BMP Induced Inflammation:  
A Comparison of rhBMP-7 and rhBMP-2

Myeong-Jae Yoo, MD,  
Kwang-Bok Lee, MD

Departments of Orthopedic Surgery, Chonbuk National University Medical School,  
Research Institute of Clinical Medicine, Chonbuk National University Hospital, Jeonju,  
Korea
Background

- rhBMP-2 and rhBMP-7
  - important osteoinductive adjuvants in orthopaedic surgery
- United States Food and Drug Administration (FDA) for use in human surgery
- in July 2008, the FDA
  - recommended against the offlabel usage of BMPs
- rhBMP-7: widely used in bone graft substitutes
Purpose

• The assessment of therapeutic strategies to ameliorate or treat these reactions

• Compare the inflammatory reactions to rhBMP-7 with those to BMP-2 using our in vitro and in vivo animal model
 MATERIAL AND METHODE

- In Vitro Study
  - Experimental doses of rhBMPs in this study
    - the rodent model of spinal fusion utilizing rhBMP-7 and rhBMP-2
    - the dose-for-weight equivalent to the baseline dose
      (a human undergoing spine fusion)
  - Secretory levels of pro-inflammatory cytokines
    - IL-6 and TNF-a proteins
    - by Quantikine HS ELISA kits
MATERIAL AND METHODE

- In Vivo Study
  - Animal Surgery
    - seven treatment groups with five animal subjects in each group
      (0, 1, 3, 5, 10, and 20 mg of rhBMP-7)
    - compared to data from our previous study
      (examine the inflammatory characteristics of rhBMP-2)
  
- Subcutaneous (SC) & Intramuscular (IM) implantation
  - MRI Evaluation
  - Gross Morphology and Histological Evaluation
RESULT

- Mean values of IL-6 and TNF-a production (In Vitro Study)

Figure 1.
Cytokine production (A, IL-6; B, TNF-a) tended to be less in the presence of rhBMP-7 than in rhBMP-2.
### RESULT

- The volumes of the soft tissue edema (MRI Measurements)

![Table 1.](image)

Table 1.

Inflammatory Volume following Subcutaneous Implantation
RESULT

- The volumes of the soft tissue edema (MRI Measurements)

Figure 2.
Mean soft tissue edema volumes following subcutaneous implantation of rhBMP-7 and -2 at (A) 3 h, (B) 2 days, (C) 4 days, and (D) 7 days postoperatively.
RESULT

- The volumes of the soft tissue edema (MRI Measurements)

Figure 3. Mean soft tissue edema volumes following intramuscular implantation of rhBMP-7 and -2 at (A) 3 h, (B) 2 days, (C) 4 days, and (D) 7 days post-surgery.
RESULT

Gross Morphology Analysis

<table>
<thead>
<tr>
<th>BMP type</th>
<th>Total</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>10</th>
<th>20 (μg)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pairwise comparison&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross morphology (mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMP 7</td>
<td>60.1 ± 14.1</td>
<td>50.2 ± 2.6</td>
<td>52.9 ± 6.4</td>
<td>51.4 ± 2.8</td>
<td>61.6 ± 11.4</td>
<td>60.0 ± 5.5</td>
<td>76.6 ± 20.1</td>
<td>&lt;0.001</td>
<td>0 1 3 5 10 20</td>
</tr>
<tr>
<td>BMP 2*</td>
<td>65.0 ± 23.0</td>
<td>50.2 ± 2.6</td>
<td>52.8 ± 3.1</td>
<td>55.0 ± 7.9</td>
<td>57.0 ± 11.5</td>
<td>63.4 ± 6.3</td>
<td>111.8 ± 13.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.301</td>
<td>0.968</td>
<td>0.367</td>
<td>0.511</td>
<td>0.348</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4.
Gross morphologic findings following subcutaneous implantation of rhBMP-7 (A1–3) and -2 (B1–3); control 0 mg (A1 and B1), low-dose 1 mg (A2 and B2), and high-dose 20 mg (A3 and B3)
A granuloma-like mass developed in all cases. Statistically significant difference between rhBMP-7 and -2 treatment groups.
RESULT

Microscopic Findings

<table>
<thead>
<tr>
<th>BMP type</th>
<th>Total</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>10</th>
<th>20 (µg)</th>
<th>p-value$^a$</th>
<th>Pairwise comparison$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMP 7</td>
<td>5.0 ± 1.7</td>
<td>4.0 ± 1.1</td>
<td>3.9 ± 0.2</td>
<td>4.2 ± 0.4</td>
<td>6.3 ± 1.0</td>
<td>7.9 ± 1.0</td>
<td>&lt;0.001</td>
<td>0 1 3 5 10 20</td>
<td></td>
</tr>
<tr>
<td>BMP 2$^c$</td>
<td>5.6 ± 2.6</td>
<td>4.0 ± 1.1</td>
<td>3.9 ± 0.6</td>
<td>4.1 ± 1.0</td>
<td>4.1 ± 0.7</td>
<td>7.4 ± 0.6</td>
<td>10.2 ± 1.0</td>
<td>0.888</td>
<td>0.742</td>
</tr>
</tbody>
</table>

Figure 5.
Microscopic findings (× 10, scale bar: 500 mm) following intramuscular implantation of rhBMP-7 (A1–3) and -2 (B1–3); control 0 mg (A1 and B1), low-dose 1 mg (A2 and B2), and high-dose 20 mg (A3 and B3).
The two green outlines in each image illustrates the soft tissue inflammation area measurement (mm2) using Aperio ImageScope software.

Table 3. Inflammatory Volume of the Subcutaneous Implantation
Conclusion

• rhBMP-7 induced a dose-dependent inflammatory reaction
  - maximal at 3 h (subcutaneous) and 2 days (intramuscular)

• Compared to rhBMP-2, rhBMP-7
  - less soft tissue edema formation, especially in high-dose treatments

• To test BMP delivery systems and materials
  - reduce inflammation
  - a more safe use of the BMPs
DISCLOSURE

All the Authors are aware of the content of the paper and do not have any financial or other interests that might be construed as a conflict of interest.