG following PLF. Good clinical efficacy and safety of E.BMP-2 in spinal fusion were also revealed in this study. It was also suggested that HA showed suitability as a carrier for E.BMP-2. Thus, E.BMP-2 with an HA carrier can be an alternative bone graft material in spinal fusion.

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