Inhibition of 5-LOX, COX-1 and COX-2 Increases Tendon Healing and Reduces Muscle Inflammation after Rotator Cuff Repair

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Introduction: The repair of rotator cuff tears is often complicated by muscle atrophy, tendon retraction, and fatty degeneration of the diseased muscle (1). The inflammatory and fibroproliferative response has been implicated in the development of fatty degeneration after rotator cuff injuries (2). Licofelone is a novel anti-inflammatory drug that inhibits both 5-lipoxygenase (LOX) as well as cyclooxygenase (COX) enzymes and has a better cardiovascular profile and gastrointestinal tolerability than other non-steroidal anti-inflammatory medications (3). We hypothesized that licofelone can reduce muscle fatty degeneration and enhance the formation of a stable enthesis following rotator cuff repair.

Methods: Based on anatomical similarities with humans and previous studies, a rat model was selected to study rotator cuff healing. Eighteen 6-month old male Sprague-Dawley rats were used for this study. Operations were performed using sterile techniques. Supraspinatus tears were incited and tendons were secured and marked within a silicone sleeve to prevent the tendon from spontaneously reattaching. Thirty days after inducing the supraspinatus tear, a second procedure was done to repair the supraspinatus to its native footprint. Ad libitum weightbearing and cage activity was allowed postoperatively. Rats were treated with licofelone (40mg/kg dissolved in 1mL of 1% methylcellulose delivered by oral lavage BID) or vehicle (1mL of 1% methylcellulose) for 14 days. This dose was selected based on a previous study that demonstrated drug efficacy of licofelone. Two weeks after repair rats were anesthetized; the supraspinatus muscles, tendons and humeral heads were removed for analysis. Gross histology, gene expression, fiber contractility and tendon mechanical properties testing were then conducted as described in previous studies (4).

Results: Analysis of the shoulder/tendon interface has shown that the scar and callus formed in the licofelone treated rats was less than in controls (Figure 1a). Load to failure of the repaired supraspinatus tendons show a significant (p=0.0017) difference between the control and licofelone treated group with the licofelone group failing at higher loads (Figure 1b). Gene expression analysis reveals over a two-fold decrease in matrix metalloproteinase expression as well as an overall decrease in inflammatory markers, and a decrease in total macrophage markers. Quantitative PCR analysis also shows over a four-fold decrease in perilipin and FSP27 which indicates a decrease in lipid droplet size as well as an almost two-fold decrease in lipogenic markers PPARγ and C/EBPα (Figure 2).
Discussion: Licofelone appears to have an effect on the size of scar and callus formation in the rat rotator cuff repair model with less scar tissue present in the licofelone treated group. The decrease in expression of pro-lipogenic markers as well as an overall decrease in inflammatory markers is promising as these results may demonstrate the overall reduction of fatty degeneration that normally occurs after rotator cuff tears. Tendon mechanical testing has shown the load that the repaired tendons can withstand is significantly higher in licofelone treated rats. It appears that the post-operative treatment of rotator cuff repairs with licofelone may reduce the markers of fatty degeneration and enhance the development of a stable bone-tendon interface.

Significance: This study demonstrates that the inhibition of 5-LOX, COX-1 and COX-2 modulates the healing process of repaired rotator cuff tendons. These results suggest that the treatment of patients with Licofelone following rotator cuff repair surgery could improve the development of a stable enthesis and enhance postoperative outcomes.

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