Kartogenin: A Novel Cell Free Treatment Modality for Tendon-Bone Junction Injuries

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Category: Basic Sciences/Biologics

Keywords: Kartogenin,Tendon-bone junction, Achilles Tendon, Fibrocartilage Zone, Chondrogenesis, Platelet-Rich Plasma (PRP)

Introduction/Purpose: Tendon-bone junction (TBJ) injuries are very common and optimal treatment modalities are lacking. TBJ injuries often heal without formation of the fibrocartilage transition zone increasing the risk of rerupture. Current treatments only attach tendons to bones but do not promote healing or regeneration of the fibrocartilage zone. Therefore, we developed a novel approach to heal wounded TBJ using a small molecule called kartogenin (KGN). KGN was previously shown to induce chondrogenesis of tendon stem/progenitor cells (TSCs) in vitro and enhance wound healing in injured rat TBJs in vivo after short-term treatment (2 weeks). It is not known whether these effects can be maintained longterm. Therefore, we studied the long term (3 months) effects of KGN on achilles-tendon-bone junction healing.

Methods: KGN stock was prepared in DMSO and diluted to 100 μM with PRP solution. PRP was obtained from the blood of Sprague–Dawley rats and the platelet concentration in PRP was adjusted to 3 times higher than that in whole blood. Thrombin (10 kU/ml) served as the PRP activator. 42 female rats (2.5 – 3 months old) were used. 1 mm diameter defects were created at the Achilles tendon-bone junction area in each hind leg of all rats. Rats were divided into 3 treatment groups: Group 1 (KGN+PRP): KGN (100 μM) +25 μl PRP + 5 μl thrombin; Group 2 (PRP): 25 μl PRP + 5 μl thrombin; and Group 3 (Control): 30 μl saline. All the rats were sacrificed at 3 months, and hind legs harvested for analyses. N= 6 hind legs were used for histological and qPCR analysis. N = 16 hind legs were used for mechanical testing.

Results: Single treatment of KGN+PRP demonstrates improved TBJ healing (Fig. 1A) compared to PRP only and control groups (Fig. 1B, C). Fibrocartilage-like tissue regeneration occurred only in the KGN+PRP treated group (Fig. 2A). These results were further confirmed by qPCR, which showed significantly higher expression of cartilage-related genes (Data not shown). Furthermore, the cartilage-like transition zone in the KGN+PRP group also stained positive for Col-I, Col-II, Scx and Sox-9 indicating the regeneration of fibrocartilage tissues in the KGN+PRP treated TBJ (Fig. 3A, B). Mechanical testing showed that the KGN+PRP (47±12 N) and PRP (50±13 N) groups had significantly higher ultimate strength than the controls (39±16 N). There was no significant difference in ultimate strength between the KGN+PRP group and PRP group.

Conclusion: In this study, we have shown that KGN injection enhanced healing of the wounded TBJ by promoting the formation of a fibrocartilage transition zone. Thus, KGN can be used as a mode of cell free therapy to promote regeneration of the fibrocartilage transition zone in injured TBJs. PRP alone enhanced healing of the TBJ but did not induce fibrocartilage regeneration. PRP + KGN are advantageous due to the numerous growth factors located within PRP and PRPs ability to serve as a KGN carrier. Future research is needed to optimize KGN and PRP dosage regimens and the optimal delivery methods.

Foot & Ankle Orthopaedics, 1(1)
DOI: 10.1177/ 2473011416S00214