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Review Article

The use of bone morphogenetic proteins (BMP) and pseudarthrosis, a literature review☆

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ABSTRACT

Bone morphogenetic proteins (BMP) are multi-functional growth factors to promote bone healing with the proposal of less morbidity compared to the usual methods of bone graft harvest. Pseudoarthrosis occur when the fusion attempt fails, a solid fusion is not achieved, or there is motion across the segment leading to it, and it can be clinically symptomatic as pain, deformity, neurocompression, or hardware failure. BMPs are used at spinal fusion as a tool for the treatment of degenerative, traumatic, neoplastic and infectious conditions of the spine. This review shows that the use of BMPS is effective and secure when compared with iliac crest bone graft (ICGB); however, depending of the location of usage (cervical spine, lumbar spine or sacrum) and the medical status of the patient (presence of comorbidities, tobacco usage), it is more likely to exhibit complications. Therefore, the use of these proteins must be an informed decision of patient and physician preferences.

O uso de proteínas morfogenéticas ósseas (BMP) e pseudoartroses, uma revisão de literatura

Palavras-chave:
Proteínas morfogenéticas ósseas 2
Proteína morfogenética óssea 7
Pseudoartrose

RESUMO

Proteínas morfogenéticas do osso (Bone morphogenetic proteins [BMP]) são fatores de crescimento multifuncionais que promovem cicatrização óssea, propondo menos comorbidades comparado aos métodos usuais de colheita de enxerto ósseo. Pseudoartroses ocorrem quando a tentativa de fusão óssea falha, uma fusão sólida não é atingida ou quando há movimentação do segmento que leva à pseudoartrose, que pode ser clinicamente sintomática com dor, deformidade, neurocompressão ou falha na colocação de material de síntese. As BMPs são usadas em fusão colunar como ferramenta para o tratamento de

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trauma degenerativo, condições neoplásicas e infecciosas da coluna. A presente revisão da literatura mostra que o uso de BMPs é efetivo e seguro quando comparado com enxerto ósseo ilíaco. No entanto, a depender do local de uso (coluna cervical ou lombar ou sacro) e do estado médico do paciente (presença de comorbidades, tabagismo) é mais propício o aparecimento de complicações. Portanto, o uso dessas proteínas deve ser decidido após uma decisão conjunta de preferências médicas e do paciente.

Introduction

Bone morphogenetic proteins (BMP) are multi-functional growth factors that belong to the transforming growth factor beta (TGF-beta) superfamily, they were introduced in the medical scenario to promote bone healing with the proposal of less morbidity compared to the usual methods of bone graft harvest; it is the only bone inducer with level I of clinical evidence. The Food and Drug Administration (FDA) approved its use in July of 2002 for anterior approaches of lumbar spine fusion procedures.

The spinal fusion is a tool for the treatment of degenerative, traumatic, neoplastic and infectious conditions of the spine, it can be achieved with interbody fusion, posterior or posterolateral fusion and circumferencial fusion. The most used examples of BMP's are recombinant human BMP-2 (rhBMP-2 is approved for anterior lumbar interbody fusions – ALIF) and recombinant human BMP-7 (rhBMP-7 has received a humanitarian device exemption for revision posterolateral lumbar fusion operation).

Implants containing BMP's are promising to its safety and it is as effective as iliac crest bone graft (ICBG). Adopting the use of it brings high costs and it has safety concerns with reported complication specifics to its use, including osteolysis, ectopic bone formation, radiculitis, cervical soft tissue swelling and pseudoarthrosis.

Nowadays the greatest use of BMP is for off label treatments as an adjunt to allograft or autograft bone – often replacing the use of ICBG in mandibular reconstruction, unspecific oral and maxillofacial facial surgeries, cervical spine fusion, pseudoarthrosis fusion. But it is still in the need of further investigation related to its collateral effects.

Pseudoarthrosis occur when the fusion attempt fails, a solid fusion is not achieved, or there is motion across the segment leading to it, and it can be clinically symptomatic as pain, deformity, neurocompression or hardware failure. There are two types: hypertrophic/hypercascular and atrophic/avascular, the last one is applicable osteoinductive treatment with BMP. This review intends to correlate and clarify the use of BMP's and its bias on pseudoarthrosis, when it is a correction or cause factor.

Methods

A qualitative systematic review of articles about the use of Bone Morphogenetic Protein in Pseudarthrosis was developed on a basis of preselected data. It was performed a search of literature from the online database BVS and SCOPUS from January 2006 to November 2015. The search was focused from the following terms: (1) 'Pseudarthrosis' {Medical Subject Headings} [MeSH term]; and (2) 'Bone Morphogenetic Proteins' {Medical Subject Headings} [MeSH term], these terms were chosen to define our central matter of the paper and all articles were evaluated with rigor to proper sampling.

The analysis of the articles follows predefined eligibility criteria. We adopt the following inclusion criteria: (1) original articles with full text online access; (2) From the relevant source titles: 'Spine', 'Injury', 'Spine Journal', 'Journal of Bone and Joint Surgery Series A', 'Journal of Neurosurgery Spine' and 'Journal of Orthopaedic Research'; (3) Observational, experimental or quasi-experimental studies; (4) Writings in English only; (5) Studies which focus on the use of BMP in pseudarthrosis.

Exclusion criteria were: (1) other projects, such as case reports, case series, literature review and comments, (2) The non-original studies, including editorials, comments, prefaces, brief comments and letter to the editor; (3) Productions that did not accomplish the proposed theme; and (4) the articles in which the objective of the study did not matched the theme purposed by the systematic review in question.

We found applicable 85 articles that, when screened, resulted in 24 articles that met the criteria of evidence and were included in this review (Table 1).

Discussion

BMPs were developed with the goal of improving clinical outcomes through the promotion of bony healing and reducing morbidity from ICBG (still considered 'gold standard' to multilevel spine fusion).[1,2] Spinal fusion procedure is indicated for a variety of pathological states including spinal instability secondary to trauma, infection, or neoplasm as well as intractable axial pain caused by degenerative disorders.[3] Achieving fusion is difficult because of poor local bone quality and long fusions have a negative variable that inhibits a solid fusion, and the BMP is been researched as a potential solution for this problem.

Bone morphogenetic and osteogenetic proteins are multifunctional growth factors that belong to the transforming growth factor-b superfamily. Although osteogenetic proteins are primarily considered osteogenic factors, further investigations have shown that these proteins are also essential for embryogenesis and organogenesis, and that they have pleiotropic roles in cell growth, differentiation, migration, and apoptosis. The most used examples of BMP's are rhBMP-2

Table 1 – The use of bone morphogenetic proteins and pseudarthrosis review.

