

## The Use of Bone Morphogenetic Protein in Spinal Transforaminal Lumbar Interbody Fusion: Our Experience

Eduardo Colom-Beauchamp, MD\*; David Beaton-Comulada, MD\*;  
Julio A. Rodriguez, BS†; José C. Pérez-López, MD\*; José Montañez-Huertas, MD\*;  
Enrique Escobar-Medina, MD\*; José Massanet-Vollrath, MD\*

**Objective:** Since its introduction and FDA approval, rhBMP-2 has been adopted by spine surgeons as a substitute for ICBG in numerous spinal fusion techniques. As broad clinical use increased, reports on potential complications associated with rhBMP-2 also increased. We provide our experience with TLIF using rhBMP-2 or ICBG in an entirely Hispanic population.

**Methods:** This was a 2-year retrospective study of 67 patients, with 26 in the rhBMP-2 group and 41 in the ICBG group, who underwent TLIF. Pertinent information was obtained through review of the medical records documenting complications, intraoperative times, and EBL, among other things.

**Results:** There were 28 post-operative complications with 15 (53.6%) in the ICBG group and 13 (46.4%) in the rhBMP-2 group. The average EBL was 572.3 mL (SD: 411.8) in the ICBG group and 397.9 mL (SD: 312.2) in the rhBMP-2 group. The average intraoperative time was 243.1 minutes (SD: 79.5) in the ICBG group and 226.5 minutes (SD: 64.7) in the rhBMP-2 group. Fifty-two patients underwent open TLIF and 15 patients underwent MI-TLIF. The average EBL was 571.2 mL (SD: 375.3) in the open TLIF group and 228.3 mL (SD: 299.3) in the MI-TLIF group. The average intraoperative time was 241.0 minutes (SD: 76.0) for patients in the open TLIF group and 218.8 minutes (SD: 65.0) for those in the MI-TLIF group. There were no new cancer events at any of the 2-year follow-up visits.

**Conclusion:** Our results suggest that the safety profile of rhBMP-2 may be inferior to that of ICBG, rejecting the possibility of ICBG being replaced by rhBMP-2 as the gold standard for spinal fusion. [*P R Health Sci J* 2017;36:173-178]

*Key words:* Morphogenetic protein, Transforaminal, Lumbar, Interbody, Fusion, TLIF

**B**one morphogenetic protein (BMP) is a member of the transforming growth factor- $\beta$  superfamily demonstrated to have significant osteogenic properties (1-5). More than 20 different types of BMP have been identified for various uses (6). However, recombinant human BMP-2 (rhBMP-2, InFUSE; Medtronic Sofamor Danek, Memphis, TN, USA) has demonstrated superior osteogenic properties (compared to the other formulations) for achieving spinal fusion. Recombinant human BMP-2 was introduced and approved by the FDA in 2002 as a possible substitute for iliac crest bone graft (ICBG) in anterior lumbar interbody fusion (ALIF) as it had superior fusion rates (94.5%) compared to those of ICBG (88%) (6-9). Since the introduction and FDA approval of rhBMP-2 as an alternative for ICBG in ALIF, 85% of rhBMP-2 use in spinal fusion surgeries has been off-label with mixed results in terms of complication rates (1, 10). Posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF) have accounted for approximately 30% of the off-label use of rhBMP-2 (11).

Several distinct approaches have been developed to achieve adequate spinal fusion. TLIF is commonly performed to obtain a 360-degree spinal arthrodesis through a posterior-only approach in conditions such as degenerative disk disease, degenerative scoliosis, pseudarthrosis, recurrent disk herniation, and spondylolisthesis. Despite the FDA approval of rhBMP-2 for use in anterior cervical discectomy and fusion cases, the FDA issued a warning after several studies encountered prevertebral swelling leading to dysphagia (11, 12). Other adverse events associated with rhBMP-2 use include dural tears, ectopic bone formation, heterotopic ossification, implant migration,

\*Department of Orthopedic Surgery, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico; †Ponce Health Sciences University, School of Medicine, Ponce, Puerto Rico

