Calcium sulfate/hydroxyapatite mediated co-delivery of BMP-2 and zoledronic acid enhances spinal fusion in a rat posterolateral spinal fusion model

Xinggui Tian1,2, Corina Vater1,2, Deepak B. Raina1, Lisa Findeisen2-3, Lucas-Maximilian Matuszewski1,2, Magnus Tägil1, Lars Lidgren1, Klaus-Dieter Schaser1, Alexander C. Disch1, Stefan Zwingerberger1,2

Email of Presenting Author: Stefan.zwingerberger@uniklinikum-dresden.de

1 University Center of Orthopaedic, Trauma and Plastic Surgery, University Hospital Carl Gustav Carus at Technische Universität Dresden, 01307 Dresden, Germany; 2 Center for Translational Bone, Joint and Soft Tissue Research, University Hospital Carl Gustav Carus at Technische Universität Dresden, 01307 Dresden, Germany; 3 Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Orthopaedics, Lund 22185, Sweden

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INTRODUCTION: Posterolateral spinal fusion (PLF) is a commonly used procedure in orthopedic surgery to treat spinal instability. However, it is challenging to achieve a robust fusion due to the long bone crawl distance, extensive soft tissue stripping, and limited contact with native bone. Bone morphogenetic protein 2 (BMP-2) is approved by the FDA for spinal fusion, but it is also a strong inducer of osteoclast-based bone resorption, leading to a reduced net bone formation and limiting its clinical application in spinal fusion. In addition, the FDA-approved carrier (absorbable collagen sponge) used to deliver rhBMP-2 is sub-optimal and causes pre-mature release of the protein. One strategy to eliminate the osteoclast inducing side effect of BMP-2 is the combined application of bisphosphonates and BMP. Systemic administration of bisphosphonates is however associated with some side-effects, which have reduced its use. Our recent study showed an excellent and cumulative effect on bone regeneration when both BMP-2 and zoledronic acid (ZA) were co-delivered from an optimized clinically approved calcium sulphate/hydroxyapatite (CaS/HA) scaffold in a rat critical-size femoral defect model (1). Therefore, the aim of this study was to evaluate whether local application of BMP-2 and ZA released from a resorbable CaS/HA scaffold is favorable for spinal fusion. We hypothesized that CaS/HA mediated controlled co-delivery of rhBMP-2 and ZA could show an improved effect in spinal fusion over BMP-2 alone.

METHODS: Based on the treatment i.e., implant type, 7 groups were set up in this study (I. CaS/HA, II. CaS/HA + BMP-2, III. CaS/HA + systemic ZA, IV. CaS/HA + local ZA, V. CaS/HA + BMP-2 + systemic ZA, VI. CaS/HA + BMP-2 + local ZA, VII. Blank (previous study of our group)). This in vivo study was performed on 132, 8-week-old male Wistar rats (n = 12 at 3 weeks and n = 10 at 6 weeks per group, animal protocol no. 25-5131/474/38). A posterolateral intertransverse process spinal fusion at L4 to L5 was performed bilaterally by implanting group dependent scaffolds (see above). At 3 weeks, 12 animals per group, and at 6 weeks 10 animals per group were euthanized for µCT analysis. At 3 weeks, differences between multiple groups were tested using one-way ANOVA with Tukey’s post hoc method in case of normally distributed and homogeneous variance data or using Kruskal-Wallis test with Tamhane T2’s post hoc method in case of normally distributed and unequal variance data. At 6 weeks, µCT analysis showed the CaS/HA + BMP-2 + local ZA group had the highest bone volume at 3 weeks, and highest bone volume and bone mineral density at 6 weeks among all treated groups (Figure 1). Biomechanical testing revealed significantly higher breaking force in CaS/HA + BMP-2 + local ZA group than other groups at 6 weeks (Figure 3).

DISCUSSION: The CaS/HA-based biomaterial functionalized with bioactive molecules rhBMP-2 and ZA enhanced bone formation and concomitant fusion outcome. The anabolic and anti-catabolic coupling effects of rhBMP-2 and ZA result in more net bone formation in spinal fusion surgery and may potentially lead to overall BMP-2 dose reduction. The carrier properties of the CaS/HA biomaterial are optimal for controlled co-delivery of both BMP-2 and ZA, as previously shown (Raina, Acta Biomater, 2019). In-vivo release data indicated that the CaS/HA biomaterial leads to significantly prolonged release of both BMP-2 and ZA when compared with the ACS biomaterial. Taken together, our findings suggest that the functionalization of the CaS/HA biomaterial with rhBMP-2 and ZA might be potentially used as an alternative to autograft bone for spinal fusion.

SIGNIFICANCE/CLINICAL RELEVANCE: All components in this study are already approved for clinical use. The treatment regime of combining CaS/HA biomaterial with co-delivery of BMP-2 and ZA may soon translate into clinical use as an alternative to autologous bone grafting for challenging procedures of PLF.


Figure 1: Micro-CT evaluation of spinal fusion. (A) Representative 3D reconstructions, (B-C) BV and BMD density at 3 weeks and (D-E) BV and BMD at 6 weeks quantified in all treatment groups using micro-CT. The red # and pink # indicated the L4 and L5 transverse process, respectively. The red * and pink * indicated the L4 and L5 lamina, respectively. Scale bars = 2 mm. Data are presented as means ± SD. *P < 0.05.

Figure 2: Representative H&E and Goldner's trichrome staining images of the explanted lumbar vertebrae at 3 weeks after surgery. Scale bars = 1000 μm.

Figure 3: Three-point bending of the explanted lumbar vertebrae 6 weeks after surgery to assess the biomechanical properties of the spinal fusion effect in all treated groups. Data are presented as means ± SD. *P < 0.05.