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/exclusion	Database
1	Dagostino PR, Whitmore RG, Smith GA, Maltenfort MG, Ratliff JK. 2014	Impact of bone morphogenetic proteins on frequency of revision surgery, use of autograft bone, and total hospital charges in surgery for lumbar degenerative disease: review of the Nationwide Inpatient Sample from 2002 to 2008.	Spine J	Study design: Nationwide Inpatient Sample (NIS) retrospective cohort assessment of 46,452 patients from 2002 to 2008. Patient sample: All patients who underwent lumbar arthrodesis procedures for degenerative spinal disease. Outcome measures: Use of BMP, revision surgery status as a percentage of total procedures, and autograft harvest in lumbar fusion procedures completed for degenerative diagnoses. Methods: Demographic and geographic/practice data, hospital charges, and length of stay of all NIS patients with thoracolumbar and lumbosacral procedure codes for degenerative spinal diagnoses were recorded. Codes for autograft harvest, use of BMP, and revision surgery were included in multivariable regression analysis.	The assessment found 46,452 patients from 2002 to 2008 undergoing thoracolumbar or lumbar arthrodesis procedures for degenerative disease. Assuming a representative sample, this cohort models more than 200,000 US patients. There was steady growth in lumbar spine fusion and in the use of BMP. The use of BMP increased from 2002 to 2008 (odds ratio [OR], 1.50; 95% confidence interval [CI], 1.48–1.52). Revision procedures decreased over the study period (OR, 0.94; 95% CI, 0.91–0.96). The use of autograft decreased substantially after introduction of BMP but then returned to baseline levels; there was no net change in autograft use from 2002 to 2008. The use of BMP correlated with significant increases in hospital charges ($13,362.39; standard deviation ± 596.28, $p < .00001$). The use of BMP in degenerative thoracolumbar procedures potentially added more than $900 million to hospital charges from 2002 to 2008.	There was an overall decrease in rates of revision fusion procedures from 2002 to 2008. Introduction of BMP did not correlate with decrease in use of autograft bone harvest. Use of BMP correlated with substantial increase in hospital charges. The small decrease in revision surgeries recorded, combined with lack of significant change in autograft harvest rates, may question the financial justification for the use of BMP.	Included	PubMed/BVS
2	Crandall DG, Revella J, Patterson J, Huish E, Chang M, McLemore R. 2013	Transforaminal lumbar interbody fusion with rhBMP-2 in spinal deformity, spondylolisthesis, and degenerative disease–part 2: BMP dosage-related complications and long-term outcomes in 509 patients.	Spine (Phila Pa 1976)	TLIF with rhBMP-2 was performed at 872 discs in 509 consecutive adults who underwent open posterior instrumented fusion and had minimum 2-year follow-up; diagnoses included degenerative disease (179), spondylolisthesis (207), deformity (123). Patient age averaged 61 years: 12% were smokers and 41% had revision surgery. TLIF was performed at 1.7 levels: single level: 229, 2 levels: 201, 3 levels: 74, 4 levels: 5. Local autograft was used for backfill around and behind each rectangular cage. Varying doses of interbody BMP were used at an average 7.3 mg per disk (range: 2–12 mg per disk).	At 5 years average follow-up, 8 patients developed pseudoarthrosis at levels of TLIF (8 of 872 discs, 0.92%). Seroma (0.4%) and ectopic bone growth (0.6%) were too infrequent to be associated with a particular BMP dose. Deep infection was 2.6% overall (1.7% of the degenerative group). Symptomatic osteolysis or cage subsidence did not occur. Significant long-term improvement was noted in clinical and functional outcomes compared with preoperation.	Five-year follow-up after TLIF with BMP, independent of industry, confirms effective arthrodesis in short and long fusions, both primary and revision. Most complications occurred in deformity patients. BMP-related complications (seroma, ectopic bone) were rare. Level of evidence: 3.	Included	PubMed

Table 1 – (*Continued*)

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/ exclusion	Database
3	Crandall DG, Revella J, Patterson J, Huish E, Chang M, McLemore R. 2013	Transforaminal lumbar interbody fusion with rhBMP-2 in spinal deformity, spondylolisthesis, and degenerative disease–part 1: Large series diagnosis related outcomes and complications with 2- to 9-year follow-up.	Spine (Phila Pa 1976)	A total of 509 consecutive adults underwent open posterior instrumented fusion, augmented with TLIF at 872 discs using a cage and rhBMP-2, with minimum 2-year follow-up. Cohort diagnoses included 179 degenerative, 207 spondylolisthesis, and 123 deformity patients. Patient age averaged 61 years, 207 had undergone prior decompression or fusion surgery. All patients underwent posterior instrumented fusion and pedicle screw instrumentation at average 3.6 levels (range, 1–16); all patients had TLIF 1.7 levels (range, 1–4 levels) with BMP and autograft, stabilized with an interbody cage.	At average 59 months follow-up, 12 patients developed pseudoarthrosis, 8 at TLIF levels (8/872 discs, 0.92%) most commonly at L5-S1 (6/8). Significant clinical improvement was noted in patients with deformity, spondylolisthesis, and degenerative disease undergoing primary and revision surgery. Overall, visual analog scale preoperative score was 6.6, at 1 year 3.8, at 2 years 3.5 ($p < 0.001$) and the preoperative ODI was 50.9, at 1 year 36.1, and at 2 years 35.0 ($p < 0$ 0.001). Pain medication requirements also declined.	The efficacy of TLIF with BMP is supported in this large series with long-term follow-up, independent of industry. Reliable fusion and improved outcomes can be expected in adults undergoing TLIF for deformity, spondylolisthesis, and degenerative disease. Most complications occurred in patients with deformity. Level of evidence: 3.	Included	PubMed
4	Shimer AL, Oner FC, Vaccaro AR. 2009	Spinal reconstruction and bone morphogenetic proteins: open questions.	Injury				Included	PubMed
5	Klimo P, Peelle MW. 2009	Use of polyetheretherketone spacer and recombinant human bone morphogenetic protein-2 in the cervical spine: a radiographic analysis.	Spine J	All patients underwent detailed postoperative radiologic analysis using a computed tomography (CT) scan obtained at least 6 months postoperatively and plain X-rays obtained at regular intervals.	Twenty-two patients had 38 levels fused using PEEK and varying doses of rhBMP-2. No anterior cervical swelling requiring additional procedures or longer than anticipated hospital stays occurred. Pseudoarthrosis, shown as a horizontal radiolucent fissure through the midportion of the PEEK cage on CT, occurred in four patients. Excessive bone growth into the spinal canal or foramina occurred in 26 (68%) patients but did not result in neurologic sequelae. Cystic regions in the core of the PEEK spacer were seen in most patients, with 15 levels (39%) having cysts measuring 3 mm or greater. Moderate or severe osteolysis of the end plates occurred in 57% of levels, and this led to subsidence of the construct and loss of some of the segmental sagittal alignment (i.e., lordosis) that had been achieved with surgery.	The unlimited supply of PEEK spacers and rhBMP-2 and their ease of use make them attractive platforms to achieve fusion. This study has demonstrated that the fusion process using rhBMP-2 is a dynamic one, with osteolysis dominating the initial phase, leading to end-plate resorption and consequently loss of some of the disk space height and sagittal alignment that was achieved with surgery. There is a high incidence of bone growth beyond the core of the PEEK spacer and cystic regions within the cage. Given our experience, we currently reserve the use of PEEK and rhBMP-2 for use in those patients who are at greatest risk of pseudoarthrosis.	Included	PubMed

Table 1 – (*Continued*)