*The author/s has/have no conflict/s of interest to disclose.*

**Author of correspondence:** Eduardo Colom-Beauchamp, MD, PO Box 365067, Section of Orthopedics, University of Puerto Rico Medical Sciences Campus, PO Box 365067, San Juan, PR 00936-5067. Email: ej\_beachamp@yahoo.com

infection, intraoperative neurologic injury, osteolysis, radiculitis, retrograde ejaculation, seroma formation, and soft tissue swelling (1, 13-17). Currently, meta-analyses and systematic reviews have failed to demonstrate rhBMP-2 to be superior to ICBG in achieving clinical success. Furthermore, there are no reported data collected from an entirely Hispanic population. This study reports our experience with the use of rhBMP-2 in TLIF in an entirely Hispanic population and speculates on whether any complications can be attributed to the use of rhBMP-2.

## Methods

With prior Institutional Review Board (IRB) approval, we conducted a retrospective case review of patients who had undergone PLIF and TLIF from January 2009 to April 2012 by searching under the Current Procedural Terminology (CPT) code 22630 (Posterior and Transforaminal Lumbar Interbody fusion). A total of 67 patients met our study inclusion criteria. The inclusion criteria for our study consisted of: (1) patients between the ages of 21 and 75 years, (2) diagnosed with degenerative disk disease, lumbar spinal stenosis, recurrent disk herniation, scoliosis, or spondylolisthesis, (3) who exclusively underwent a TLIF using ICBG or rhBMP-2, and (4) had never undergone any previous attempt of lumbar fusion. The exclusion criteria for our study were patients: (1) who underwent an exclusive PLIF (CPT Code 22630), (2) have undergone a TLIF revision surgery, (3) have undergone additional anterior lumbar interbody fusion, (4) have undergone fusion using BMP products other than rhBMP-2, and (5) previously have been exposed to rhBMP-2.

Surgical indications included degenerative disk disease, lumbar spinal stenosis, recurrent disk herniation, scoliosis, spondylolisthesis, and any combination of these. Patients consented to lumbar decompression and arthrodesis using either ICBG or rhBMP-2. All patients were educated about and informed of the off-label use of rhBMP-2, and received preoperative antibiotics. The rhBMP-2 was completely placed in the interbody cage. Autografts with demineralized bone matrix (DBM) were used for posterolateral fusion in both groups. Three orthopaedic fellowship trained spine surgeons performed all the operative procedures at a tertiary academic hospital setting. Estimated blood loss (EBL) (milliliters), intraoperative time (minutes), and rhBMP-2 dosing quantity (milligrams) were recorded for each procedure. Length of hospital stay (days) was also recorded.

Patient follow-ups, consisting of clinical examination, pain scales, and radiographic imaging, were performed at regular intervals of 2 weeks, 6 weeks, 12 weeks, 6 months, 1 year, and 2 years. Each patient was monitored for post-operative complications, including the possible need for TLIF revision. Post-operative complications included: cerebrovascular accident (CVA), dural tear, hardware failure, new-onset malignancy, paresthesia, paralysis, pseudarthrosis, radiculitis, seroma formation, and surgical wound infection. Paresthesia was

defined as a loss of sensation in a dermatomal distribution and paralysis as a loss of motor function. Radiculitis was described as worsening leg pain in a dermatomal distribution ipsilateral to where the TLIF was performed without structural evidence of hardware malpositioning. Seroma formation was delineated as an MRI-proven postoperative fluid collection that reduced the volume of the spinal canal and associated dural space. The possibility of pseudarthrosis was evaluated via flexion/extension radiographs using anteroposterior and lateral views or computed tomography imaging.

Comparisons between type of osteoinductive agent, associated complications, and rate of revision were performed using a chi-squared analysis. Comparisons between type of osteoinductive agent and EBL, intraoperative time, and hospital stay were performed using a 2-tailed t-test. Comparisons between type of surgical approach used and EBL, intraoperative time, and hospital stay were performed using a 2-tailed t-test. The results were considered significant if the p-value was less than 0.05. All statistical analyses were performed using IBM SPSS statistics version 24 (IBM Co., Armonk, NY).

