Acceleration of Fracture Healing Modulated by Compounds that Stimulate Inducible Nitric Oxide Synthase

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Purpose: Nitric oxide, synthesized in vivo by nitric oxide synthase (NOS), has been implicated in the fracture healing process. We investigated in the rat the effects on fracture healing of two upregulators of inducible nitric oxide synthase (iNOS): tadalafil, a phosphodiesterase inhibitor, and the recently reported nutraceutical COMB-4 (consisting of L-citrulline, Paullinia cupana, ginger, and muira puama), given orally for either 14 or 42 days following an open femoral fracture.

Methods: Unilateral fractures were created in 58 male rats and fixed with an intramedullary compression nail. Rats were treated daily either with vehicle, tadalafil, or COMB-4. The volume, mineral content, and bone density of the callus were measured by quantitative CT at days 14 and 42. At day 42, biomechanical testing of the healed fracture was also performed. iNOS expression was measured by immunohistochemistry.

Results: At days 14 and 42, there was no significant difference between the three groups with respect to callus volume, mineral content, and bone density. When compared to the control group, biomechanical testing at day 42 demonstrated that the COMB-4 group exhibited higher maximum strength (46%; P = 0.093) and significantly more stiffness (92%; P = 0.016) while there was no change in the tadalafil group (Fig. 1A). iNOS expression at day 14 was highest in the COMB-4 group that, as expected, returned to baseline levels at day 42 (Fig. 1B).

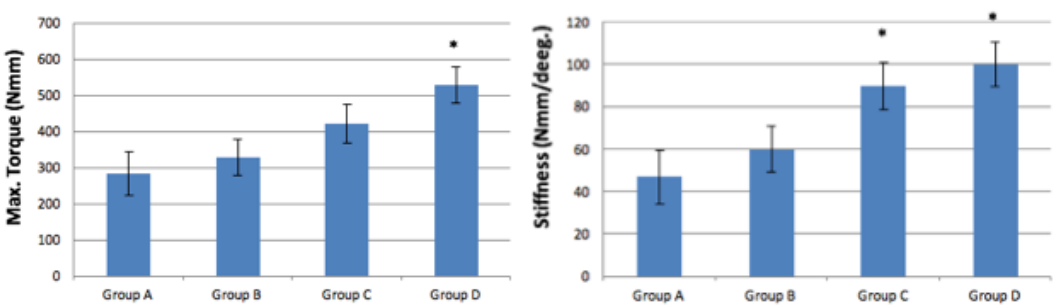

Figure 1A-B. A, Maximum Torque (strength) at 6 weeks. B, Stiffness at 6 weeks. * p<0.05 compare to Group A (bar = SD).

Conclusion: This study demonstrates an enhancement in fracture healing in the rat by an oral natural product known to augment iNOS expression. Clinical studies will be required to determine the suitability of COMB-4 as an adjunctive treatment for fractures in humans.