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/ exclusion	Database
6	Annis P, Brodke DS, Spiker WR, Daubs MD, Lawrence BD. 2015	The fate of L5-S1 with low-dose BMP-2 and pelvic fixation, with or without interbody fusion, in adult deformity surgery	Spine	Retrospective review of 61 consecutive patients with minimum 2-year follow-up at a single institution. All patients had an isolated posterior approach, 5 or more levels fused including L5–S1, use of pelvic fixation, and no prior L5-S1 procedures. The patients were divided in 2 groups for comparison on the basis of the use of an interbody cage/fusion at the L5–S1 level. Revision rates and implant-related complications were also reported.	The fusion rate at L5–S1 was 97% (59/61), with no difference between the interbody and no interbody fusion groups (97% vs. 96%, $p = 1.0$). There were no significant differences in the radiographical parameters or deformity correction between the groups. The mean amount of BMP-2 used in the interbody group was 4.1 mg (2–10), 2.5 mg (0–8) in the disk space, and 1.6 mg (0–4) in the interbody cage, whereas there was no difference in the amount of recombinant human bone morphogenic protein-2 placed posterolaterally between the 2 groups (interbody fusion = 1.6 vs. non-interbody fusion = 2.0 mg, $p = 0.08$) along with autograft and allograft. The overall revision rate for L5–S1 nonunion was 1.6%.	The use of low dose of BMP-2 at the L5–S1 level in combination with sacropelvic fixation achieved satisfactory fusion rates in adult deformity surgery. No additional benefit was encountered by adding an interbody cage.	Included	SCOPUS
7	Theologis AA, Tabaraee E, Lin T, Lubicky J, Diab M. 2015	Type of bone graft or substitute does not affect outcome of spine fusion with instrumentation for adolescent idiopathic scoliosis	Spine	Children (10–18 yr) with AIS who underwent deformity correction via a posterior approach were identified in the Spinal Deformity Study Group database. All had a minimum of 2-year follow-up. Patients were subdivided into 3 groups based on bone graft used: AIC, allograft, and bone substitute (BS). Clinical data included patient demographics, operative details, postoperative analgesic use, and perioperative complications. Lenke curve type and curve magnitude changes were radiographically analyzed. The Scoliosis Research Society-30 questionnaire was used to assess clinical outcomes.	461 patients met inclusion criteria (girls: 381, boys: 80; average age 14.7 ± 1.7) and consisted of 152 AIC patients (124 girls, 28 boys), 199 allograft patients (167 girls, 32 boys), and 110 BS patients (90 girls, 20 boys). There was no difference in age ($p = 0.41$) or gender ($p = 0.82$). The BS group had significantly smaller preoperative curves and shorter operative times. Postoperatively, patients who received BS had significantly longer hospital stays, used higher quantities of patient-controlled intravenous analgesia and used epidurals longer. The AIC group used patient-controlled intravenous analgesia significantly longer. There were no differences between the groups in regards to curve type, number of levels fused, postoperative infections, pseudarthrosis, reoperations for any indication, and Scoliosis Research Society-30 scores at the latest follow-up.	Outcomes after primary posterior spinal fusion with instrumentation are not influenced by type of bone graft or substitute.	Included	SCOPUS

Table 1 – (*Continued*)

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/ exclusion	Database
8	Lina IA, Puvanesarajah V, Liauw JA, Lo SF, Santiago-Dieppa DR, Hwang L, Mao A, Bydon A, Wolinsky JP, Sciubba DM, Gokaslan Z, Holmes C, Witham TF. 2014	Quantitative study of parathyroid hormone (1-34) and bone morphogenetic protein-2 on spinal fusion outcomes in a rabbit model of lumbar dorsolateral intertransverse process arthrodesis	Spine	Forty-eight male New Zealand white rabbits underwent bilateral posterolateral intertransverse process arthrodesis surgery at the L5–L6 level. Animals were divided into 6 groups. Two groups were treated with autograft alone or autograft and PTH (1-34), whereas the other 4 groups were treated with low-dose rhBMP-2 alone, high-dose rhBMP-2 alone, or either dose combined with PTH (1-34). All animals were euthanized 6 weeks after surgery. The L4–L7 spinal segment was removed and assessed using manual palpation, computed tomography (CT), and biomechanical testing.	CT assessments revealed fusion in 50% of autograft controls, 75% of autograft PTH (1-34) animals, 87.5% in the 2 groups treated with low-dose rhBMP-2, and 100% in the 2 groups treated with high-dose rhBMP-2. CT volumetric analysis demonstrated that all groups treated with biologics had fusion masses that were on average significantly larger than those observed in the control group ($p < 0.0001$). Biomechanical data demonstrated no statistical difference between controls, PTH (1-34), and low-dose rhBMP-2 in any testing orientation. PTH (1-34) did not increase bending stiffness when used adjunctively with either low-dose or high-dose rhBMP-2.	Although intermittent teriparatide administration results in increased fusion mass volume, it does not improve biomechnical stiffness over use of autograft alone. When delivered concurrently with high-and low-dose rhBMP-2, teriparatide provided no statistically significant improvement in biomechanical stiffness. Level of evidence: N/A	Included	SCOPUS
9	Nandyala SV, Marquez-Lara A, Fineberg SJ, Pelton M, Singh K. 2014	Prospective, randomized, controlled trial of silicate-substituted calcium phosphate versus rhBMP-2 in a minimally invasive transforaminal lumbar interbody fusion	Spine	Fifty-two patients undergoing a single-level unilateral MIS TLIF were evenly randomized into 2 cohorts as follows: the Actifuse cohort received Actifuse combined with 5 mL of bone marrow aspirate ($n = 26$; 50%), whereas the rhBMP cohort received 4.2 mg of rhBMP-2 ($n = 26$; 50%). A pre hoc G*Power analysis yielded a sample size of $n = 26$ that was determined through a 2-tailed distribution calculation. Computed tomographic analysis was performed at 6 months and 1 year postoperatively. Pre-and postoperative visual analog scale scores were obtained to assess the clinical outcomes. Arthrodesis was determined by 2 separate, blinded orthopedic surgeons and a board certified radiologist.	At 1-year follow-up, 65% (17/26) of the Actifuse cohort and 92% (24/26) of the rhBMP-2 cohort demonstrated a radiographical arthrodesis ($p = 0.01$). In both study cohorts, the 1-year postoperative visual analog scale scores significantly improved ($p < 0.001$). Pseudarthrosis rates at 1 year were 35.0% (9/26) and 7.7% (2/26) for the Actifuse and rhBMP-2 groups, respectively ($p = 0.01$, OR = 6.35, 95% CI = 1.22–33.1). A greater reoperation rate was noted in the Actifuse cohort (35.0%, 9/26) compared with the BMP-2 cohort (7.7%, 2/26; $p = 0.01$). One patient with BMP-2 also experienced symptomatic neuroforaminal bone growth (3.8%, $n = 1/26$).	Silicate-substituted calcium phosphate was associated with a significantly lower rate of arthrodesis than rhBMP-2 in a MIS TLIF. The patients with pseudarthrosis in both cohorts were all clinically symptomatic with an unimproved visual analog scale score. Additional analysis of Actifuse and other graft enhancers/extenders are needed prior to the utilization for an MIS TLIF	Included	SCOPUS

Table 1 – (*Continued*)

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/ exclusion	Database
10	Hoffmann MF, Jones CB, Sietsema DL. 2013	Complications of rhBMP-2 utilization for posterolateral lumbar fusions requiring reoperation: A single practice, retrospective case series report	Spine Journal	Inclusion criteria were posterolateral fusion with rhBMP-2 implant and age equal to or older than 18 years. Surgical indications and treatment were performed in accordance with the surgeon's best knowledge, discretion, and experience. Patients consented to lumbar decompression and arthrodesis using rhBMP-2. All patients were educated and informed of the off-label utilization of rhBMP-2. Patient follow-up was performed at regular intervals of 2 weeks, 6 weeks, 12 weeks, 6 months, 1 year, and later if required or indicated.	Average age was 59.2 years, and body mass index was 30.7 kg/mÂ. Numbers of levels fused were 1 (414, 35.8%), 2 (469, 40.5%), 3 (162, 14.0%), 4 (70, 6.0%), 5 (19, 1.6%), 6 (11, 0.9%), 7 (7, 0.6%), 8 (4, 0.3%), and 9 (2, 0.2%). Patients having complications requiring reoperation were 117 of 1158 (10.1%): symptomatic nonunion requiring redo fusion and instrumentation 41 (3.5%), seroma with acute neural compression 32 (2.8%), excess bone formation with delayed neural compression 4 (0.3%), and infection requiring debridement 26 (2.2%). Nonunion was related to male sex and previous BMP exposure. Seroma formation was significantly higher in patients with higher doses of rhBMP-2 ($p = .050$) and with more than 12 mg of rhBMP-2 ($\chi^2 = 0.025$). Bone reformation and neural compression at the laminectomy and foraminotomy sites occurred in a delayed fashion. Infection was associated with obesity and respiratory disease. Infections were noted with a greater BMP dose ($p < .001$), more than 12 mg ($\chi^2 < 0.001$), fusion more than three levels ($\chi^2 < 0.001$), and reexposed to BMP ($\chi^2 = 0.023$).	rhBMP-2 utilization for posterolateral lumbar fusions has a low symptomatic nonunion rate. Prior rhBMP-2 exposure and male sex were related to symptomatic nonunion formation. rhBMP-2-associated neural compression acutely with seroma formation and delayed with foraminal bone formation is concerning and associated with higher rhBMP-2 concentrations.	Included	SCOPUS

