

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

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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)

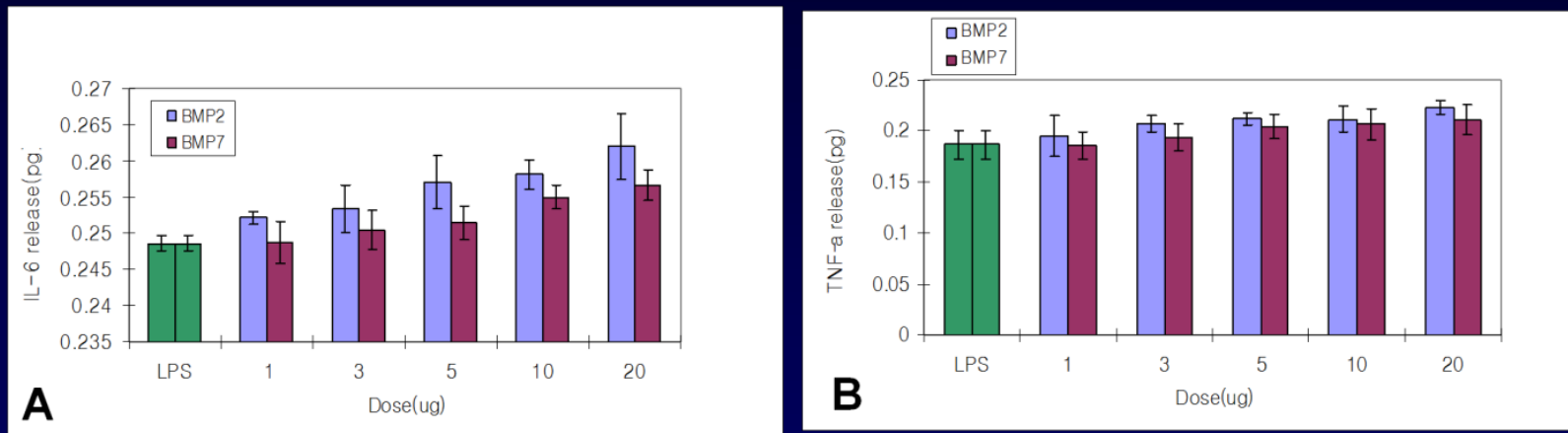


Figure 1.

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)

BMP type	Total	0	1	3	5	10	20 ( $\mu$ g)	p-value <sup>a</sup>	Pairwise comparison <sup>b</sup>
3 h									
Surgery only	98.9 $\pm$ 49.1							<0.001	0 1 3 10 5 20
BMP7	176.1 $\pm$ 51.1	102.9 $\pm$ 9.2	167.7 $\pm$ 12.3	173.1 $\pm$ 32.9	182.3 $\pm$ 64.5	198.3 $\pm$ 43.6	231.9 $\pm$ 34.3		
BMP2*	190.9 $\pm$ 71.9 <sup>c</sup>	102.9 $\pm$ 9.2	158.4 $\pm$ 38.7	172.4 $\pm$ 38.3	212.6 $\pm$ 35.1	214.2 $\pm$ 46.3	284.8 $\pm$ 35.5		
p-value <sup>d</sup>			0.621	0.975	0.774	0.591	0.049		
2 day									
Surgery only	11.5 $\pm$ 7.2							<0.001	0 1 3 5 10 20
BMP7	157.5 $\pm$ 73.7 <sup>c</sup>	54.4 $\pm$ 3.7	135.4 $\pm$ 52.2	137.0 $\pm$ 14.7	167.1 $\pm$ 58.6	213.6 $\pm$ 55.5	217.1 $\pm$ 77.2		
BMP2*	151.6 $\pm$ 91.4 <sup>c</sup>	54.4 $\pm$ 3.7	98.1 $\pm$ 25.9	100.0 $\pm$ 49.1	183.0 $\pm$ 64.2	195.6 $\pm$ 31.1	278.4 $\pm$ 99.2		
p-value <sup>d</sup>			0.190	0.145	0.918	0.545	0.308		
4 day									
Surgery only	9.7 $\pm$ 4.7							<0.001	0 1 3 5 10 20
BMP7	116.0 $\pm$ 60.8 <sup>c</sup>	53.4 $\pm$ 19.7	106.5 $\pm$ 6.9	93.8 $\pm$ 20.9	117.4 $\pm$ 33.6	163.5 $\pm$ 96.9	161.1 $\pm$ 60.9		
BMP2*	114.2 $\pm$ 67.2 <sup>c</sup>	53.4 $\pm$ 19.7	64.7 $\pm$ 11.1	81.3 $\pm$ 40.4	131.8 $\pm$ 64.1	151.2 $\pm$ 42.2	202.6 $\pm$ 61.6		
p-value <sup>d</sup>			0.013	0.554	0.669	0.801	0.316		
7 day									
Surgery only	6.8 $\pm$ 0.5							0.010	0 3 1 10 5 20
BMP7	73.8 $\pm$ 33.1 <sup>c</sup>	58.1 $\pm$ 12.2	60.6 $\pm$ 8.2	66.2 $\pm$ 13.1	73.4 $\pm$ 63.1	72.8 $\pm$ 24.6	91.5 $\pm$ 19.3		
BMP2*	84.3 $\pm$ 41.3 <sup>c</sup>	58.1 $\pm$ 12.2	78.4 $\pm$ 45.8	54.2 $\pm$ 14.1	72.1 $\pm$ 21.5	97.5 $\pm$ 25.8	145.5 $\pm$ 40.5		
p-value <sup>d</sup>			0.418	0.202	0.203	0.161	0.006		