## Results

Demographic data were analyzed and compared between groups. Sixty-seven patients, divided into ICBG and rhBMP-2 groups, met our study inclusion criteria. There were 41 patients (61.2%) in the ICBG group and 26 patients (38.8%) in the rhBMP-2 group. Of the 26 patients in which rhBMP-2 was used, 22 (84.6%) received a small dose (4.2 mg of rhBMP-2) and 4 (15.4%) received a large dose (12 mg of rhBMP-2). The mean age of the study population was 53.3 years (range: 28–75 years). Forty-one patients (61.2%) were female and 26 (38.8%) were male. Associated comorbidities included diabetes mellitus, hypertension, and smoking. Nineteen (28.4%) of our patients were receiving treatment for diabetes mellitus, 35 (52.2%) were receiving treatment for hypertension, and 17 (25.3%) were current smokers (Table 1). No statistical difference was found between groups when organized by age, gender, and medical comorbidities. Several patients had more than 1 preoperative diagnosis. Preoperative diagnoses consisted of lumbar spinal stenosis (33 patients [35.1%]), recurrent disk herniation (23 patients [24.5%]), degenerative disk disease (18 patients [19.1%]), spondylolisthesis (16 patients [17.0%]), and scoliosis (4 patients [4.3%]) (Table 2).

Fifty-two (77.6%) of the 67 patients underwent open TLIF, while the remaining 15 (22.4%) underwent minimally invasive TLIF (MI-TLIF). Of the 52 patients who underwent open TLIF, ICBG was used in 36 (69.2%) and rhBMP-2 was used in 16 (30.8%) of them. Of the 15 patients who underwent MI-TLIF, ICBG was used in 5 (33.3%) and rhBMP-2 was used in 10 (66.7%) of them (Table 1). Sixteen (23.9%) of the 67 patients required a revision. Of the 16 patients who required a revision surgery, 8 (50.0%) were in the ICBG group and 8 (50.0%) in the rhBMP-2 group (Table 2). The causes of revision surgery

**Table 1.** Demographic information

Demographic	n (%)
ICBG group	41 (61.2%)
rhBMP-2 group	26 (38.8%)
Open TLIF	52 (77.6%)
MI-TLIF	15 (22.4%)
Age (years)	
Average	53.3
Minimum	28
Maximum	75
Sex	
Female	41 (61.2%)
Male	26 (38.8%)
Comorbidities	
Hypertension	35 (52.2%)
Diabetes mellitus	19 (28.4%)
Smoking	17 (25.4%)

Note: n = sample size

included basilar artery occlusion, dural tear, hardware failure, infection, progression to adjacent lumbar stenosis, progression of scoliosis, radiculopathy, seroma formation, and pseudarthrosis. There were 28 post-operative complications, with 15 (53.6%) in the ICBG group and 13 (46.4%) in the rhBMP-2 group. Of these 28 complications, there were 9 (32.1%) radiculopathies, 7 (25.0%) seromas, 6 (21.4%) surgical wound infections, 1 (3.6%) CVA, 1 (3.6%) dural tear, 1 (3.6%) hardware failure, 1 (3.6%) paralysis (foot drop), and 1 (3.6%) pseudarthrosis. Of the 9 cases of radiculopathy, 5 (55.6%) were in the rhBMP-2 group. There was no statistical significance between the type of osteoinductive agent used and the frequency of revision

**Table 2.** Preoperative diagnoses

Preoperative Diagnosis	ICBG group n (%)	rhBMP-2 group n (%)	Total n (%)
Lumbar spinal stenosis	19 (57.6%)	14 (42.4%)	33 (35.1%)
Recurrent lumbar disk herniation	13 (56.5%)	10 (43.5%)	23 (24.5%)
Degenerative disk disease	12 (66.7%)	6 (33.3%)	18 (19.1%)
Spondylolisthesis	10 (62.5%)	6 (37.5%)	16 (17.0%)
Scoliosis	4 (100%)	0 (0.0%)	4 (4.3%)