Table 1 – (*Continued*)

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/ exclusion	Database
11	Singh K, Nandyala SV, Marquez-Lara A, Cha TD, Khan SN, Fineberg SJ, Pelton MA. 2013	Clinical sequelae after rhBMP-2 use in a minimally invasive transforaminal lumbar interbody fusion	Spine Journal	A retrospective review of 610 consecutive patients undergoing an MIS-TLIF (2007–2010) by a single surgeon at our institution was performed (mean age 48.7 years, range 26–82 years). All patients underwent an MIS laminectomy with bilateral facetectomy, single TLIF cage, unilateral pedicle screw fixation, and 12 mg (large kit) or 4.2 mg (small kit) of rhBMP-2. The BMP-2 collagen-soaked sponge was placed anteriorly in the disk space, followed by local bone graft, and then the cage was filled only with local bone and no BMP-2. Patients were evaluated at 6 months and 1 year with computed tomography (CT) scan. Those demonstrating neuroforaminal bone growth, osteolysis/cage migration, or pseudarthrosis were reviewed, and cost data including direct cost/procedure for both index and revision surgeries were collected.	Of the 573 patients, 10 (1.7%) underwent 15 additional procedures based on recalcitrant radiculopathy and CT evidence of neuroforaminal bone growth, vertebral body osteolysis, and/or cage migration. Thirty-nine patients (6.8%) underwent reoperation for clinically symptomatic pseudarthrosis. Bone overgrowth was associated with nerve impingement and radiculopathy in all 10 patients (small kit, $n = 9$; large kit, $n = 1$). Osteolysis and cage migration occurred in 2 (20%) of these same 10 patients. Average total costs were calculated per procedure ($19,224), and the costs for reoperation equaled $14,785 per encounter for neuroforaminal bone growth and $20,267 for pseudarthrosis.	Symptomatic ectopic bone formation, vertebral osteolysis, and pseudarthrosis are recognized complications with the use of rhBMP-2 in MIS-TLIFs. Potential causes include improper dosage and a closed space that prevents the egress of the postoperative BMP-2 fluid collection. Management of these complications has a substantial cost for the patient and the surgeon and needs to be considered with the off-label use of rhBMP-2.	Included	SCOPUS
12	Kim HJ, Buchowski JM, Zebala LP, Dickson DD, Koester L, Bridwell KH. 2013	RhBMP-2 Is superior to iliac crest bone graft for long fusions to the sacrum in adult spinal deformity	Spine	A total of 63 consecutive patients, from 1997 to 2006, comprised of 31 patients in the BMP group and 32 patients in the ICBG group, operated on at a single institution with a minimum 4-year follow-up (4–14 yr) were analyzed. Inclusion criteria were ambulators who were candidates for long fusions (thoracic as the upper level) to the sacrum. Exclusion criteria were revisions, neuromuscular scoliosis, ankylosing spondylitis, and patients who had both BMP and ICBG used for fusion. Oswestry Disability Index and 3 domains of the Scoliosis Research Society score were used to assess outcomes.	The 2 groups were similar with respect to age, sex, smoking history, comorbidities, BMI, number of fusion levels and Cobb angles. Eight patients in the BMP group underwent a posterior only, whereas 23 underwent combined anterior and posterior (A/P) surgery. All 32 patients in the ICBG had A/P fusion. The average BMP level was 11.1 mg (3–36 mg). The rate pseudarthrosis was 6.4% (2/31) in the BMP and 28.1% (9/32) in the ICBG group ($p = 0.04$) using Fisher exact test and odds ratio = 5.67. The fusion rates for BMP group were 93.5% and 71.9% for the ICBG group. Oswestry Disability Indexes were similar between groups. However, the BMP group demonstrated superior sum composite Scoliosis Research Society scores in pain, self-image and function domains ($p = 0.02$).	BMP is superior to ICBG in achieving fusion in long constructs in adult deformity surgery. The rate of pseudarthrosis was signifi cantly higher in the ICBG group than BMP group. The concentration and dosage of recombinant human bone morphogenetic protein 2 (rhBMP-2) used seems to have an effect on the rate of fusion and pseudarthrosis rate because no patient receiving more than 5 mg per level had apparent or detected pseudarthroses ($n = 20/20$).	Included	SCOPUS

Table 1 – (*Continued*)

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/ exclusion	Database
13	Frenkel MB, Cahill KS, Javahary RJ, Zacur G, Green BA, Levi AD. 2013	Fusion rates in multilevel, instrumented anterior cervical fusion for degenerative disease with and without the use of bone morphogenetic protein	Journal of Neuro-surgery: Spine	The authors conducted a retrospective cohort study of patients who underwent multilevel (2+ level) anterior cervical fusions performed for degenerative disk disease with or without the concurrent use of BMP-2 from 1997 to 2012. The dosage throughout the study ranged from 2.1 to 0.26 mg/level (mean 1.0 mg/level). All patients were evaluated postoperatively by means of radiographs and CT scans to determine fusion status.	The overall fusion rate for the patients treated without BMP ($n = 23$) was 82.6% compared with a 100% fusion rate in the group treated with BMP ($n = 22$) ($p = 0.04$). The pseudarthrosis rates increased with number of fusion levels in patients who did not receive BMP, whereas all patients in the group treated with BMP had solid arthrodesis. Furthermore, there were 2 instrumentation failures in the non-BMP group. There was a direct correlation between the incidence of complications and the dosage of BMP used per level, with no complications reported at doses equal to or less than 1.1 mg/level.	The overall rate of bony arthrodesis was increased following the use of BMP in multilevel anterior cervical fusion. Traditional methods without BMP had a high rate of pseudarthrosis. The complications associated with the use of BMP appeared to be dose related and of low incidence when BMP is used in doses equal to or less than 1.1 mg/level.	Included	SCOPUS
14	Lu DC, Tumialán LM, Chou D. 2013	Multilevel anterior cervical discectomy and fusion with and without rhBMP-2: A comparison of dysphagia rates and outcomes in 150 patients - Clinical article	Journal of Neuro-surgery: Spine	The authors retrospectively reviewed 150 patient records. Group 1 (BMP group) consisted of 100 patients who underwent multilevel ACDF with PEEK cages filled with rhBMP-2 and instrumented with a cervical plate. Group 2 (allograft group) included a matched control cohort of 50 patients who underwent multilevel ACDF with allograft spacers and anterior plate fixation (without rhBMP-2). Patient demographics were not significantly different between the groups. Fusion was assessed by means of dynamic radiographs and/or CT at routine intervals. Complications, dysphagia incidence, standardized dysphagia score, Nurick grades, and fusion rates were assessed.	The mean follow-up for the BMP group (Group 1) was 35 months while the mean follow-up for the allograft group (Group 2) was 25 months. There was a complication rate of 13% in the BMP group compared with 8% in the allograft group ($p < 0.005$). There was no significant difference in overall dysphagia incidence between the BMP group and the allograft group (40% vs 44%, respectively; $p > 0.05$). However, there was a significant difference in the severity of dysphagia (using the SWAL-QOL dysphagia scoring system) between the 2 groups: 0.757 for the BMP group versus 0.596 for the allograft group ($p < 0.005$). In subgroup analysis, the use of rhBMP-2 significantly increased the severity of dysphagia in patients undergoing 2-level ACDF ($p < 0.005$). However, the severity of dysphagia did not differ significantly between groups when 3- or 4-level ACDF cases were compared. There was no pseudarthrosis in Group 1 (the BMP group) compared with a 16% pseudarthrosis rate in Group 2 (the allograft group) ($p < 0.05$). There was a weak correlation between the total rhBMP-2 dose and the dysphagia score (Kendall tau rank correlation coefficient 0.166, $p = 0.046$).	The use of rhBMP-2 in patients undergoing 2-level ACDF significantly increases the severity of dysphagia (dysphagia score) without affecting the overall incidence of dysphagia. However, there is no statistically significant difference in the incidence or severity of dysphagia between patients undergoing 3-level or 4-level ACDF treated with PEEK/rhBMP-2 and those treated with only allograft. The use of rhBMP-2 appears to reduce the risk of pseudarthrosis. This benefit is most pronounced in patients who undergo 4-level ACDF and are smokers.	Included	SCOPUS