Table 1.  
Inflammatory Volume following Subcutaneous Implantation

# RESULT

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

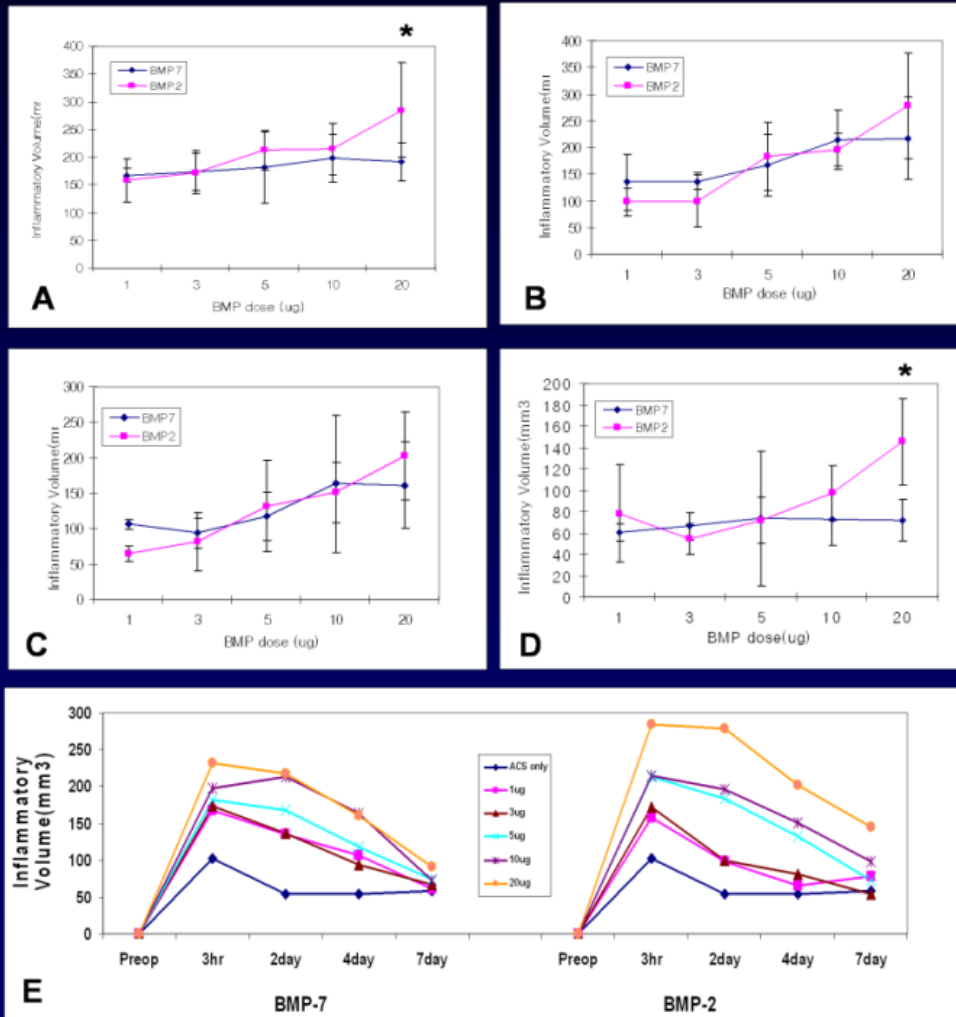


Figure 2. Mean soft tissue edema volumes following