**Table 3.** Comparison of general outcomes

Comparisons	Group		Approach		Two-tailed t-test p-value
	ICBG	rhBMP-2	Open	MIS	
Estimated blood loss (mL)	572.3	397.9	571.2	228.3	p = 0.08 p = 0.01*
Intraoperative time (minutes)	243.1	226.5	241.4	218.8	p = 0.39 p = 0.35
Hospital stay (days)	4.7	4.7	5.0	3.7	p = 0.95 p = 0.21
Required revision	8 (50.0%)	8 (50.0%)	15 (93.8%)	1 (6.2%)	

Note: \*p-value<0.05. First p-value in each row corresponds to comparison made between surgical approach and second p-value corresponds to comparison made between groups.

surgery ( $X^2 = 1.1$ ;  $p = 0.29$ ). No statistical significance was found between the type of osteoinductive agent and associated post-operative complications ( $X^2 = 0.36$ ;  $p = 0.84$ ).

The average EBL for all 67 patients was 505.9 mL, with a mean of 572.3 mL (SD=411.8) in the ICBG group and 397.9 mL (SD=312.2) in the rhBMP-2 group. The average intraoperative time for all 67 patients was 236.7 minutes, with a mean of 243.1 minutes (SD=79.5) in the ICBG group and 226.5 minutes (SD=64.7) in the rhBMP-2 group. The average hospital stay for all patients and in both groups was 4.7 days (SD=2.6 in the ICBG group; SD=4.2 in the rhBMP-2 group) (Table 3). The EBL decrease of 174.4 mL in the rhBMP-2 group was approaching significance ( $p=0.08$ ). The 16.6 minute difference in intraoperative observed between groups was not statistically significant ( $p=0.39$ ). The length of hospital stay between groups was not statistically significant ( $p=0.95$ ).

The average EBL was 571.2 mL (SD=375.3) in the open TLIF group and 228.3 mL (SD=299.3) in the MI-TLIF group. The average intraoperative time was 241.0 minutes (SD=76.0) for patients who underwent open TLIF and 218.8 minutes (SD=65.0) for patients who underwent MI-TLIF. The average hospital length of stay was 5.0 days (SD=3.0) for patients who underwent open TLIF and 3.7 days (SD=4.2) for patients who underwent MI-TLIF. The 342.9 mL difference observed between groups was statistically significant ( $p=0.01$ ). The 22.2-minute difference observed between groups was not statistically significant ( $p=0.35$ ). The 1.3-day difference observed between groups was not statistically significant ( $p=0.21$ ).

## Discussion

Currently, ICBG serves as the “gold standard” for spinal fusion techniques (18). However, given the complications (including donor site pain, hematoma, infection, and neurovascular damage) associated with ICBG harvesting, orthopaedic surgeons have searched for a safer alternative (2, 19). Since the 2002 FDA approval of rhBMP-2 in 2002 for ALIF, the use of rhBMP-2 has increased, ranging from 0.7% (in all spinal fusion techniques) to 30% (in all PLIF and TLIF approaches), with 85% of its use being off-label or physician-directed (11). An increase in the off-label use of rhBMP-2 supports the active desire of the orthopaedic spine community to find a safer alternative for achieving arthrodesis. As new techniques and surgical adjuvants are developed, caution must be used when employing these new options. A recent controversy regarding the studies used for the FDA approval of rhBMP-2 was brought to light in 2011 when revelations that several surgeons involved in the clinical trials had significant conflicts of interests with potentials for bias in the publications (20). Since then, the initial benefits (e.g. the low

percentage of complications) reported in the original studies have been called into question. The increased off-label use of rhBMP-2, associated complications, and current controversies compelled us to present our experience using rhBMP-2 to achieve spinal fusion.

In terms of patient demographics, including age, gender, and medical comorbidities, our findings parallel those of the current literature, further demonstrating that the outcomes and complications associated with rhBMP-2 are independent of age, gender, and medical comorbidities. The difference found between the type of osteoinductive agent and the frequency of revision is also consistent with what has been described in the current literature. A meta-analysis of effectiveness outcomes at 24 months and rates of overall success demonstrated no consistent difference between ICBG and rhBMP-2 groups (21). Although greater fusion rates were reported in the rhBMP-2 group, these results were not statistically significant. In our study, we had one patient, in whom rhBMP-2 was not used, who suffered from pseudarthrosis. This finding is consistent with the superior fusion rate of rhBMP-2 reported by Fu et al. However, the pseudoarthrosis may have been a result of osteopenia and other patient related factors as opposed to the type of osteoinductive agent used.

