AN ACL DENERVATION MODEL FOR DETERMINATION OF THE EFFECTS OF SENSORY AFFERENTS ON JOINT FUNCTION

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INTRODUCTION

Anterior cruciate ligament (ACL) injuries are extremely common. Patients sustaining ACL injury also incur damage to other joint tissues with resultant dysfunction. Surgical ACL reconstruction (ACLR) is performed to regain knee stability and allow return to function in a timely manner. Autografts and allografts used for ACLR must undergo cellular repopulation, revascularization, and re-innervation for joint function to return to normal. The most common complications after ACL injury and ACLR include continued dysfunction, re-tear, and secondary osteoarthritis (OA). These complications may be inter-related and may stem from the inability to fully restore ACL, and whole-joint, integrity and function. Importantly, 50-100% of ACLR patients experience early onset OA with radiographic evidence seen as early as 5 years after ACL injury. These sequelae indicate that current management strategies for ACL injuries are suboptimal and have profound clinical implications regarding long-term prognosis and related healthcare costs.

Several mechanisms for development of OA secondary to ACL injury have been reported, including altered tibiofemoral biomechanics after injury, chondrocyte death due to initial trauma, and neuromuscular control deficits. Recent evidence indicates that an absence of sensory information may play a critical role in the development of OA. To investigate this potential mechanism, we developed a novel large animal model to assess the relative contributions of sensory afferents in the ACL and the joint to knee function and early development of OA. We hypothesized that ACL sensory denervation would manifest in knee joint dysfunction and development of early OA.

METHODS

With IACUC approval, purpose-bred, adult research dogs (n=9 dogs, 18 knees) underwent aseptic arthroscopic surgery to create 6 treatment cohorts (Table 1). An immunotoxin was used to induce sensory denervation. OX7-saporin has been reported to successfully denervate 80% of the sensory nerve fibers projecting to the knee. Once injected, this immunotoxin was taken up by a nerve through endocytosis and transported back to the cell body where it deactivated the ribosomes, killing the nerve. For this study, OX7-saporin (50ug) was injected into the ACL for the ACL insufficient (denervated) group and into the knee joint for the Joint insufficient (whole-joint denervation) group. Partial transection of the ACL was performed to provide a positive control of known mechanical dysfunction (ACL deficient group) and sham procedures were performed in the contralateral knees (Table 1).

Table 1: Project Cohort Description

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Control</th>
<th>Representative</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACL denervation</td>
<td>ACL saline (n=3)</td>
<td>ACL Insufficient</td>
</tr>
<tr>
<td>(n=3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACL transection</td>
<td>ACL sham transection (n=3)</td>
<td>ACL Deficient</td>
</tr>
<tr>
<td>(n=3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint denervation</td>
<td>Joint Saline (n=3)</td>
<td>Joint Insufficient</td>
</tr>
<tr>
<td>(n=3)</td>
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After intervention, dogs were enrolled in a regimented exercise program in which they were leash-walked for 20 minutes/day 5 days/week. Gait analysis was performed at weeks 1, 4, 8, and 12 using a pressure-sensitive walkway. Clinically relevant functional assessments of the knees were performed by a board-certified veterinary surgeon,
blinded to treatment, at weeks 4, 8, and 12. At week 12, the animals were humanely euthanatized for arthroscopic, gross, and histologic assessments. Two different raters assessed the histological results in blinded fashion.

RESULTS AND DISCUSSION
The ACL insufficient group demonstrated joint dysfunction as evidenced by reduced limb loading and comfortable range of motion compared to the contralateral control limb. Interestingly, knee dysfunction and ACL pathology scores associated with ACL denervation were relatively more severe than that associated with whole-joint denervation, but less severe than ACL deficiency. These results indicate that sensory dysfunction of the ACL has effects on knee joint health and function, which has profound implications for management of ACL injuries.

Early onset OA secondary to ACL injury is likely a multi-factorial process. Aberrant biomechanics, arthrogenic muscle inhibition, and trauma to the subchondral bone have been strongly associated with the degradation of articular cartilage seen in OA. The present findings indicate that it is necessary to elucidate the effects of ACL afferents on osteoarthritic changes in the knee after ACL injury as the neurologic function of the ligament appears to play important roles in this disease process. This novel model may provide a platform to: (1) investigate the neural mechanisms of osteoarthritis and (2) understand the consequences of selective sensory ablation on joint function. The current study has limitations. In addition to the small number of dogs included in each cohort, the relatively short duration of the study limits the conclusions that can be made from these observations. The effects of the toxin OX7-saporin on sensory afferents in the dog have not been validated, but are part of our ongoing analyses.

CONCLUSION
To the investigators’ knowledge, this is the first study to investigate the effects of local sensory denervation of the ACL on knee joint function and health. Further development and use of this novel model holds importance as the ACL is a major sensory structure for knee joint function. After ACL injury, there is disruption in the sensory-motor connection to the knee, which ACL reconstruction does not immediately re-establish. The results of our study indicate denervation of the ACL may lead to joint dysfunction and subsequent osteoarthritic changes. These findings have implications for management of patients with ACL injuries, including rehabilitation programs that focus on re-establishment of sensory-motor function, which may ameliorate rapid development of OA knee.

REFERENCES

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