Table 1 – (*Continued*)

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/ exclusion	Database
15	Hsu WK, Polavarapu M, Riaz R, Roc GC, Stock SR, Glicksman ZS, Ghodasra JH, Hsu EL. 2011	Nanocomposite therapy as a more efficacious and less inflammatory alternative to bone morphogenetic protein-2 in a rodent arthrodesis model	Source of the Document Journal of Orthopedic Research	This study evaluates a combination therapy (TrioMatrix®; Pioneer Surgical, Inc., Marquette, MI) comprised of a demineralized bone matrix (DBM), hydroxyapatite, and a nanofiber-based collagen scaffold in a rodent spine fusion model. Thirty-six athymic rats that underwent a posterolateral intertransverse spinal fusion were randomly assigned to 1 of 5 treatment groups: absorbable collagen sponge alone (ACS, negative control), 10 μg rhBMP-2 on ACS (positive control), TrioMatrix®, Grafton® (Osteotech, Inc., Eatontown, NJ), and DBX® (Synthes, Inc., West Chester, PA).	Both TrioMatrix® and rhBMP-2-treated animals demonstrated 100% fusion rates as graded by manual palpation scores 8 weeks after implantation. This rate was significantly greater than those of the ACS, Grafton®, and DBX® groups. Notably, the use of TrioMatrix® as evaluated by microCT quantification led to a greater fusion mass volume when compared to all other groups, including the rhBMP-2 group. T2-weighted axial MRI images of the fusion bed demonstrated a significant host response associated with a large fluid collection with the use of rhBMP-2; this response was significantly reduced with the use of TrioMatrix®.	Our results therefore demonstrate that a nanocomposite therapy represents a promising, cost-effective bone graft substitute that could be useful in spine fusions where BMP-2 is contraindicated.	Included	SCOPUS
16	Adogwa O, Parker SL, Shau D, Mendelhall SK, Cheng J, Aaronson O, Devin CJ, McGirt MJ. 2011	Long-term outcomes of revision fusion for lumbar pseudarthrosis: Clinical article	Journal of Neurosurgery: Spine	. This is a retrospective study of 47 patients who underwent revision lumbar arthrodesis for pseudarthrosis-associated back pain. Baseline 2-year outcomes were assessed using the following: visual analog scale (VAS) for back pain, Oswestry Disability Index (ODI), Zung Self-Rating Depression Scale, time to narcotic independence, time to return to work, EuroQol health-state utility, and physical and mental quality of life (Short Form [SF]-12 Physical and Mental Component Summary scores).	The mean duration of time between prior fusion and development of symptomatic pseudarthrosis was 2.69 years. Bone morphogenetic protein was used in 4 cases (8.5%) of revision arthrodesis. A significant improvement in VAS back pain (7.31 ± 0.81 vs. 5.06 ± 2.64, $p = 0.001$), ODI (29.74 ± 5.35 vs. 25.42 ± 6.0, $p = 0.001$), and physical health SF-12 (23.83 ± 6.89 vs. 27.85 ± 8.90, $p = 0.001$) scores was observed when comparing baseline and 2-year post-revision arthrodesis scores, respectively, with a mean cumulative 2-year gain of 0.35 quality-adjusted life years. The median time to narcotics independence was 12.16 (interquartile range 1.5–24.0) months and the median time to return to work was 4 months (interquartile range 3–5 months). By 2 years after revision surgery, no patients had experienced pseudarthrosis. The SF-12 Mental Component Summary (44.72 ± 7.90 vs. 43.46 ± 7.51, $p = 0.43$) and Zung Self-Rating Depression Scale scores (39.36 ± 7.48 vs. 41.39 ± 10.72, $p = 0.37$) were not significantly improved by 2 years	The authors' study suggests that revision lumbar arthrodesis for symptomatic pseudarthrosis provides improvement in low-back pain, disability, and quality of life. Revision lumbar arthrodesis should be considered a viable treatment option for patients with pseudarthrosis-related back pain. Mental health symptoms from pseudarthrosis-associated back pain may be more refractory to revision surgery.	Included	SCOPUS

Table 1 – (*Continued*)

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/ exclusion	Database
17	Mannion RJ, Nowitzke AM, Wood MJ. 2011	Promoting fusion in minimally invasive lumbar interbody stabilization with low-dose bone morphogenic protein-2 - But what is the cost?	Spine Journal	Study design: Prospective observational study of consecutive patients undergoing minimally invasive lumbar interbody fusion with percutaneous pedicle screws. Patient sample: Thirty patients aged between 22 and 78 years (mean 53 years). Outcome measures: Thin-slice lumbar computed tomography scanning with multiplanar reconstruction at 6 and 12 months postoperative. Methods: Thirty-six spinal levels were instrumented in total, of which four underwent posterior lumbar interbody fusion and 32 underwent transforaminal lumbar interbody fusion. Bone graft harvested locally was placed in the disk space with low-dose BMP-2 (1.4 mg per level).	Thirty-three of 36 spinal levels showed complete fusion at a mean postoperative scan time of 7.1 months. Two levels demonstrated partial fusion at 6 months, which was complete at 12 months. There was one case of nonunion at 12 months, which also demonstrated vertebral body osteolysis. Despite very low-dose BMP-2, two cases of asymptomatic heterotopic ossification were observed, and there were two cases of perineural cyst formation, one of whom required revision of the interbody cage.	The use of BMP with autograft in the disk space during minimally invasive lumbar interbody fusion is associated with a high rate of early fusion. Even with very low-dose BMP used in this study, complications related to BMP usage were not avoided completely.	Included	SCOPUS
18	Mulconrey DS, Bridwell KH, Flynn J, Cronen GA, Rose PS. 2008	Bone Morphogenetic Protein (RhBMP-2) as a substitute for iliac crest bone graft in multilevel adult spinal deformity surgery: Minimum two-year evaluation of fusion	Spine	Prospective analysis was performed for 98 patients (308 levels; mean age, 51.4 years) who underwent multilevel anterior or posterior spinal fusion (PSF) with minimum 2-year follow-up (average, 2.6 years). Group 1 (10 mg/level) contained 47 patients (109 levels; 2.33 levels/patient) who underwent anterior spinal fusion (ASF): BMP on an absorbable collagen sponge (ACS) with a titanium mesh cage. Group 2 (20 mg/level) included 43 patients (156 levels; 3.63 levels/patient) with PSF: BMP on an ACS with local bone graft (LBG) and bulking agent [tricalcium phosphate/hydroxyapatite (TCP-HA)]. Group 3 (40 mg/level) contained 8 patients (43 levels; 5.38 levels/patient) with PSF: rhBMP-2 and TCP-HA with no autologous bone. Confounding negative factors were present in the study population: medical comorbidities (26%), tobacco use (17%), revision surgery (34%), previous laminectomy (51%), and preoperative pseudarthrosis (27%). Postoperative films (AP, lateral, oblique) were evaluated by independent observers. Average fusion grade was based on a published scale.	Overall fusion rate was 95%. (group 1 91%, group 2 97%, group 3 100%). No confounding factor demonstrated a detrimental statistical significance to fusion.	In multilevel ASF, BMP (10 mg/level) generates fusion without autogenous bone. In multilevel PSF, BMP (20 mg/level) with LBG and TCP-HA produced fusion. BMP (40 mg/level) and TCP-HA without LBG achieved fusion. In multilevel spinal fusion, rhBMP-2 eliminated the necessity for iliac crest bone graft and yielded an excellent fusion rate.	Included	SCOPUS