The difference found between the type of osteoinductive agent used and associated post-operative complications is consistent with that of a meta-analysis reporting no significant difference between complications (including lumbar radiculitis) in the ICBG and rhBMP-2 groups (20). The decrease of 174.4 mL EBL observed in the rhBMP-2 group of our study may have been confounded due to a greater propensity towards using rhBMP-2 in patients who underwent MI-TLIF. This was confirmed when we compared surgical approaches and the EBL associated with each approach, demonstrating a statistically significant decrease of 342.9 mL EBL in the MI-TLIF group. Our findings are consistent with those in the current literature that report significantly reduced EBL when performing arthrodesis via a minimally invasive approach (20, 22-30).

The 16.6-minute decrease in operative time observed in the rhBMP-2 group was supported by the current literature, which reported statistically significant decreases in operative times when rhBMP-2 was used (7, 8, 31). However, it is possible for intraoperative time to be affected by many other variables, such as the number of levels fused, intraoperative complications, and surgical approach. These factors must be considered as possible confounding variables.

No difference was observed between the type of osteoinductive agent used and length of hospital stay. A review of the literature comparing the type of osteoinductive agent used and length of hospital stay yielded mixed results. Poeran et al. reported a statistically significant increase in length of hospital stay in the rhBMP-2 group, while Halanski et al. reported a statistically significant decrease in length of hospital stay in the rhBMP-2 group (9, 32). Our findings, and those reported by other authors, may have been affected by

the surgical approach used and associated complications, both intraoperative and postoperative.

The statistically significant decrease of 342.9 mL EBL observed in our MI-TLIF group is highly consistent with that of the current literature, which reported significantly reduced EBL in patients who underwent minimally invasive lumbar arthrodesis (22-24, 26, 28-30, 33). Moreover, our findings explain the aforementioned decrease in EBL (that approached significance) in the rhBMP-2 group.

The 22.2-minute decrease in operative time observed in our MI-TLIF group has not been previously reported in the literature. The results of our literature review were mixed associating minimally invasive arthrodesis with prolonged and equivalent operative times when compared to open arthrodesis. Kulkarni et al., Sidhu et al., and Wu et al. all reported significantly greater operative times in their MI-TLIF group, MI-PLIF group, and minimally invasive posterior approach group, respectively (24, 28, 31). To the contrary, however, Goldstein et al., Gu et al., Schizas et al., Tian et al., and Xie et al. found no significant differences between MI-TLIF and open TLIF in intraoperative times (22, 23, 27, 29, 30). However, no study has demonstrated a decrease in intraoperative time when performing MI-TLIF via a minimally invasive approach. It is unknown to us whether other variables, such as surgeon proficiency, the number of levels fused, intraoperative complications, or some combination of any or all of the aforementioned, were responsible for this difference in intraoperative time.

The decrease in hospital stay of 1.3 days favoring the minimally invasive group was consistent with the findings in the current literature. A retrospective study comparing the safety and effectiveness of minimally invasive and open sacroiliac joint fusion reported a significantly shorter length of hospital stay in the minimally invasive group (31). Furthermore, multiple studies have reported shorter hospital stays in patients who underwent arthrodesis via a minimally invasive approach (22-30).

