Evaluation of rhPDGF-BB in Combination with a Flowable Collagen Matrix for the Treatment of Acute Achilles Tendon Injury

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INTRODUCTION: Rupture of the Achilles tendon occurs frequently in the general population, affecting athletes and non-athletes of all ages. Most Achilles injuries occur in men between the ages of 30 and 50 years of age [1]. The mechanical rigors on the Achilles tendon and the limited cell source and vascular supply available at the repair site contribute to the incidence of postoperative failures after primary repair. Tendon augmentation procedures, incorporating the use of autograft, allograft and xenograft materials for repair, have been utilized, though incomplete healing and/or graft failure is not uncommon. The documented incidence of repair failures highlights the need for treatments which include stimulators of wound repair and regeneration. Platelet-derived growth factor-BB (PDGF-BB) is a well characterized wound healing protein known to be chemotactic and mitogenic for cells of mesenchymal origin, including tendon (tenoblast/tenocyte) cells. Additionally, PDGF-BB has been shown to improve wound healing when applied to animal models of tendon injury [2,3]. We hypothesized that recombinant human platelet-derived growth factor-BB (rhPDGF-BB) combined with a flowable collagen matrix would improve healing of an acute Achilles tendon injury, as assessed biomechanically and histologically.

METHODS: Treatment Groups: Three treatment groups (n=8/group) were used in the repair of an acute Achilles tendon transection in this study: (1) suture+collagen matrix, (2) suture+collagen matrix+150µg rhPDGF-BB, and (3) suture+collagen matrix+500µg rhPDGF-BB. Surgical Procedure: The Achilles tendon of 24 skeletally mature ewes (3.5+ years) was surgically exposed and transected 4 cm from the calcaneal attachment. A single #0 FiberWire suture was passed through the tendon ends using a Mason-Allen technique and the tendon ends were tied in close approximation to each other. The subcutaneous tissue was closed, forming a pouch over the transection site and the flowable collagen matrix, with or without rhPDGF-BB was applied between the tendon ends before the wound was closed using standard surgical procedure. The animals were bandaged with a splint on the lower leg and allowed to ambulate normally immediately post-op. Animals were sacrificed 8 weeks post-surgery. Biomechanical Testing: Specimens (n=6/group) were cleaned and potted using high strength polymethylmethacrylate and mounted in a custom-designed testing fixture that was rigidly attached to the materials testing system loading frame (MTS MiniBionix). A custom clamp designed to preserve the natural cross section of the Achilles tendon was used to apply uniaxial traction forces to the construct at an angle of approximately 135° to the potted metatarsus to model the physiological force vector of the tendon. Three cameras (Motion Analysis) were used to record the spatial movement of four retroreflective markers at 60 Hz and allowed for real-time monitoring of local tissue displacement/plantar within the reparative tissue. Preconditioning was performed by applying an initial preload of 10 N, followed by cyclic loading (in load-control) from 10 to 50 N at 0.25 Hz for 60 cycles. Preconditioning was followed by a quasi-static load-to-failure ramp at 1 mm/s. From this load-to-failure test, the quasi-static stiffness, ultimate load-to-failure, and elongation were determined. Histology: Specimens (n=2/group) were prepared for histologic evaluation. Tissue samples were prepared for histology and stained with hematoxylin and eosin. All tissue sections were evaluated to assess the quality of the reparative/healing tissue, the native tendon/reparative tissue interface, vascularization, inflammation, and collagen density/fiber orientation. Statistical Analysis: A One-Way ANOVA and post-hoc Tukey’s test were performed using SigmaStat 3.1 to identify significant differences in continuous biomechanical parameters between treatment groups. Significance was set at p<0.05. Data are shown as mean ± SEM.

RESULTS: Animal Observations: Two animals from the 0.3 mg/ml group had hematomas within the repair tissue and were omitted from the analysis (n=4 for biomechanics). One animal from the 1.0 mg/ml group was sacrificed at 7 weeks due to complications unrelated to the study (n=1 for histology). Biomechanical Testing: Consistent trends were observed towards improved biomechanical properties in group 3 (500 µg rhPDGF-BB) in ultimate force (Group 1: 922.04±149.91 N, Group 2: 1188.31±266.12, Group 3: 1451.71±125.08, p=0.101), global stiffness (Group 1: 96.61±8.56 N/mm, Group 2: 93.81±7.17, Group 3: 113.11±7.14, p=0.209), and elongation (Group 1: 14.55±2.42 mm, Group 2: 16.16±2.61, Group 3: 18.02±2.14, p=0.577), although these did not reach significance. All quantified biomechanical parameters in the 1.0 mg/ml rhPDGF-BB group were, on average, increased compared to control (57.4%, 17.1%, and 23.8%, respectively). The local repair stiffness (Group 1: 215.23±33.23 N/mm, Group 2: 223.72±11.46, Group 3: 312.56±20.86) was significantly increased in the samples treated with 1.0 mg/ml rhPDGF-BB compared to control samples (p=0.039).

DISCUSSION: The flowable collagen matrix hydrated with 500 µg of rhPDGF-BB enhanced the biomechanical healing response compared to the flowable collagen matrix alone. While the low number of animals per group reduced the statistical power for this study, the biomechanical data observed for the group treated with 500 µg rhPDGF-BB were consistently increased compared to the flowable collagen controls. Additionally, the ultimate force observed in this study for the 500µg rhPDGF-BB group was increased compared to other studies which utilized either a matrix with platelet-rich plasma [4] or CDMP-2 [5] to augment Achilles tendon repair in an ovine model. Gap formation was observed between the transected tendon ends, which can be attributed to the single suture used in the repair. The minimal suture design allowed for the biomechanical testing of the repair tissue rather than measuring the strength of additional suture used in more traditional repair techniques. Although there were slight differences in inflammation and vascularity observed histologically, the small number of samples (n=2 (collagen only), n=2 (150 µg rhPDGF-BB), and n=1 (500 µg rhPDGF-BB)) did not allow for definitive conclusions. The robust healing response at 8 weeks and collagen alignment, in addition to the biomechanical data, suggest that when combined with a flowable collagen matrix, rhPDGF-BB may have promise as a therapeutic treatment for Achilles tendon repair.