INTRODUCTION:
Bone graft material and reliable fusion rates are an essential part of successful spinal fusion. Efforts to enhance spinal fusion and to eliminate autogenous iliac crest bone graft (ICBG) harvest are being researched. The use of osteobiologics to enhance fusion has therefore become an important role in these procedures. In 2002, the U.S. Food and Drug Administration approved rhBMP-2 for the repair of symptomatic, posterolateral lumbar spine pseudarthrosis. Despite restricted approval for other procedures, off-label use of BMPs has become a permanent trend. About 85% of the procedures using BMP were performed in an off-label manner. BMP-2 in combination with bone void fillers (BVF) without or in combination with iliac crest autograft for posterolateral intertransverse process fusion has been studied. With osteoporosis, poor bone quality, or multilevel fusions, larger amounts of graft material is required. The adjunctive use of rhBMP-2 has been demonstrated to result in larger and more consistent fusion masses.

For lumbar fusions no consistent dosage per level can be found in the current literature. Dosage and concentration per level varies from 4.2 mg to 40 mg and 1.5mg/mL to 2.0 mg/mL, respectively. Despite the desire of surgeons and patients to avoid pseudarthrosis and ICBG harvest morbidity, the cost of rhBMP-2 treatment and possible complications remain an important concern. Therefore multiple studies have been performed to lower rhBMP-2 dosage without sacrificing reliable fusion rates.

The purpose of this study was to define the amount of rhBMP-2 necessary to achieve reliable fusion rates in posterolateral spine fusion while concurrently reducing complication rates.

METHODS:
This study was an IRB approved retrospective cohort review of patients undergoing instrumented lumbar posterolateral fusion utilizing rhBMP-2 at a single spine center. Consecutive patients were identified that had initial treatment from 2002 through 2009, 7 years. Inclusion criteria were: posteriorlateral fusion with rhBMP-2 implant and age ≥ 18 years. Exclusion criteria: thoracic fusions, anterior lumbar interbody fusion, posterior or transforminal lumbar interbody fusion, BMP products other than rhBMP-2, follow up < 6 months, and insufficient medical or radiographic data. Of 1755 lumbar fusions, we identified 760 patients (mean age 62.5 years, 308 male, 452 female, BMI 30.95 kg/m²) who underwent instrumented lumbar fusions with 1752 levels supplemented with rhBMP-2. The mean follow up period was 18 months (6-79). Mean length of hospital stay was 5.04 days. Comorbidities were recorded. All patients underwent local autografting utilizing posterior elements and were consented to decompression, arthrodesis and off label use of rhBMP-2. Surgical treatment was performed in accordance with the surgeon’s best knowledge. Therefore bone graft and bone graft extenders were used at the surgeon’s discretion. The surgeon determined the amount of BMP kits. The mean total BMP-2 dose was 12.5 mg per patient (4.2-36.0). The mean dosage per level was 7.7 mg (1.5 – 24.0).

Results related to the performed procedure were recorded.

RESULTS:
65 patients had surgical complications (8.55%): 35 patients had an intraoperatively diagnosed dural tear (4.6%). 26 patients had postoperative surgical site infection (3.4%). 23 patients had symptomatic postoperative fluid accumulations (3.0%), and 5 patients had malpositioned implants (0.66%). 27/760 patients underwent excessive debridement as an isolated procedure (3.6%) because of infection or seroma formation. 40 patients required redo arthrodesis because of a symptomatic non-union (5.3%). 47 patients developed add-on stenosis (6.2%). One patient (0.1%) had symptomatic osseous overgrowth, which required redo neural decompression. 17 (2.2%) patients underwent hardware removal because of painful or prominent hardware.

In our patient sample, 40 patients (5.7%) underwent redo surgery for non-union. Nonunion was not related to diabetes or smoking ($\chi^2=0.123$).

We found an average of 7.18 mg rhBMP-2 per level for those who developed a stable fusion compared to an average of 6.22 mg rhBMP-2 for those who developed a non-union (p=0.096).

<table>
<thead>
<tr>
<th>BMP-2/level</th>
<th>Nonunion (n)</th>
<th>Nonunion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.0 mg</td>
<td>6</td>
<td>6.90</td>
</tr>
<tr>
<td>4.0 – &lt; 6.0 mg</td>
<td>9</td>
<td>8.18</td>
</tr>
<tr>
<td>≥ 6.0 mg</td>
<td>18</td>
<td>5.94</td>
</tr>
<tr>
<td>≥ 12.0 mg</td>
<td>7</td>
<td>3.18</td>
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Patients with postoperative infections (26) underwent fusion utilizing an average of 5.41 mg rhBMP-2 per level compared to 7.07 mg rhBMP-2 for those who had uncomplicated wound healing (p=0.065). No difference in rhBMP-2 dose per level for patients who developed a fluid collection compared to those who had no postoperative fluid collection (6.67 mg, 7.02 mg respectively, p=0.458).

DISCUSSION:
Posterolateral arthrodesis is a commonly performed orthopaedic procedure and an integral component of the surgical management of degenerative lumbar spine disease. Surgeons are still in search for the ultimate fusion procedure and supplement. The use of ICBG is currently the gold standard with posteriorlateral fusions. Better results were previously demonstrated in patients with additional posterior instrumentation. Despite improved mechanical stability, multiple methods have been developed to optimize the biological environment for fusion. Allograft bone seems to have similar properties compared to ICBG but includes the risk for disease transmission. Processing allograft bone by acid extraction results in loss of the mineralized components (demineralized bone matrix). Collagen and non-collagenous proteins, including growth factors are persevered. Promising adjuncts are BMPs, which have been shown to induce bone formation and increase fusion rates. Therefore, BMPs utilization in spinal fusions increased to 25% nationally (2006).

In order to achieve the highest possible fusion rate, different dosages per level have been researched. Early studies suggested that 18 to 32 mg rhBMP-2 per side resulting in 36 to 64 mg rhBMP-2 per level are optimal to achieve solid fusion. Multiple clinical studies have been performed using 40 mg per level fused. Fusion rates up to 100% were reported. But there is also growing concern of adverse effects. A systematic literature review showed that the use of BMP in the lumbar spine can be associated with radiographic graft resorption, extradiscal, ectopic, and heterotopic bone formation, radiculopathies, epidural cyst formation, and seromas.

Our finding of 3.18% nonunion rate in patients who underwent instrumented posterolateral fusion in combination with ≥ 12 mg rhBMP-2 per level is comparable to Singh et al. who found a 97% fusion rate for these patients. Comparing the nonunion rates in our findings, there is no statistically significant difference for fusion rates for 6 mg rhBMP-2 compared to 12 mg rhBMP-2 per level. We found similar pseudarthrosis rates in redo-surgeries for dosages 6 mg and more per level.

We did not find higher rates of infection or fluid collection in patients undergoing fusion with higher levels of rhBMP-2. Infection rate was related to numbers of levels fused and BMI. Therefore, size of surgical approach, length of surgery, and soft tissue damage seems to be more relevant than rhBMP-2 dose. Development of a fluid collection was not related to rhBMP-2 dose and no threshold prevented this severe symptomatic complication. Further studies concerning fluid collections after BMP utilization are warranted.

In our study, a wide variety of grafts and BVF have been used. In accordance with previous studies in nonhuman primates, fusion depends not only on rhBMP-2 dosage but also on the use of autograft, allograft, and bone void fillers.

SIGNIFICANCE:
Orthopaedic spine surgeons should consider a lower dose of rhBMP-2 than originally recommended to achieve fusion. Yet, surgical approach, length of surgery, and soft tissue damage seems to have greater relevance for infection.