From the time that rhBMP-2 was introduced as a possible alternative for use in spinal fusion procedures, its safety has been questioned. A great concern that has delayed FDA approval for the use of rhBMP-2 in non-ALIF procedures has been the association of rhBMP-2 with the development of malignancy. Many studies have evaluated the potential carcinogenic effect of rhBMP-2. A retrospective cohort that assessed the risk of developing pancreatic cancer with the use of rhBMP-2 found no associated increased risk (31). Another study reported rhBMP-2 as an inhibitor of malignant gastric epithelial cells (34). In contrast, the YODA group's analysis reported nearly twice the number of cancer cases with the use of BMP-25, even though the absolute risk for cancer development in rhBMP-2 recipients was as low as 3% (20, 35). Furthermore, the use of BMP in patients with cancers requiring spinal fusion has been contraindicated (36). Despite these findings, there were no new cancer cases in either of our study groups at the 2-year follow-up visits. Perhaps a longer follow-up time and an increase in the number of sample subjects might be required to increase the power of

the study. However, in 2010, the FDA advisory committee found a fourfold increase in new malignancies in patients treated with rhBMP-2 at the 24-month follow-up (37). At the 60-month follow-up, the patients treated with rhBMP-2, compared to those in the ICBG group, exhibited an almost threefold increase in new-onset malignancies when compared to the ICBG group. Therefore, a two-year follow-up may be argued as adequate time for observing new-onset malignancies in patients treated with rhBMP-2 according to the results reported by the FDA advisory committee. Nonetheless, a longer follow-up period for assessing new-onset malignancies is still recommended.

This study presented several limitations. First, 3 different surgeons performed the surgeries. This may have affected intraoperative time, rates of revision, and associated complications (as might be related to surgeon proficiency). Second, our study population consisted of 67 patients. Increasing the study population would increase the power of the study and possibly yield statistically significant results. Another limitation of this study was the retrospective analytic design. A prospective analysis of our population may help clear some of the controversies surrounding rhBMP-2 use in our population. Lastly, further analysis comparing complications and rate of revisions may yield additional significant results. Future directions of this study should take these considerations into account.

Numerous reports in the literature present the risks and benefits of rhBMP-2 use in spinal fusion. Some studies have demonstrated that rhBMP-2 increases fusion rates when compared to ICBG. However, the increased fusion rates may come at a price given the reported complications associated with rhBMP-2 use. Our experience with an entirely Hispanic population has shown us that overall results are similar to those currently reported in the literature. Furthermore, we found that our orthopaedic surgeons are able to complete minimally invasive arthrodesis at a faster pace than other orthopedic surgeons are able to do. We are unsure whether this finding is associated with surgeon proficiency or other factors, such as the number of levels fused and intraoperative complications. Our results suggest that the safety profile of rhBMP-2 may be inferior to that of ICBG, rejecting the possibility of ICBG being replaced by rhBMP-2 as the gold standard for spinal fusion.

## Resumen

**Objetivos:** A partir de la aprobación por la FDA, rhBMP-2 ha sido utilizado para sustituir autoinjertos de hueso en cirugías de fusión de columna. Recientemente, el perfil de seguridad ha sido cuestionado debido que estudios sugieren una mayor tasa de complicaciones. El propósito de este estudio fue describir nuestra experiencia en cirugías de TLIF, utilizando rhBMP-2 y ICBG, en una población totalmente Hispana. **Métodos:** Realizamos un estudio retrospectivo con 67 pacientes sometidos a TLIF, con 26 en el grupo de rhBMP-2 y 41 en el de autoinjerto. Recopilamos información del expediente médico para comparar la tasa de complicaciones, el tiempo y la cantidad de sangrado

intraoperatorio. **Resultados:** Se reportaron 28 complicaciones postoperatorias, con 13 (46.4%) en el grupo de rhBMP-2. El promedio de sangrado y tiempo intraoperatorio en el grupo de rhBMP-2 fue 397.9 mL (SD: 312.2) y 226.5 minutos (SD: 64.7), respectivamente. Cincuenta y dos pacientes fueron sometidos a TLIF convencional y 15 fueron sometidos a TLIF mínimamente invasiva. El promedio de sangrado y tiempo intraoperatorio en el grupo de TLIF convencional fue 571.2 mL (SD: 375.3) y 241.0 minutos (SD: 76.0), respectivamente. El promedio de sangrado y tiempo intraoperatorio en el grupo de TLIF mínimamente invasivo fue 228.3 mL (SD: 299.3) y 218.8 minutos (SD: 65.0), respectivamente. No hubo incidente de cáncer a los dos años de seguimiento. **Conclusiones:** Nuestros resultados sugieren que el uso de rhBMP-2 pudiera estar vinculado a un mayor número de complicaciones, comparado a ICBG, que rechaza la posibilidad de su uso como posible estándar de cuidado para fusiones de columna.

