

Bone Morphogenetic Protein-2 vs Platelet Derived Growth Factor for the Management of Non-unions: A Comparison of Commercially Available Formulations

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INTRODUCTION: Non-unions remain relatively common, with an estimated 10% of all long bone fractures going on to non-union. Such non-healing fractures present significant challenges for orthopaedic surgeons and patients, requiring multiple complex procedures and significantly impacting patients' quality of life. The current gold standard for management of such non-unions is autologous bone grafting. However, this approach is limited by the volume of graft available, surgical site morbidity, and rates of recurrent non-union. An alternative approach to address these issues is to use osteoinductive molecules to facilitate bone healing. Among those compounds investigated, bone morphogenetic protein-2 (BMP-2) and platelet-derived growth factor (PDGF) have been incorporated into commercially available bone graft alternatives. Though both molecules can facilitate bone healing, their individual and comparative efficacy in the management of non-unions is unknown. Accordingly, we compared two commercially available products utilizing these molecules in a small animal model of atrophic non-union, employing a critical sized defect.

METHODS: All experiments were approved and carried out in accordance with the Animal Care Committee of Unity Health, Toronto, Canada. Fifty adult male Fischer 344 rats (250-300g) had a 5 mm mid-diaphyseal defect created in the right femur. This defect was then stabilized with a mini-plate and screws, with the defect treated per the animal's random allocation to 1 of 5 treatment groups (n=10 per group): 1) Control – empty defect, 2) PDGF carrier - β -tricalcium phosphate (β -TCP) carrier, 3) PDGF treatment - β -TCP carrier with PDGF (β -TCP+PDGF), 4) BMP-2 carrier – absorbable collagen scaffold (ACS) carrier, 5) BMP-2 treatment – ACS carrier with BMP-2 (ACS+BMP-2). PDGF and BMP-2 carriers and treatments were generated from commercially available products and prepared per the manufacturer's protocols. PDGF carrier and treatment was generated from the Augment bone graft product (BioMimetic Therapeutics, LLC, Franklin, Tennessee). Similarly, BMP-2 carrier and treatment were generated from the Infuse bone graft product (Medtronic Sofamor Danek, Inc., Memphis, Tennessee). Total dose delivered to defects were 0.015 mg of PDGF and 0.01 mg of BMP-2 for the PDGF and BMP-2 treatment respectively. Ten weeks post-operatively, final radiographic images were obtained for assessment by two blinded orthopaedic surgeons. Femora were subsequently harvested and were analyzed by microscopic computed tomography (microCT) and torsional biomechanical testing.

RESULTS: BMP-2 treatment resulted in 100% rate of radiographic union (Table 1), with greater mean radiographic score (mean \pm standard deviation) compared to control (7.1 \pm 0.3 vs 3.9 \pm 2.3, p = 0.0009) and PDGF treatment (7.1 \pm 0.3 vs 4.6 \pm 1.5, p = 0.011) (Figure 1). MicroCT analysis demonstrated significantly greater trabecular tissue volume and separation with BMP-2 treatment compared to control (39.4 \pm 10.4 vs 3.7 \pm 4.1 mm³, p < 0.0001 & 0.79 \pm 0.17 vs 0.31 \pm 0.15 mm, p < 0.0001) and PDGF treatment (39.4 \pm 10.4 vs 1.1 \pm 1.3 mm³, p < 0.0001 & 0.79 \pm 0.17 vs 0.24 \pm 0.23 mm, p < 0.0001). Likewise, superior mechanical properties were found with BMP-2 treatment, with greater ultimate torque and yield point (median [interquartile range]) compared to PDGF treatment (98[69-161] vs 0 N \cdot mm, p < 0.0001 & 41.7[34.1-76.9] vs 0 N \cdot mm, p < 0.0001), and greater maximum stiffness than control (28.8[23.5-38.3] vs 0.95[0-10.1] N \cdot mm⁰, p = 0.0159) and PDGF treatment (28.8[23.5-38.3] vs 0 N \cdot mm⁰, p < 0.0001) (Figure 2).

DISCUSSION: This study found superior outcomes with BMP-2 treatment compared to PDGF treatment for the management of non-unions in a small animal bone defect model. The potency of BMP-2 treatment was demonstrated by the superior healing on both imaging and functional testing with a 100% rate of union. Importantly, the dosage of the molecules delivered to the defect site were similar (0.015 mg for PDGF and 0.01 mg for BMP-2), allowing for an accurate comparison of their biological activity in this application. Moreover, by employing commercially available products, we were able to assess the potency of these molecules using clinically relevant carriers (β -TCP and ACS), improving the clinical applicability of this investigation. However, such clinical relevance is limited by the use of a small animal model of atrophic non-union which incompletely mimics the clinical scenario in which these molecules and products could be employed. As such, further studies investigating these molecules in a clinical context are warranted.

SIGNIFICANCE/CLINICAL RELEVANCE: Our findings suggest that BMP-2 treatment is superior to PDGF treatment in the setting of a bone defect and further investigation comparing these commercially available growth factors in clinical studies is warranted.

IMAGES AND TABLES:

	Non-union/Partial Union	Union
Control	90% (9)	10% (1)
β -TCP	80% (8)	20% (2)
β -TCP+PDGF	80% (8)	20% (2)
ACS	50% (5)	50% (5)
ACS+BMP-2	0% (0)	100% (10)

Table 1. Rates of radiographic non-union and partial union vs complete union in each group. Values are represented as percentage of animals per group, and number of animals achieving a given degree of union per group. β -TCP = PDGF carrier, β -TCP+PDGF = PDGF treatment, ACS = BMP-2 carrier, ACS+BMP-2 = BMP-2 treatment

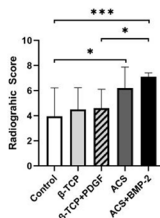


Figure 1. Mean radiographic union scores as assessed by two blinded orthopaedic surgeons. Higher scores indicate a greater degree of union, with complete union indicated by a score of 8. Values are represented as mean \pm standard deviation. β -TCP = PDGF carrier, β -TCP+PDGF = PDGF treatment, ACS = BMP-2 carrier, ACS+BMP-2 = BMP-2 treatment. * denotes p < 0.05, *** p < 0.001.

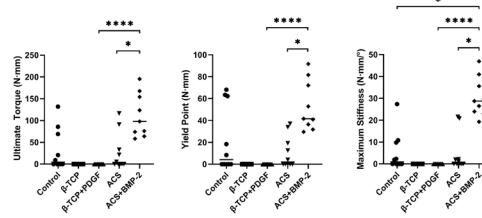


Figure 2. Results of mechanical testing for ultimate torque, yield point, and maximum stiffness. Individual values are presented, with group median indicated by horizontal bar. β -TCP = PDGF carrier, β -TCP+PDGF = PDGF treatment, ACS = BMP-2 carrier, ACS+BMP-2 = BMP-2 treatment. * denotes p < 0.05 and **** p < 0.0001.