Supplemental Intra-Articular Lubricin with and without Hyaluronic Acid Delays the Progression of Post-Traumatic Arthritis in the Anterior Cruciate Ligament Deficient Rat Knee

INTRODUCTION:
Lubricin and hyaluronic acid (HA) are thought to contribute to the lubrication of the articular surface in normal synovial joints, where hyaluronate plays a supporting role. The objective of this study was to determine whether supplementing the synovial fluid of an ACL-deficient joint with lubricin and/or HA would reduce cartilage damage six weeks following injury in the rat model. The hypotheses were: 1) that intra-articular supplementation of lubricin would reduce cartilage damage following ACL transaction when compared to those treated with a sham saline injection; 2) that intra-articular supplementation of HA would reduce cartilage damage when compared to the sham treated animals; and 3) that intra-articular supplementation of lubricin plus HA would act synergistically to further reduce cartilage damage when compared to sham treated animals or those treated with HA or LUB in isolation.

METHODS:
Following IACUC approval, 36 male Lewis rats, 3 months of age, underwent unilateral ACL transaction. They were randomized to four treatment groups: 50µl injections of either 1) saline (PBS), 2) hyaluronic acid (HA) (3.33 mg/mL Healon, Advanced Medical Optics, Upsala, Sweden), purified human lubricin (LUB) (200 mcg/mL), and 4) LUB and HA (LUB+HA) (200 mcg/mL LUB+3.33 mg/mL HA). Intra-articular injections were given twice weekly for four weeks starting one week after ACL transaction. Knees were harvested one week after the final injection. Anteroposterior (AP) and lateral radiographs of each limb, serum samples, and synovial fluid lavages were obtained at the time of harvest. Cartilage from resected joints was stained with Safranin O/Fast green to assess cartilage degeneration using the OARSI score. Four investigators blinded to treatment identity performed scoring. Radiographs were scored in a blinded fashion for the severity of degeneration using a modification of the Kellgren-Lawrence scale. Four investigators blinded to treatment identity performed scoring. Radiographs were scored in a blinded fashion for the severity of degeneration using a modification of the Kellgren-Lawrence scale. Four investigators blinded to treatment identity performed scoring. The modified Kellgren-Lawrence score was greatest in the PBS- (2.1±0.7) and HA- (1.8±0.8) treated groups. LUB (1.3±1.0) and LUB+HA (1.3±0.8) treatment resulted in a lower average scores (Figure 2). LUB treatment significantly lowered the Kellgren-Lawrence score relative to the PBS and/or HA conditions (p=0.048). There was no evidence that the LUB effect was HA dependent (p=0.62).

RESULTS:
The mean OARSI score (mean±standard deviation) was greatest in the HA- (8.2±2.9) and saline-treated animals (7.5±2.1). The score was lower in the LUB-treated subjects (6.4±2.7) and lowest in the subjects treated with LUB+HA (5.1±3.2). All groups showed some evidence of cartilage damage that included surface fibrillation, hyper- and hypocellularity, and loss of proteoglycan staining. The main effects of lubricin, hyaluronic acid, and their interaction showed LUB treatment had a significant effect in lowering the OARSI histology score (p=0.035). There was no effect of HA (p=0.77) and no evidence that the LUB effect was HA dependent (p=0.32).

DISCUSSION:
The results of our study confirm the hypothesis that intra-articular lubricin reduces the radiographic and histologic progression of post-traumatic OA. Intra-articular HA did not delay radiographic or histologic progression of OA compared to saline. The results of this study also suggest that treatment with lubricin and HA is not synergistic in preventing OA progression. Prior studies suggest that both supplemental intra-articular HA and lubricin may modulate the inflammatory response to injury, but statistically significant differences in inflammatory mediators and cartilage breakdown products were not seen in this study. Future investigations will explore the metabolic effects of intra-articular HA and lubricin supplementation. Our results are consistent with results previously published by Flannery et al, who also found that supplemental intra-articular lubricin delayed the progression of post-traumatic OA in a rat meniscectomy model. One limitation of our study is that we do not include intermediate time points during treatment, which would allow for the analysis of changes in inflammatory marker expression. We also did not include cartilage matrix composition analysis or mechanical testing. Future investigations will focus on the biochemical and mechanical effects of lubricin supplementation after ACL injury. Intra-articular lubricin supplementation appears to be a promising therapy for the prevention of post-traumatic joint degeneration.

REFERENCES:

Supported by: National Institutes of Health (RO1-AR049199; R01-AR050180; R21-AR055937 and P20-RR024484) and the RIH Orthopaedic Foundation.