## References

- Celeste AJ, Iannazzi JA, Taylor RC, et al. Identification of transforming growth factor beta family members present in bone-inductive protein purified from bovine bone. *Proc Natl Acad Sci U S A* 1990;87:9843-9847.
- Hofstetter CP, Hofer AS, Levi AD. Exploratory meta-analysis on dose-related efficacy and morbidity of bone morphogenetic protein in spinal arthrodesis surgery. *J Neurosurg Spine* 2016;24:457-475.
- Itoh H, Ebara S, Kamimura M, et al. Experimental spinal fusion with use of recombinant human bone morphogenetic protein 2. *Spine (Phila Pa 1976)* 1999;24:1402-1405.
- Urist MR. Bone: formation by autoinduction. 1965. *Clin Orthop Relat Res* 2002;(395):4-10.
- Wang EA, Rosen V, Cordes P, et al. Purification and characterization of other distinct bone-inducing factors. *Proc Natl Acad Sci U S A* 1988;85:9484-9488.
- Wozney JM, Rosen V. Bone morphogenetic protein and bone morphogenetic protein gene family in bone formation and repair. *Clin Orthop Relat Res* 1998;(346):26-37.
- Boden SD, Zdeblick TA, Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. *Spine (Phila Pa 1976)* 2000;25:376-81.
- Burkus JK, Gornet MF, Dickman CA, et al. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 2002;15:337-349.
- Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine (Phila Pa 1976)* 2002;27:2396-2408.
- Galimberti F, Lubelski D, Healy AT, et al. A Systematic Review of Lumbar Fusion Rates With and Without the Use of rhBMP-2. *Spine (Phila Pa 1976)* 2015;40:1132-1139.
- Ong KL, Villarraga ML, Lau E, et al. Off-label use of bone morphogenetic proteins in the United States using administrative data. *Spine (Phila Pa 1976)* 2010;35:1794-1800.
- Shields LB, Raque GH, Glassman SD, et al. Adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 use in anterior cervical spine fusion. *Spine (Phila Pa 1976)* 2006;31:542-547.
- Cahill KS, Chi JH, Day A, et al. Prevalence, complications, and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. *JAMA* 2009;302:58-66.
- Joseph V, Rampersaud YR. Heterotopic bone formation with the use of rhBMP2 in posterior minimal access interbody fusion: a CT analysis. *Spine (Phila Pa 1976)* 2007;32:2885-2890.

