Optimal Murine Cranial Defect Reconstruction Utilizing a Novel Collagen Scaffold and rhBMP2 with Analysis Utilizing Confocal Microscopy

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Introduction

Although tremendous advancements in the surgical reconstruction of craniofacial defects have been made, a large proportion of patient outcomes remain unfavorable. Patients with combat and civilian trauma, craniectomy for various intracranial pathologies and large en-bloc tumor resections are often left with few reconstructive options. Technical challenges that exist in the reconstruction of larger, more complex craniofacial defects are pronounced due to a higher incidence of infection, soft tissue erosion, extrusion, and migration. This study aims to further delineate the role of bone morphogenetic protein-2 (rhBMP2) by determining the smallest dose required for maximal bone regeneration when delivered in a novel collagen scaffold.

Methods

Utilizing a murine model, C57BL/6 (n=) mice received two identical 5mm full-thickness craniectomy defects (61.6 mm^2) using a standardized micro-drill core bit. The mice were divided into 10 groups consisting of: craniectomy only (Group 1, n=3), craniectomy with doses of 0.1µg rhBMP2 (Group 2, n=3), 1.0µg rhBMP2 (Group 3, n=3), 2.5µg rhBMP2 (Group 4, n=3), 5.0µg rhBMP2 (Group 5, n=3), craniectomy with collagen only (Group 6, n=3), and craniectomy, collagen and doses of 0.1µg rhBMP2 (Group 7, n=5), 1.0µg rhBMP2 (Group 8, n=5), 2.5µg rhBMP2 (Group 9, n=5), 5.0µg rhBMP2 (Group 10, n=5). Mice underwent CT imaging at 2 and 8 weeks to assess volumetric calvarial bone regeneration and explant analysis at 8 weeks using confocal microscopy.

Results

The mice in Group 1 (craniectomy only), Groups 2-5 (craniectomy plus rhBMP2) and Group 6 (craniectomy plus collagen) showed appreciable but little total percent defect healing at 8 weeks (Group 1=1%, Group 2=9%, Group 3=12%, Group 4=13%, Group 5=19%, and Group 6=4%). Groups 7-10 (craniectomy plus collagen plus rhBMP2) showed a much higher stepwise increase in total percent of defect healed (Group 7=19%, Group 8=23%, Group 9=31%, and Group 10=38%). Additionally, a stepwise increase in total hydroxyapatite aggregates and hydroxyapatite aggregate size was observed in Groups 2-5, and Groups 6-10. Maximum angiogenesis was seen in Group 8.

Conclusions

Current surgical reconstruction of large craniofacial defects remains challenging and associated with a high incidence of complications. The determination of an optimal dose of rhBMP2 delivered in a novel collagen scaffold, as outlined here in a murine cranial defect, facilitates further evaluation of rhBMP2 when used alone or in combination with other biologic products to reconstruct large craniofacial defects.

Percent Defect Healing