Table 1 – (*Continued*)

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/ exclusion	Database
19	Buttermann GR. 2007	Prospective nonrandomized comparison of an allograft with bone morphogenic protein versus an iliac-crest autograft in anterior cervical discectomy and fusion	Spine Journal	Purpose: The objective of this pilot study was to compare the success of BMP combined with bone allograft with iliac bone autograft in ACDF patients. Study design/setting: The institutional review board approved a prospective but nonrandomized study of 66 consecutive patients who had primary one- to three-level ACDF with either iliac-crest bone autograft or BMP allograft (0.9 mg BMP per level) followed prospectively over a 2- to 3-year period. Patient sample: Consecutive patients who had primary one- to three-level ACDF with either iliac-crest bone autograft ($n = 36$) or BMP-allograft ($n = 30$). Patients in both iliac bone graft and BMP-allograft groups had comparable preoperative pain and disability. Outcome measures: Visual analog scale pain, pain drawing, Oswestry index, pain medication use, opinion of treatment success, and neurological recovery.	Given the nonrandomized nature of the study, the study groups were not matched. Within this limitation, both groups of patients had similar improvement in all outcome scales (visual analog scale pain, pain drawing, Oswestry index, pain medication use, and opinion of treatment success) and neurological recovery over the 2- to 3-year follow-up period. Patients in the iliac bone graft group had two pseudarthroses and two complications of the iliac-crest donor site. In the BMP-allograft group, one patient had a pseudarthrosis, but 50% had neck swelling presenting as dysphagia, which was substantially more common than the 14% present in the iliac bone graft group. Patients in the BMP-allograft group had slightly shorter surgery time, but implant and hospitalization costs were higher.	ACDF performed with BMP (0.9 mg BMP per level) allograft is as effective as iliac bone graft in terms of patient outcomes and fusion rates. Safety concerns related to neck swelling and higher initial costs were associated with patients in the bone morphogenic protein group.	Included	SCOPUS
20	Allen RT, Lee YP, Stimson E, Garfin SR. 2007	Bone morphogenetic protein-2 (BMP-2) in the treatment of pyogenic vertebral osteomyelitis	Spine	Between 2003 and 2005, 14 patients who underwent circumferential fusion for PVO were included in this study. Average patient age was 54 years (range, 27–77 years). Eight (57%) patients had 3 or more vertebral bodies involved. Diagnostic studies included radiographs, CT, MRI, and markers of infection [(C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood count (WBC)]. All patients underwent anterior fusion with rhBMP-2 inserted in structural allograft (11 patients) or titanium cylindrical cages (3 patients), followed by posterior instrumented fusion with autogenous iliac crest graft (8 occurring on the same day). Follow-up averaged 22 months (range, 11–30 months). All were studied with plain radiographs, including flexion-extension lateral films and fine cut CT scans with reconstruction. Pain ratings were recorded by visual analog scores (VAS).	Clinical resolution of infections, normalization of lab values, and bony fusion, based on dynamic radiographs and CT scans, were seen in all patients at latest follow-up. Staphylococcus aureus was the most frequently identified organism (8 patients). Four (29%) patients had positive blood cultures (all MRSA). Predisposing comorbidities were present in 12 patients. Six patients had epidural abscesses. Eight (57%) patients presented with neurologic deficits, ranging from paraparesis to quadriplegia. Complete recovery was seen in 7 (quadriplegia unchanged). At 1 year, mean VAS pain scores improved significantly ($p < 0.05$) from 7.9 (range, 3–10) to 2.8 (range, 0–6). Perioperative complications (non-BMP related) occurred in 2 patients. There were no surgically-related deaths.	rhBMP-2 use, in combination with antibiotics and circumferential instrumented fusion, provides a safe and successful surgical treatment of medically nonresponsive PVO, with solid fusions obtained, good clinical results, and no adverse side effects from the BMP.	Included	SCOPUS

Table 1 – (*Continued*)

n.°	Authors and Year	Title	Journal	Sample	Main findings	Conclusion	Reason for inclusion/ exclusion	Database
21	UFurlan JC, Perrin RG, Govender PV, Petrenko Y, Massicotte EM, Rampersaud YR, Lewis S, Fehlings MG. 2007	Use of osteogenic protein-1 in patients at high risk for spinal pseudarthrosis: A prospective cohort study assessing safety, health-related quality of life, and radiographic fusion	Journal of Neurosurgery: Spine	Outcome measures included documentation of adverse events, radiographic evaluation of fusion by an independent musculoskeletal radiologist blinded to treatment, the Oswestry Disability Index (ODI), and the 36-Item Short Form Health Survey (SF-36). The health-related quality of life (HRQOL) assessments (ODI and SF-36) were given at baseline and at 3, 6, 12, 18, and 24 months after the surgical OP-1 implant.	The study consisted of 17 male and 13 female patients, with a mean age of 53 years (range 20–77 years). Fourteen patients underwent operations for cervical disease, and 16 for lumbar disease, with a median postoperative follow-up of 24 months (range 13–46 months). There were significant improvements in the physical health (from 28.7 ± 1.5 to 34.2 ± 3; $p = 0.025$) and mental health (from 43.7 ± 2 to 47.5 ± 3.1; $p = 0.015$) summary scores on the SF-36. The mean postoperative ODI score at 6, 9, 12, and 18 months was significantly lower than the baseline ODI score, after taking into consideration a 10-point measurement error ($p = 0.0003$, $p = 0.003$, $p = 0.004$, and $p = 0.032$, respectively). At 24 months, however, the differences in ODI scores were no longer significant. Of the 30 patients, 24 (80%) were deemed to have a solid fusion. There were no allergic reactions to OP-1 and no symptomatic postoperative hematomas.	Our results suggest that the use of OP-1 is safe and may contribute to high fusion rates, as demonstrated by radiographs, reduced levels of disability, and improved HRQOL in patients considered to be at a high risk for developing a nonunion after spinal reconstructive surgery.	Included	SCOPUS
22	Lawrence JP, Waked W, Gillon TJ, White AP, Spock CR, Biswas D, Rosenberger P, Troiano N, Albert TJ, Grauer JN. 2007	rhBMP-2 (ACS and CRM formulations) overcomes pseudarthrosis in a New Zealand white rabbit posterolateral fusion model	Spine	Seventy-two New Zealand white rabbits underwent posterolateral lumbar fusion with iliac crest autograft. To establish pseudarthroses, nicotine was administered to all animals. At 5 weeks, the spines were explored and all pseudarthroses were redecorticated and implanted with no graft, autograft, rhBMP-2/ACS, or rhBMP-2/CRM. At 10 weeks, fusions were assessed by manual palpation and histology.	Eight rabbits (11%) were lost to complications. At 5 weeks, 66 (97%) had pseudarthroses. At 10 weeks, attempted pseudarthrosis repairs were fused in 1 of 16 of no graft rabbits (6%), 5 of 17 autograft rabbits (29%), and 31 of 31 rhBMP-2 rabbits (with ACS or CRM) (100%). Histologic analysis demonstrated more mature bone formation in the rhBMP-2 groups.	The 2 rhBMP-2 formulations led to significantly higher fusion rates and histologic bone formation than no graft and autograft controls in this pseudarthrosis repair model.	Included	SCOPUS
23	White AP, Maak TG, Prince D, Vaccaro AR, Albert TJ, Hilibrand AS, Grauer JN. 2006	Osteogenic protein-1 induced gene expression: Evaluation in a posterolateral spinal pseudarthrosis model	Spine	Messenger ribonucleic acid was isolated from nicotine-exposed New Zealand white rabbit lumbar pseudarthroses following attempted no graft, autograft, and osteogenic protein-1 pseudarthrosis repairs. Reverse transcriptase polymerase chain reaction was used to assess the expression of angiogenin, angiopoietin, intercellular adhesion molecule, platelet-derived growth factor-β, vascular endothelial growth factor, bone morphogenetic proteins 2 and 7, type I collagen, and osteonectin. Glyceraldehyde-3-phosphate dehydrogenase was used as a constitutively expressed control.	Levels of gene expression in the osteogenic protein-1 group were higher than those of the autograft group, which were higher than the no graft group for the majority of the genes studied.	In the rabbit pseudarthrosis model, gene expression data supported the hypothesis that successful pseudarthrosis repair is related to the induction of osteogenic and angiogenic cytokines by osteogenic protein-1.	Included	SCOPUS