subcutaneous implantation of rhBMP-7 and -2 at (A) 3 h, (B) 2 days, (C) 4 days, and (D) 7 days postoperatively



# RESULT

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

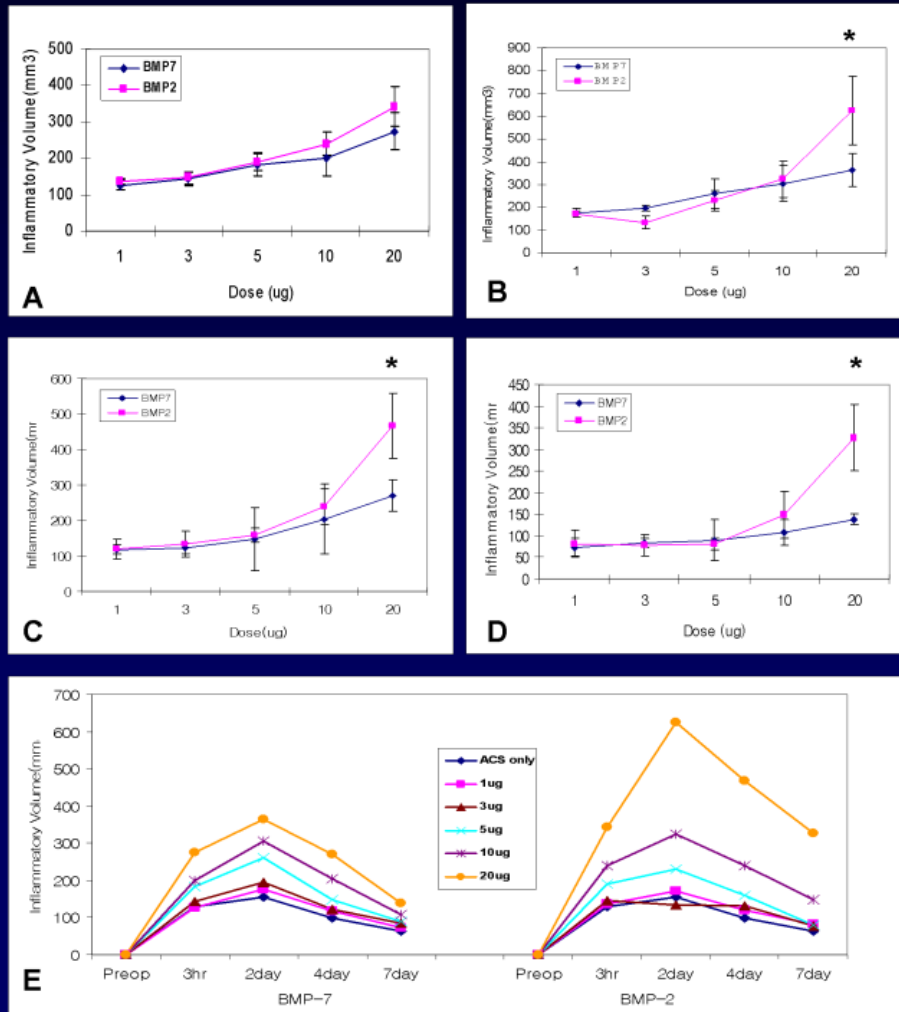


Figure 3.

