Does Intra-Articular Decorin Reduce Contractures in a New Rabbit Model of Joint Fibrosis?

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Background: Joint fibrosis resulting from inflammatory or degenerative conditions, trauma, or surgery is common and difficult to overcome. The intimate biological mechanisms underlying joint fibrosis remain poorly understood. While the pathophysiology of joint stiffness is not fully appreciated, there are some molecules that show exciting promise for the treatment of orthopedically related fibrosis. Of exceptional note is the small leucine-rich endogenous proteoglycan decorin. Decorin co-localizes with TGF-β and inactivates its actions. 1,2 Decorin has displayed antifibrotic effects in lung,3,4 cardiac,3 and hypertrophic scar tissue.6 We have recently developed and validated an animal model of joint contracture.7 Using this model, we tested the hypothesis that decorin is an anti-fibrotic agent in joint contractures.

Methods: Eighteen skeletally mature New Zealand White (NZW) female rabbits weighing between 2.7 and 3.4 kg were used for the study. All rabbits had their right knees operated on to create 3-mm defects in the non-cartilaginous portions of the femoral condyles, hyperextend the joint to disrupt the posterior capsule, and immobilize the joint in maximum flexion with a Kirschner-wire for 8 weeks.7 The rabbits had their immobilization removed and were allowed free activity in a cage for 16 weeks before being sacrificed. After sacrifice at 24 weeks, the rabbit limbs were harvested. The amount injected (1 mL) was confirmed on fluoroscopy. The amount injected (1 mL) was standardized and based upon the results of pilot studies.

The 6 right limbs in the experimental group (Group 0) received four 500 μg/ml intra-articular injections of decorin over 8 days, for a total of 2 mg. The 6 right limbs in the first control group (Group 1) received four intra-articular injections of bovine serum albumin (BSA) over 8 days. The 6 right limbs in the second control group (Group 2) received no injections. All injections started at the 8-week time point and were given every other day. Injection of the solution into the knee joint was confirmed on fluoroscopy. The amount injected (1 mL) was standardized and based upon the results of pilot studies.

The sample size was calculated assuming a 5% type 1 error and 80% power to detect an effect size of 30 degrees with a standard deviation of 20 degrees. The knee joint flexion angles in each of the groups were measured and compared to the non-operative limb. Direct comparison between groups was also accomplished. Comparison was performed using a two-sample t-test assuming unequal variances. Significance level was set at p < 0.05. Data are presented as an average value ± standard deviation.

Results: There was no statistical difference in the flexion contracture angles between those right limbs that received intra-articular decorin versus those that received intra-articular BSA (65.8 ± 19.3° vs. 69.1 ± 31.1°; p = 0.41). Likewise, there was no statistical difference between those right limbs that received intra-articular decorin as opposed to those who had no injection (65.8 ± 19.3° vs. 71.5 ± 9.3°; p = 0.27) (Table I). The lack of significance remained when the control left limbs were taken into account (p > 0.40).

Discussion: Joint contractures are detrimental to the functional capability of patients and often require delicate surgical intervention. To date, however, there are no known effective pharmacologic treatments and/or preventative measures for arthrofibrosis. A contributing factor may be that while advances in operative treatment of joint stiffness continue, the pathophysiology remains poorly understood. Furthermore, the previously published models of rabbit joint contractures do not produce a severe or permanent contracture, making it difficult to detect any effects from pharmacological treatments.5 A new rabbit model of joint contractures must be utilized to fully understand, prevent, and treat the pathophysiology of human joint contractures.7 Decorin appears to be a promising anti-fibrotic agent in musculoskeletal ailments given its endogenous nature, lack of systemic side effects, ability to selectively bind and inactivate TGF-β, and anti-fibrotic effects in other organ systems. However, in this model, when administered intra-articularly at 8 weeks, 2 mg of decorin had no statistically or clinically significant effect on joint contractures. Further studies investigating the route of administration, timing, dosing, and frequency are required before definitive conclusions may be drawn on the effects of decorin on joint contractures.

References:

Figure 1. Validated device utilized for mechanical testing.

Table I. Summary of Flexion Contracture Angles in Degrees

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Operative (Right) Limb Flexion Contracture Angle (Mean ± SD)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>No Injection</td>
<td>71.5 ± 9.3°</td>
<td>p = 0.27</td>
</tr>
<tr>
<td>Decorin Injection</td>
<td>65.8 ± 19.3°</td>
<td>p = 0.41</td>
</tr>
<tr>
<td>BSA Injection</td>
<td>69.1 ± 31.1°</td>
<td></td>
</tr>
<tr>
<td>Decorin Injection</td>
<td>65.8 ± 19.3°</td>
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