(approved for anterior lumbar interbody fusions – ALIF) and rhBMP-7 (has received a humanitarian device exemption approval for repair of lumbar pseudarthrosis).

By July of 2002, the FDA approved the use of rhBMP-2 combined with a biologic carrier of collagen (bovine type I collagen) as a substitute for single level ALIF.[1,2,4–6] According to Nadyala et al.[7] the rhBMPs are currently the most effective osteobiologic agents to increase the rate of arthrodesis but are often used as an off label application. Mulconrey et al.[1] describes sustainable results of success, by multiple centers, demonstrating to be superior to ICBG for ALIF. Its use had a rapidly increasing in the United States, despite the initial high costs.[5]

The study of Klimo et al.[8] has demonstrated that the fusion process using rhBMP-2 is a dynamic one, with osteolysis dominating the initial phase, leading to end-plate resorption and consequently loss of some of the disk space height and sagittal alignment that was achieved with surgery. The rhBMP-7 has been documented as a potential treatment alternative for different diseases, including bone disease, stroke, inflammatory bowel disease, prostate cancer, and chronic renal disease.[9] More explicitly, rhBMP-7 plays an important role in bone formation by inducing differentiation of pluripotent mesenchymal cells into active osteoblasts, Furlan et al.[9] concludes that it can induce a stable, mature, posterolateral spinal fusion mass more rapidly than an autologous bone graft, and the resulting fusion mass may be biomechanically stiffer in the early stages (up to 3 months) of healing.

BMP had a 98% vs. ICBG 76% of fusion rate, once been extended its use to off label posterior spinal fusion, anterior/posterior cervical fusion. To Mulconrey et al.[1] at a single level research of 2 years, BMP demonstrate a superior posterolateral spinal fusion rate (88%) than ICBG (73%). Those patients had decreased blood loss, shorter length of surgery and shorter hospital stay.[1,10] According to Hoffmann et al.[5] rhBMP-2 is more effective with a reduction in radiographic nonunion compared with BMP-7, demineralized bone matrix, and activated growth factor.

It must be evaluated all the variables in the spinal fusion, the detrimental factors to fusion are medical comorbidities, tobacco use, preoperative pseudarthrosis, preoperative laminectomy, age, increasing number of surgical levels. Others are osteoporosis, minimal local bone graft, previous and long fusion.[1] Failures have been attributed to poor vascularity of a scarred fusion bed and persistence of systemic inhibitors, such as nicotine.[11] To Furlan et al.[9] the population at risk for a spinal nonunion are patients with connective tissue disorders, individuals with a history of major diseases that could adversely affect bone healing, patients receiving medications that negatively affect bone healing, patients with a history of previous nonunion fusions, and/or patients with limited availability or poor quality of autogenous bone graft.

Singh et al.[4] and Hsu et al.[12] emphasizes that applying BMP is not without risk, the FDA in 2008 issued a public health warning to its use in cervical spine fusion alerting to wound complications, dysphonia, dysphagia and ectopic bone formation. In the lumbar spine, reports have demonstrated radiculitis, pseudarthrosis, seroma/hematoma formation, and heterotopic ossification with rhBMP-2 use. Apprehension about its pro-oncogenic potential has limited its use in the pediatric population, although this trend may be changing.[2,5,12] Both Singh et al.[4] and Hoffmann et al.[5] groups theorizes that the lack of postoperative dead space in Minimally invasive transforaminal lumbar interbody fusion (MIS-TLIFs) surgery may lead to an inflammatory state because of the high concentration of BMP-2, resulting in edema and seroma, theoretically inducing radiculitis, vertebral osteolysis and neuroforaminal bone growth.[4,5]

Pyogenic vertebral osteomyelitis is one of less common complications after spinal fusion, present late or in patients with multiple medical morbidities such as diabetes, HIV or rheumatoid conditions; the use of BMPs to correct this hostile environment of pyogenic infection it is proven effective managed by circumferential instrumented fusion in combination with antibiotics, according to Allen et al.[13] it has good evidence of bony fusion, no infection recurrence and the patients had clinical improvement.

Hoffmann et al.[5] affirms that there is no significant authentic immunologic antibody response to rhBMP-2 or type I bovine collagen, and the reexposure does not lead to a symptomatic antibody formation according to serology testing.

Pseudoarthrosis occur when the fusion attempt fails, a solid fusion is not achieved, or there is motion across the segment leading to it, and it can be clinically symptomatic as pain, deformity, neurocompression or hardware failure. The risks factors are: osteoporosis, cervical kyphotic deformity, revision fusion surgery, multilevel surgery, or a history of smoking.[10] Adogwa et al.[14] suggests that revision surgery of lumbar arthrodesis for symptomatic pseudarthrosis is a viable treatment that improves low-back pain, disability and quality of life. Pseudarthrosis after spine fusion leads to poor clinical outcomes and a significant cost to patients and the healthcare system.[12]

The study of Lu et al.[10] says it is interesting to note that a majority (63%) of the allograft cohort patients who exhibited pseudarthrosis were smokers, whereas all the patients who were in the BMP group had a solid fusion regardless of smoking status. The use of rhBMP-2 appears to reduce the risk of pseudarthrosis, but this benefit is most pronounced in patients treated with 4-level anterior cervical discectomy fusion (ACDF) who are smokers.