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

BMP type	Total	0	1	3	5	10	20 (μg)	p-value <sup>a</sup>	Pairwise comparison <sup>b</sup>
Gross morphology (mm <sup>3</sup> )									
BMP 7	60.1 ± 14.1	50.2 ± 2.6	52.9 ± 6.4	51.4 ± 2.8	61.6 ± 11.4	60.0 ± 5.5	76.6 ± 20.1	<0.001	0 1 3 5 10 20
BMP 2*	65.0 ± 23.0	50.2 ± 2.6	52.8 ± 3.1	55.0 ± 7.9	57.0 ± 11.5	63.4 ± 6.3	111.8 ± 13.2		
p-value <sup>a</sup>		0.301							
p-value <sup>c</sup>			0.986	0.367	0.511	0.348	0.006		

Table2.  
Inflammatory Volume  
of the Subcutaneous  
Implantation by Gross  
Analysis

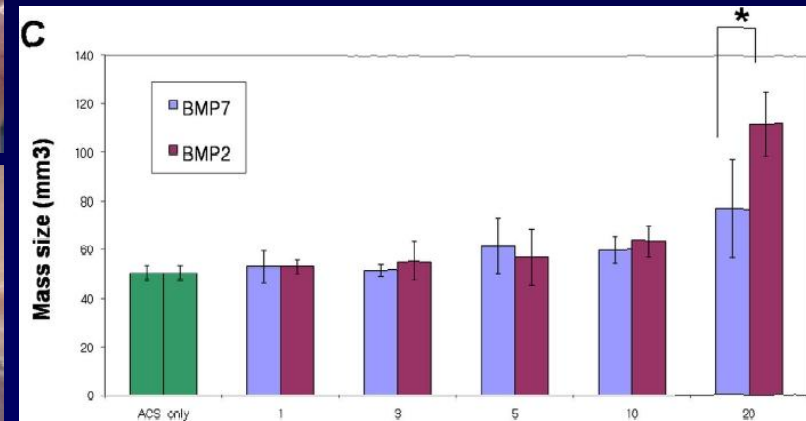
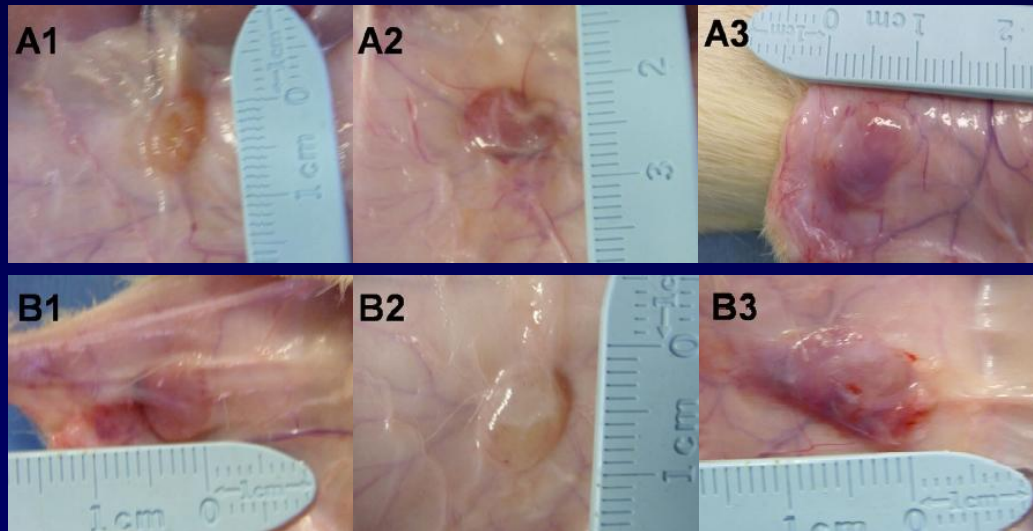


Figure 4.

