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VASCULAR ENDOTHELIAL GROWTH FACTOR AND BONE MARROW STROMAL CELLS EHANCE ANGIOGENESIS AND RESORPTION OF A CORALLINE CARRIER IN LARGE SEGMENTAL BONE DEFECTS

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BACKGROUND: Bone defect and bone nonunion are common occurrences and represent major problems in orthopedics and require massive bone grafts for reconstruction. Auto- or allo-grafting are the most currently used therapeutic approaches. However, autograft is limited by the availability of bone in a patient and allograft can cause immunological rejection and bear the risk of transmitting diseases. Recent efforts have been made to develop artifical grafts. As natural and synthetic biomaterials lack osteogenic and osteoinductive properties lack the osteogenic and osteoinductive properties of bone autografts they were combined with bone marrow cells (BMSC) or osteoinductive growth factors. These combinations worked well in animal trials or small and well vascularized areas such as the skull. However, some studies showed that these combinations still did not work in badly vascularied tissue. In a previous study, it was demonstrated that vascularisation of segmental bone defects can be achieved by the administration of vascular endothelial growth factor (VEGF) on a collagen sponge which then worked as a gene activated matrix.
OBJECTIVES: To evaluate the angiogenesis and osteogenesis in large segmental bone defects by the administration of VEGF165 gene plasmid or BMSCs on a solid scaffold, Biocoral.
MATERIALS AND METHODS: A 15-mm segmental defect was created in the middle of rabbit radius. Biocoral implants combined with empty plasmids, pVEGF165 plasmids, BMSCs or VEGF165 transfected BMSCs were placed into the bone defects. Serial radiographs were taken in two standard projections every 4 weeks after surgery. Rabbits were sacrificed 16 weeks after operation, samples were excised en bloc and were fixed and embedded with Technovit 9100 New®. Every bone block was examined with a μ-CT system. Three longitudinal 300μm-thick sections were obtained from each specimen by sawing and were ground to approximately 15μm. Histological and histomorphological evaluations were carried in Masson-Goldner and Toluidin-Giemsa stained slices. The numbers of blood vessels in the bone defects were

calculated in CD31 immunohistochemically stained slices.
RESULTS: Counting of the vessels revealed an increase in vessel formation either by the VEGF plasmid or preloading of the carrier with BMSCs compared to the coralline carrier alone. Along with increased angiogenesis the resorption of the scaffold was accelerated. Although we could not find any positive results of direct VEGF gene delivery in new bone formation by μCT evaluation, the newly formed bone was better organized histologically in the VEGF group than in the control group. Sufficient bone formation was only seen when the coral scaffold was filled with BMSCs. After application of VEGF transfected cells, the scaffold vanished before it was substituted by new bone. Compared to BMSCs alone the application of VEGF transfected cells did not support but inhibit bone formation.
CONCLUSION: We could demonstrate that the application of VEGF-expressing cells enhances vascularization and resorption of the coralline bone substitute. On the other side, the transfection of BMSCs with a VEGF165-plasmid reduced their ability to form new bone in our model. As Biocoral® degraded quite fast, even if no cells or growth factors were used, it might have been inappropriate for this setting while other more solid bone substitutes would have benefited from the effect of VEGF.
KEYWORDS: Biomaterial; Bone healing; Blood supply; Vascular endothelial growth factor; Bone marrow stromal cell; Bone tissue engineering; Gene therapy; Nonunion