Interleukin 1-Receptor Antagonist Inhibits Arthrofibrosis in a Post-Traumatic Knee Immobilization Model

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ABSTRACT INTRODUCTION: Post-traumatic extra-articular contracture and intra-articular adhesions are major causes of joint stiffness, which can be markedly detrimental to a patient's quality of life. A prophylactic treatment regimen to help prevent the development of arthrofibrosis would be highly desirable. Inflammation contributes to the development of arthrofibrosis as demonstrated by past animal studies that have shown intra-articular corticosteroid injection and oral delivery of the cysteinyl leukotriene receptor inhibitor, monetlukast, can reduce joint stiffness in a post-traumatic knee immobilization model (1). IL-1 receptor antagonists (IL1-RA) act as anti-inflammatory agents and intra-articular injection of these agents has been shown to prevent post-traumatic osteoarthritic changes in animal studies (2). Furthermore, pilot clinical studies have suggested intra-articular IL1-RA injection can help restore motion in knees with established arthrofibrosis (3). Based on these findings, we hypothesized that intra-articular IL1RA injection may inhibit the development of joint contracture after post-traumatic knee injury. Our objective was to evaluate the ability of an intra-articular IL1-RA injection, to prevent joint contracture after post-traumatic knee immobilization in a rat model.

METHODS: After approval by the institutional animal care and use committee, 20 male retired-breeder Sprague Dawley rats were randomly divided into two groups: control (CTL) and anakinra (IL1-RA). All animals underwent intra-articular surgical trauma of the right knee with the placement of an immobilization suture, securing the knees in 150° of flexion. The operation began with an incision of the medial aspect of the right hind limb. Once exposed, the medial and lateral condyles were scraped 6 times with a no. 15 blade scalpel. The joint capsule was closed with a running stitch of 3-0 chromic (proinflammatory) suture. Incisions were made at the medial and lateral aspects of the mid tibia, where the immobilization suture, #2 Ethibond suture (Ethicon, Inc., Somerville, NJ), was passed around the mid femur and midtibia and subsequently tied at the mid-femur. The skin was then closed with wound clips and skin adhesive. Postoperative analgesia was administered by buprenorphine SR injection (0.5mg/kg, 3 days Postop). An operation was not performed on the left knee. On post-operative days 1 and 8, the CTL group received 0.1 ml intra-articular saline and the IL1-RA group received a 0.1 ml injection of Anakinra (14.5 mg/ml). The rats were euthanized fourteen days after surgery. The hindlimbs were disarticulated at the hip. The immobilization femorotibial angles were measured on lateral radiographs on the operative limbs with the immobilization suture and musculature intact. Subsequently, the musculature was removed and femorotibial angles were measured in digital images of the operative and non-operative limbs with a 0.015 N•m extension moment applied. Angles were measured with the capsule/ligamentous tissues intact and with the posterior capsule cut. A contracture angle was calculated as the difference in angle between operative and non-operative limb. Treatment differences in outcome measure were evaluated by unpaired Student's t-test ($P<0.05$).

RESULTS SECTION: Over the course of the study, one animal died due to post-surgical complications and three additional animals were euthanized early due to continued wound dehiscence. The initial/final body weights did not differ between the groups the immobilization knee flexion angle with suture installed did not differ ($P=0.761$) between the groups (CTL: 152±9; IL1-RA: 150±11). The joint contracture angles (larger angle= more contracture) were reduced ($P<0.05$) by 12 degrees with the IL1-RA treatment for both the capsule intact ($P=0.024$) and capsule cut ($P=0.019$) dissection states (Fig.1).

DISCUSSION: Our findings support the hypothesis that intra-articular IL1-RA injection may help prevent joint stiffness after post-traumatic knee immobilization in the rat. While the treatment effect of IL1-RA on joint contracture was modest and it was not able to fully prevent the contracture, the therapy was applied with the knee surgically immobilized in marked knee flexion which may have limited the treatment effect. As the IL1-RA treatment was only given by weekly injection and past work has shown it be fairly rapidly cleared from the joint, it is unclear if an extended release formulation of IL1-RA may have greater preventative effects on joint contracture. While our study does not provide data on the specific mechanism of IL1-RA's effect on the contracture process, the treatment differences found for both dissection states is suggestive that it may be altering more than one process (capsular contracture, articular adhesion, etc..) that contributes to arthrofibrosis.

SIGNIFICANCE: The findings of our study are of clinical significance as they suggest that intra-articular injection of IL1-RA might be explored as a new potential therapy for prevention of arthrofibrosis after joint trauma.

REFERENCES: 1) Efird et al. 2014. 2) Furman et al. 2014. 3) Brown et al. 2010.
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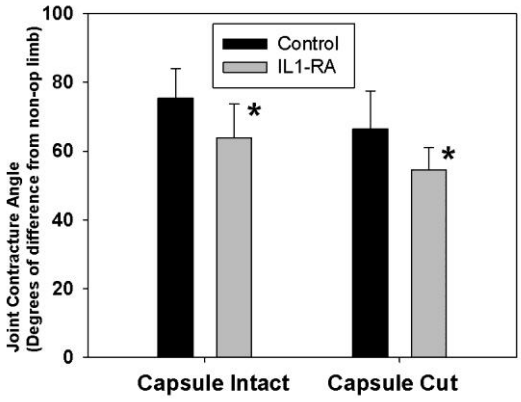

Fig. 1 Joint contracure angle (mean/sd) as a function of treatment and dissection state.
* Signficantly different from Control ($P<0.05$)