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Space Maintenance and New Bone Formation with Polyurethane Biocomposites in a Canine Saddle Defect

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Statement of Purpose: Large mandibular defect reconstruction presents a continual challenge in oral and maxillofacial surgery. Growth factors such as recombinant human bone morphogenetic protein-2 (rhBMP-2) incorporated in scaffolds for tissue engineering promote cellular infiltration, induce osteoblast differentiation, and enhance new bone formation. Biodegradable polyurethane (PUR) biocomposites containing allograft bone particles are reported to be effective carriers for rhBMP-2 and support new bone growth.[1] Moreover, incorporation of allograft bone particles increases the mechanical properties of the graft, which is important for space maintenance in mandibular defects. However, allograft presents biological challenges, as even a low dose of rhBMP-2 combined with allograft can result in transient resorption.[2] Additionally, combining recombinant human growth factor with allograft bone introduces regulatory concerns. Mastergraft (MG) is an osteoconductive, biphasic ceramic composed of 85% β-tricalcium phosphate (β-TCP) and 15% hydroxyapatite (HA) that is similar in mineral content to natural bone.[3] 45S5 Bioactive glass (BG) is a resorbable material that has been used effectively in a variety of bone regeneration applications.[4] In the present study, we investigated the ability of injectable PUR/MG and PUR/BG biocomposites with two doses of rhBMP-2 to heal saddle defects in the canine mandible.

Methods: The biodegradable polyurethane was synthesized from a lysine triisocyanate (LTI) and polyethylene glycol (PEG) prepolymer, a polyester triol (450 g/mol), and triethylene diamine catalyst. Treatment groups included the biocomposite containing 45% MG or 45% BG with a low dose of 100 μg/mL rhBMP-2 or a high dose of 400 μg/mL rhBMP-2 (n=4/group). The lyophilized rhBMP-2 was hand-mixed with the PUR and injected into saddle defects (4/animal) measuring approximately 7-8 mm apicocoronal by 8-10 mm mesiodistal. The biocomposite was shaped through the creation of a pocket of soft tissue into which the composite could be injected (Fig 1). The biocomposite hardened within 7-9 min with a porosity of 45-55%. Animals were sacrificed at 16 weeks and new bone formation evaluated by radiographs, μCT, histology, and histomorphometry.

Figure 1. PUR/MG biocomposite delivery into the defect

Results: In a previous study using a PUR/MG biocomposite with 200 μg/mL rhBMP-2, new bone growth was observed in rat calvarial defects at 4 and 8 weeks, as evidenced by the representative histological section in Fig. 2, where new bone is red, cells are blue, and remaining MG particles are black. While healing progressed from 0 to 8 weeks, the rate of new bone formation slowed at later time points, which was attributed to rapid polymer degradation ($t_{1/2}$ = 3 mos. *in vitro*) and slow MG resorption. In the canine mandibular ridge study, we aimed to balance the rates of polymer degradation, matrix resorption, and new bone formation to enhance healing. A 450 g/mol polyester triol ($t_{1/2}$ = 7 mos. *in vitro*) was used to decrease the degradation rate of the PUR. To investigate how the matrix resorption rate controls healing, fast-resorbing BG and slow-resorbing MG particles were investigated. Thus, the canine mandibular ridge study was designed to answer the following questions: (1) Will the biocomposite bone grafts maintain space and prevent prolapse in mandibular ridge defects? (2) How does the resorption rate of the matrix particles regulate new bone formation and healing? (3) What is the rhBMP-2 dose that optimized healing?

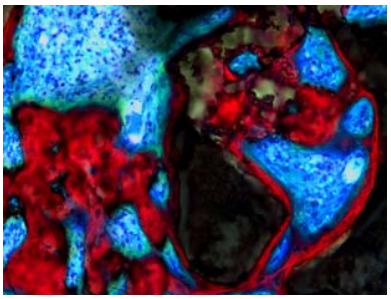

Figure 2. PUR/MG biocomposite with 200 μg/mL rhBMP-2 at 8 weeks in a rat calvarial defect at 20x

Conclusions: PUR/MG biocomposites with rhBMP-2 support new bone formation and remodeling in a rat calvarial defect. We have applied this biocomposite to a canine saddle defect model to test the hypothesis that the bone-like mechanical properties of the graft will provide space maintenance and that bone formation will be enhanced with a faster resorbing matrix. In ongoing experiments we are investigating the *in vitro* osteoclastic resorption potential of a variety of synthetic matrices, including β-TCP and BG, relative to bone.

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