Institutionen för Molekylär Medicin och Kirurgi

Craniofacial bone reconstruction with Bone Morphogenetic Protein-2

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ABSTRACT

Bone defects in the craniofacial area are a clinical challenge and can be the result of trauma, tumour resection or congenital malformations. The golden standard for reconstruction is autologous bone grafts, but bone may not always be readily available and donor-site morbidity might follow. Alternatives to autologous tissue are sought in the field of tissue engineering, where a range of biomaterials, bone forming cells and growth factors are combined, searching to engineer the missing tissue. The use of bone morphogenetic proteins (BMPs) together with different carriers has been explored ever since Marshall Urist discovered the BMPs in 1965. In this thesis we use BMP-2, together with different carriers in an attempt to reconstruct cranial defects in different species.

In paper Ia we look into ectopic bone induction with BMP-2 and heparin/chitosan in a rat model. The resulting bone induction is compared to BMP-2 and type I collagen, and found to be superior in the BMP-2 and heparin/chitosan group. In the following clinical study, paper Ib, BMP-2, heparin/chitosan and titanium mesh are used for the reconstruction of large cranial defects in humans. The patients demonstrate a postoperative inflammatory reaction and weak bone formation, and the results are disappointing and discourage the use of heparin/chitosan in a clinical setting. The healing of cranial defects in minipigs with BMP-2 and hyaluronan-based hydrogel is studied in paper II. The defects treated with BMP-2 and hyaluronan-based hydrogel demonstrate 119 percent ossification, indicating complete healing and bone overgrowth to some extent. Animals treated with hydrogel alone show 58 percent ossification and 53 percent ossification in the control group, showing a significant difference in induced bone volumes between the BMP-treated animals and animals treated with hydrogel alone. Bone healing of cranial defects in rats comparing hyaluronic acid hydrogel and type I collagen is studied in paper III. Immunohistochemistry and histomorphometric analysis show more active bone formation in the BMP-2 and hydrogel group with significant increase in bone formation two to four weeks after surgery compared to BMP-2 and collagen or hydrogel alone. In the last study (paper IV) cranial reconstruction after neurosurgery with BMP-2 and hydrogel is studied. Boreholes are randomized into treatment with BMP-2 and hydrogel, hydrogel alone, autologous bone and Tisseel™ or Spongostan™ (negative control). Bone healing in holes treated with BMP-2 and hydrogel or autologous bone and Tisseel™ is significantly increased compared to negative control.

In conclusion tissue engineering of bone with heparin/chitosan and hyaluronan-based hydrogel with BMP-2 show good bone inductive capacity, superior to type I collagen and BMP-2. Hyaluronan-based hydrogel has more attractive qualities regarding the inflammatory response and BMP-2 and hydrogel produce bone comparable to bone autografts.

Keywords: Bone morphogenetic protein, bone induction, heparin, chitosan, hyaluronan, hydrogel