Flexor Tendon Healing Strength In Vivo Following Application of Anti-Adhesion Compound 5-Fluorouracil

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Introduction: Various pharmacologic agents have been used in the past in an attempt to modify adhesion formation following tendon injury and repair, although results have been mixed. The ideal pharmacological agent should have no systemic side effects, should not interfere with tendon healing, should be limited to a single application, and should be directed at peritendinous growth factor expression and ECM production. 5-fluorouracil (5-FU) may be such a drug. 5-fluorouracil is an antimetabolite used both as a cancer chemotherapeutic agent and in glaucoma filtration surgery. A single exposure to 5-FU for as short duration as 5 minutes has been shown to have antiproliferative effects on fibroblasts for several days, which may be adequate to inhibit tendon adhesions prior to beginning post-operative motion protocols. A five-minute exposure to 5-FU has been shown to significantly decrease post-operative flexor tendon adhesions in chicken and rabbit models [1,2]. As a part of our study on the effect of 5-FU on surface lubrication, we evaluated the effect of topical 5-FU on tendon healing in a canine model of flexor tendon injury and repair.

Materials and Methods: This study was approved by our Institutional Animal Care and Use Committee. Mixed breed dogs (20-25kg) were used in this study. One forelimb in each dog was randomly selected for surgery. In the second and fifth digits, the flexor digitorum profundus (FDP) tendons were sharply transected 5 mm proximal to the distal edge of the proximal pulley, with the digit extended. The tendons were then repaired with a modified Pennington repair [3]. Following tendon repair, a single 5-minute exposure of 5-FU at a concentration of 50 mg/mL or saline was applied to one flexor tendon at the repair site. Then the incisions were closed in layers. A radial neurectomy proximal to the triceps innervation was performed to prevent postoperative weightbearing on the operative limb. Commencing on postoperative day five, and daily thereafter, the dogs began a modified synergistic therapy program for tendon mobilization [4]. The dogs were sacrificed at ten, twenty-one, or forty-two days after surgery. The sample sizes for each group are noted in Table 1.

<table>
<thead>
<tr>
<th>Time</th>
<th>5-FU</th>
<th>Control</th>
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<tr>
<td>10 days</td>
<td>&gt;10</td>
<td>&gt;8</td>
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<tr>
<td>21 days</td>
<td>&gt;9</td>
<td>&gt;7</td>
</tr>
<tr>
<td>42 days</td>
<td>&gt;10</td>
<td>&gt;10</td>
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Table 1: Sample Size

Following sacrifice the tendons were dissected from the digit and subjected to mechanical strength testing. The tendon was clamped in a servohydraulic testing machine and distracted at a rate of 20mm/min until complete failure. A differential variable reluctance transducer (DVRT) was attached to tendon and spanned the laceration site to measure the gap formation during testing. Maximum force and resistance to gap formation (linear slope of the force versus gap formation curve) were compared for the two treatment groups and the two time points. Data were analyzed using 2-factor Anova with a Tukey-Kramer post-hoc test.

Results: After dissecting the tendons it was observed that 5 tendons had a gap of 2mm or greater and thus were excluded from testing. The results of the maximum force and resistance to gap formation are shown in Figures 1 and 2. For the overall group effects, the maximum force was higher in the 42 day versus 10 and 21 day tendons (p<0.01). However, there was no significant difference in treatment (p=0.17) and no significant interaction between the two variables (p=0.91). Similarly, the overall group results of resistance to gap formation showed that 42 day tendons had a significantly higher resistance to gap formation than 10 and 21 day tendons (p=0.01); however there was no significant difference noted between 5-FU and control tendons (p=0.99).

Discussion: The topical application of 5-FU in the canine model of complete tendon laceration does not have a deleterious effect on the mechanical strength of the healing tendon. Further studies in the laboratory will determine whether the use of 5-FU can reduce the incidence or severity of adhesion formation and whether it affects that surface lubrication.

References:

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