Effect on Bone Remodeling
by Teriparatide (PTH1-34) in BMP2-induced Rat Spinal Fusion Model

Tokimitsu Morimoto, Takashi Kaito, Masafumi Kashii, Yohei Matsuo, Tsuyoshi Sugiuira, Motoki Iwasaki, Hideki Yoshikawa.
Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan.

Disclosures:

Introduction:
Although clinical bone morphogenetic protein (BMP) therapy is effective, required doses are very high. The use of high dose BMP often results in complications such as ectopic or heterotopic bone formation because of a difficulty in spatial control of BMP-induced bone formation. Teriparatide (PTH1-34) is approved to treat osteoporosis and is a potent anabolic agent that stimulates dominantly osteoblastic proliferation and bone formation compared to osteoclastic bone resorption with the short-term administration. However, long-term administration of PTH1-34 is known to stimulate both osteoblastic and osteoclastic activity. This unique action of PTH1-34 can be expected to accelerate the remodeling process of excessively induced new bone. The aim of this study is to elucidate the effect of long term administration of PTH1-34 on bone remodeling in a BMP-induced rat spinal fusion model.

Methods:
A total of 35 Sprague Dawley male rats aged 8 weeks were operated with posterolateral fusion at L4-5 by two different BMP-2 treatments; (1) 0µg (control), (2) 50µg (high dose). Each of the BMP-2 treatments was studied in combination of intermittent PTH1-34(180µg/kg/w) or saline injection since 2 weeks before the operation to 12 weeks after operation. Bony fusion at L4-5 was quantified using plain radiographs and manual palpation test. Bone volume and microstructural indices of the newly formed bone were evaluated by micro CT. Serum bone markers and histology were also evaluated.

Results:
Radiographs demonstrated no bone formation in the control group and 100% fusion in the BMP treated group with or without PTH1-34 administration. Microstructural indices of the newly formed bone were significantly improved (both trabecular and cortical bone indices) by the PTH administration. However, tissue volume (TV) of the newly formed bone was significantly decreased by PTH1-34 administration. Micro CT coronal and axial reconstruction images clearly demonstrated improved bone quality and remodeling process of the newly formed bone in the PTH1-34 treatment group(Figure lower). Bone formation marker (osteocalcin) and bone resorption marker (I-CTP) was significantly increased in the PTH1-34-treated group (p<0.01).

Discussion:
Long-term intermittent PTH1-34 administration significantly accelerated the remodeling process of the BMP-induced newly formed bone and significantly improved the quality of the newly formed bone in a BMP-induced rat spinal fusion model. Thus, PTH1-34 may promote the remodeling process of BMP-induced newly formed bone depending on
the mechanical requirements in a similar fashion with normal fracture healing process. These results suggest its potential clinical applications in BMP-induced spinal fusion surgery.

**Significance:**
This is the first report revealed the accelerated remodeling of BMP-induced fusion mass by PTH1-34. This fact has a great impact on clinical BMP use because this effect by PTH1-34 administration enables spatial control of BMP-induced fusion mass.

**Acknowledgments:**

**References:**
TV of the newly formed bone

Micro CT image of the spines in each group
Time course of TV at the fused spine segments

![Diagram showing the time course of TV at the fused spine segments with different treatment groups: BMP 2.0μg + Saline, BMP 2.0μg + PTH 1-34, BMP 2.5μg + Saline, BMP 2.5μg + PTH 1-34. The graph includes a shaded remodeling window.](Image)