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

BMP type	Total	0	1	3	5	10	20 (μg)	p-value <sup>a</sup>	Pairwise comparison <sup>b</sup>
Microscopic morphology (mm <sup>2</sup> )									
BMP 7	5.0 ± 1.7	4.0 ± 1.1	3.9 ± 0.2	3.9 ± 0.2	4.2 ± 0.4	6.3 ± 1.0	7.9 ± 1.0	<0.001	0 1 3 5 10 20
BMP 2*	5.6 ± 2.6	4.0 ± 1.1	3.9 ± 0.6	4.1 ± 1.0	4.1 ± 0.7	7.4 ± 0.6	10.2 ± 1.0		
p-value <sup>a</sup>		0.438							
p-value <sup>c</sup>			0.888	0.742	0.641	0.322	0.046		

Table3. Inflammatory Volume of the Subcutaneous Implantation

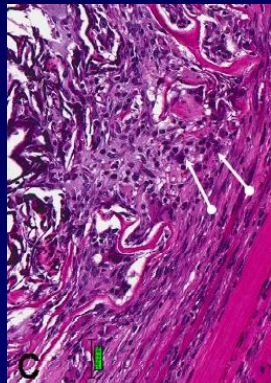
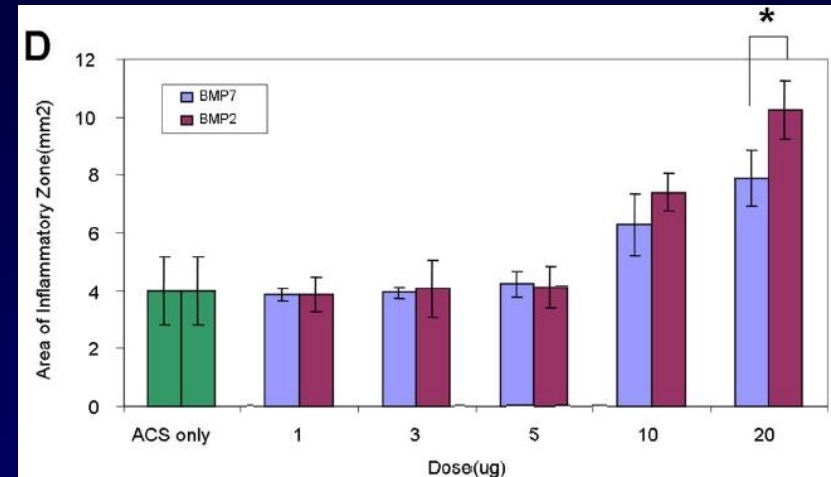
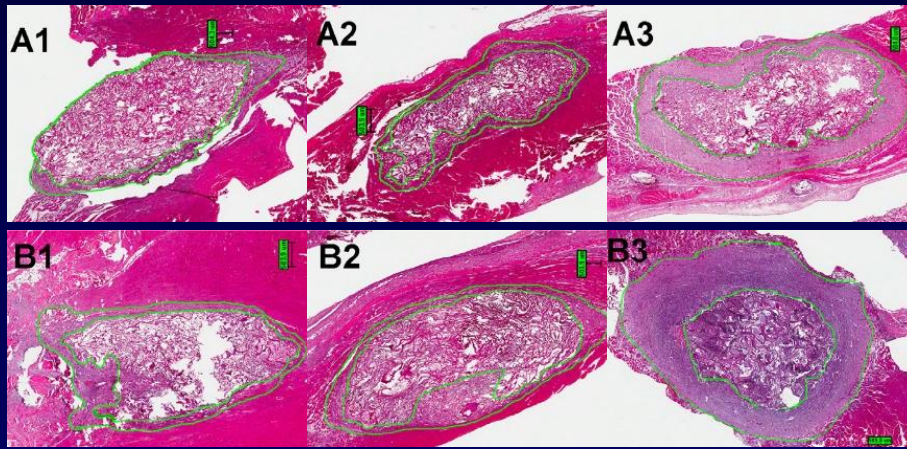


Figure 5. Microscopic findings (10x, scale bar: 500 μm) following intramuscular implantation of rhBMP-7 (A1–3) and -2 (B1–3); control 0 mg (A1 and B1), low-dose 1 mg (A2 and B2), and high-dose 20 mg (A3 and B3). The two green outlines in each image illustrate the soft tissue inflammation area measurement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

# 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.