15. Malham GM, Parker RM, Ellis NJ, et al. Anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2: a prospective study of complications. *J Neurosurg Spine* 2014;21:851-860.
16. Mindea SA, Shih P, Song JK. Recombinant human bone morphogenetic protein-2-induced radiculitis in elective minimally invasive transforaminal lumbar interbody fusions: a series review. *Spine (Phila Pa 1976)* 2009;34:1480-1484; discussion 1485.
17. Vaidya R, Weir R, Sethi A, et al. Interbody fusion with allograft and rh-BMP-2 leads to consistent fusion but early subsidence. *J Bone Joint Surg Br* 2007;89:342-345.
18. Rihn JA, Patel R, Makda J, et al. Complications associated with single-level transforaminal lumbar interbody fusion. *Spine J* 2009;9:623-629.
19. Carlisle E, Fischgrund JS. Bone morphogenetic proteins for spinal fusion. *Spine J* 2005;5(6 Suppl):240S-249S.
20. Fu R, Selph S, McDonagh M, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. *Ann Intern Med* 2013;158:890-902.
21. Singh K, Ahmadiania K, Park DK, et al. Complications of spinal fusion with utilization of bone morphogenetic protein: a systematic review of the literature. *Spine (Phila Pa 1976)* 2014;39:91-101.
22. Goldstein CL, Macwan K, Sundararajan K, et al. Comparative outcomes of minimally invasive surgery for posterior lumbar fusion: a systematic review. *Clin Orthop Relat Res* 2014;472:1727-1737.
23. Gu G, Zhang H, Fan G, et al. Comparison of minimally invasive versus open transforaminal lumbar interbody fusion in two-level degenerative lumbar disease. *Int Orthop* 2014;38:817-824.
24. Kulkarni AG, Bohra H, Dhruv A, et al. Minimal invasive transforaminal lumbar interbody fusion versus open transforaminal lumbar interbody fusion. *Indian J Orthop* 2016;50:464-472.
25. Ledonio CG, Polly DW, Jr., Swiontkowski MF. Minimally invasive versus open sacroiliac joint fusion: are they similarly safe and effective? *Clin Orthop Relat Res* 2014;472:1831-1838.
26. Patel AA, Zfass-Mendez M, Lebowitz NH, et al. Minimally Invasive Versus Open Lumbar Fusion: A Comparison of Blood Loss, Surgical Complications, and Hospital Course. *Iowa Orthop J* 2015;35:130-134.
27. Schizas C, Tzinieris N, Tsiridis E, et al. Minimally invasive versus open transforaminal lumbar interbody fusion: evaluating initial experience. *Int Orthop* 2009;33:1683-1688.
28. Sidhu GS, Henkelman E, Vaccaro AR, et al. Minimally invasive versus open posterior lumbar interbody fusion: a systematic review. *Clin Orthop Relat Res* 2014;472:1792-1799.
29. Tian NF, Wu YS, Zhang XL, et al. Minimally invasive versus open transforaminal lumbar interbody fusion: a meta-analysis based on the current evidence. *Eur Spine J* 2013;22:1741-1749.
30. Wu AM, Chen CH, Shen ZH, et al. The Outcomes of Minimally Invasive versus Open Posterior Approach Spinal Fusion in Treatment of Lumbar Spondylolisthesis: The Current Evidence from Prospective Comparative Studies. *Biomed Res Int* 2017;2017:8423638. doi: 10.1155/2017/8423638.
31. Xie L, Wu WJ, Liang Y. Comparison between Minimally Invasive Transforaminal Lumbar Interbody Fusion and Conventional Open Transforaminal Lumbar Interbody Fusion: An Updated Meta-analysis. *Chin Med J (Engl)* 2016;129:1969-1986.
32. Halanski MA, Elfman CM, Cassidy JA, et al. Comparing results of posterior spine fusion in patients with AIS: Are two surgeons better than one? *J Orthop* 2013;10:54-58.
33. Poeran J, Opperer M, Rasul R, et al. Change in Off-Label Use of Bone Morphogenetic Protein in Spine Surgery and Associations with Adverse Outcome. *Global Spine J* 2016;6:650-659.
34. Mines D, Gu Y, Kou TD, et al. Recombinant human bone morphogenetic protein-2 and pancreatic cancer: a retrospective cohort study. *Pharmacopidemiol Drug Saf* 2011;20:111-118.
35. Zhang J, Ge Y, Sun L, et al. Effect of bone morphogenetic protein-2 on proliferation and apoptosis of gastric cancer cells. *Int J Med Sci* 2012;9:184-192.
36. Simmonds MC, Brown JV, Heirs MK, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. *Ann Intern Med* 2013;158:877-889.
37. Tannoury CA, An HS. Complications with the use of bone morphogenetic protein 2 (BMP-2) in spine surgery. *Spine J* 2014;14:552-559.

## Appendix

Abbreviation	Abbreviation Meaning
ALIF	Anterior Lumbar Interbody Fusion
BMP	Bone Morphogenetic Protein
CPT	Current Procedural Terminology
CVA	Cerebrovascular Accident
EBL	Estimated Blood Loss
FDA	Food and Drug Administration
IBM	International Business Machines
ICBG	Iliac Crest Bone Graft
IRB	Institutional Review Board
MI-TLIF	Minimally Invasive Transforaminal Lumbar Interbody Fusion
PLIF	Posterior Lumbar Interbody Fusion
rhBMP-2	recombinant human Bone Morphogenetic Protein-2
SPSS	Statistical Package for the Social Sciences
TLIF	Transforaminal Lumbar Interbody Fusion
YODA	Yale University Open Data Access