Pseudoarthrosis is one of the most common complications after long adult spinal fusion to the sacrum and typically occurs at the thoracolumbar and lumbosacral junctions.[15] Is a major limitation of multilevel anterior cervical fusion, traditional techniques have a 20% of patients who develop pseudarthrosis, one strategy used to help decrease the rate of it is to have posterior instrumentation to increase the rigidity of the construct, however it adds morbidity by increase the time of surgery. Frenkel et al.[16] demonstrate that BMP usage in anterior cervical approach has almost 100% rate of solid arthrodesis regardless of level, but its study does not have statistical significance.

According to Singh et al.[4] 6.8% of patients who underwent a MIS-TLIF procedure were identified as having pseudarthrosis, they all were clinically symptomatic and underwent a revision arthrodesis – a contralateral MIS-TLIF. Patients with revision surgery because of pseudarthrosis are younger than those who did not have a revision ($p < .001$), it is a group of

patients with a high prevalence of smokers compared with the ones who did not need revision (41.3% vs. 26.7%, $p < .054$). The need for review procedure for those patients costs an average of $20,267 (American dollars) of hospital direct costs and physician charges.

Pseudarthrosis at L5–S1 is one of the most common complications of long fusions to the sacrum in adult deformity surgery. Strategies for decreasing it include interbody fusion, use of BMP-2 at the lumbosacral junction, and the use of sacro-pelvic fixation, individually or in combination.[17] The repair in the lumbar spine presents a challenging surgical problem with high failure rates been reported, resulting from poor vascularity in a scarred fusion bed, inadequate posterior bony surface area, loss of sagittal alignment, and exposure to adverse systemic factors such as nicotine. Higher fusion rates were noted with rhBMP-7 than autograft in this setting (82% vs. 42%) in those cases. Another potential bone graft alternative that has been extensively studied is rhBMP-2, demonstrated by Lawrence et al.[18] to overcome the inhibitory effects of nicotine in a model of primary spinal fusion and appears to be an effective alternative in its preclinical model for a scenario with innumerous risk factors for pseudarthrosis repair.

Future studies should be conducted to elucidate the underlying control over the observed gene expression involved in pseudarthrosis, the expression of certain osteogenic and angiogenic genes that have been previously demonstrated to be inhibited by nicotine. For the White et al.[11] model it had up-regulation in the implantation of osteogenic protein-1 at the pseudarthrosis site. Gene expression data supported the hypothesis that the discrepancy in fusion success may be due to osteogenic protein-1's ability to up-regulate osteogenic and angiogenic cytokines required for fusion, and, thus, overcome nicotine's inhibition of local gene expression.

According to Mulconrey et al.[1] rhBMP-2 has the ability to create solid fusion in the presence of negative variables and in multilevel spinal fusion, eliminating the necessity for iliac crest bone graft, to Hoffmann et al.[5] non-union rates in lumbar spine fusion with rhBMP-2 are low, a high dosage (>12 mg) is associated with higher chance of postoperative seroma and infection requiring invasive intervention, such as reutilization of it.

Frenkel et al.[16] indicates that cervical fusion approach with BMP its possible without increase in complication rates if using lower doses of BMP, following the safety concern of the FDA notification, any multilevel anterior cervical procedure, even without BMP, can lead to dysphagia and airway problems. Although according to Lu et al.[10] the use of rhBMP-2 in patients undergoing 2-level ACDF significantly increases the severity of dysphagia, without affecting the overall incidence of it. MIS-TLIFs showed neural compromise by a case series evaluated,[1] although rhBMP-2 is effective for arthrodesis in the unilateral MIS-TLIF the complication of this off-label usage are present – neuroforaminal bone growth, osteolysis and pseudarthrosis.[4]

Kim et al.[15] confirms that BMP is superior to ICBG in achieving fusion in long constructs in adult deformity surgery. The rate of pseudarthrosis was significantly higher in the ICBG group than BMP group, the concentration and dosage of rhBMP-2 used seems to have an effect on the rate of fusion and pseudarthrosis rate because no patient receiving more than 5 mg per level had apparent or detected pseudarthrosis ($n = 20/20$).

To Buttermann[19] (2008) BMP seems to have greater indication in patients having three- or greater-level ACDF, patients who are undergoing revision, patients who have morbid obesity or diabetics and are at risk of bone graft site complications, and patients who have osteoporosis in which the iliac-crest bone graft itself may be subject to collapse or exhibits a risk of subsidence.

Veillette and McKee[6] agree that for lumbar spine fusion the use of BMP showed an increased fusion rate, with a decrease of revision procedures in the same period, but it has no correlation with decrease in the use of ICBG and the use of BMP correlates with substantial increase in hospital chargers. It may question financial justification. Kim et al.[15] justify that for long fusions to the sacrum BMP use significantly decreases pseudarthrosis rates in this patient population when compared with ICBG alone. Which corroborates with Annis et al.[17] study where the use of low dose of BMP-2 at the L5–S1 level in combination with sacro-pelvic fixation achieved satisfactory fusion rates in adult deformity surgery.

Currently, most of the burden of the increased costs is borne by the hospitals and surgeon providers. However, over the long term, the costs may be similar and have yet to be determined conclusively.[19] The future market for BMP-2 in lumbar fusion surgery will depend on the clinical significance of increased fusion in the context of possible side effects and cost considerations, as well as the potential arrival of newer and safer fusion-promoting agents.[20] To Frenkel et al.[16] the BMP-group has a faster fusion progress in a 3-month follow-up than in non-BMP group.

The efficacy of TLIF with BMP is supported in the large series with long-term follow-up of Crandal et al.[21] Reliable fusion and improved outcomes can be expected in adults undergoing TLIF for deformity, spondylolisthesis, and degenerative disease. Most complications occurred in patients with deformity.

Furlan et al.[9] results suggest that the use of rhBMP-7 is safe and may contribute to high fusion rates, as demonstrated by radiographs, reduced levels of disability, and improved quality of life in patients considered to be at a high risk for developing a nonunion after spinal reconstructive surgery. At Theologis et al.[22] study shows no difference in outcomes between autogenous iliac crest, allogeneic bone graft, and bone substitutes in primary posterior spine fusion with instrumentation in idiopathic scoliosis. This study contributes to the growing body of evidence that rhBMP-7 is safe for surgical use in the clinical arena. The use of an rhBMP-7 implant may be a contributing factor to the elevated rate of radiographic fusion, improved quality of life, and reduced degree of disability after spinal fusion that was observed in its group of patients at a high risk for developing pseudarthrosis. It does not confer additional benefit when bone fusion is likely to occur in a normal fashion; however, in patients with one or more risk factors for impaired bone healing, the adjuvant use of it may negate these effects, allowing adequate bone fusion to occur.

Crandall et al.[23] five-year follow-up after TLIF with BMP, confirms effective arthrodesis in short and long fusions, both primary and revision surgeries. Most complications occurred in deformity patients, the BMP-related ones (seroma, ectopic bone) were rare.

Even with very low dose BMP used in the study of Mannion et al.[20] complications related to BMP usage were not avoided completely, it was observed asymptomatic heterotopic ossification and two cases of perineural cyst formation, one of whom required revision. Hoffmann et al.[5] points out the need of additional research to determine dose dependency and genetic predisposition to react to BMPs, such as over (ectopic bone and seroma) or underreaction (nonunion).

Final remarks

Our review shows that the use of BMPs is effective and secure compared to ICGB, but depending of the location of usage (cervical spine, lumbar spine or sacrum) and the medical status of the patient (presence of comorbidities, tobacco usage) its more probable to exhibit complications, such as neuroforaminal bone growth, osteolysis, pseudarthrosis, seroma, hematoma. This data determine that the usage of BMPs must be an agreement between patient and physician, an informed decision discussing the benefits and risks of BMP for each case.

Conflicts of interest

The authors declare no conflicts of interest.

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