MODULATION OF CARTILAGE INJURY WITH GROWTH HORMONE AND/ OR POLYSULFATED GLYCOSAMINOGLYCANS IN A CANINE MODEL OF OSTEOARTHRITIS

**Millis, D.L.**, **Korvick, D.L.**, **Dean, D.D.**, **Wang W.D.**, **J.P. Weigel.**, **E.C. Buusman, **Anthassian K.A. **College of Veterinary Medicine, University of Tennessee, Knoxville, TN 37901. **TEI (423) 974-8319, **FAX (423) 974-5554, **dmillis@vth.edu

Introduction

Transection of the canine anterior cruciate ligament (ACL) is an animal model used to study osteoarthritis (OA) and evaluate treatment methods. Following ACL transection, the release of cytokines and proteases from synovial cells and chondrocytes results in the loss of collagen and proteoglycans from the cartilage matrix with cartilage softening (Setton 1995, 1997). Previous work by others has shown that a two pronged approach to reduce production of degradative enzymes with PSGAG and increase matrix production with intra-articular IGF-1 was effective in preventing matrix loss in early OA (Rogachefsky 1993). A limitation of the previous study was that intermittent administration of IGF-1 may be less effective in stimulation of matrix production than continuous administration. Systemic administration of recombinant growth hormone (GH) in dogs has previously been shown to promote IGF-1 synthesis in the liver and increase circulating levels of IGF-1 (Wilkins ’96). The purpose of this study was to determine if early intervention with PSGAG and systemic growth hormone could alter the development of OA as determined from histological, biochemical and mechanical examination of the tissues in the canine model.

Methods:

Adult dogs (25 kg) were randomly assigned to five groups: Intact control (CONT, n=6), ACL transected (TRANS,n=6), ACL transected with PSGAG (PG,n=6), ACL transected with GH (GH,n=6), and ACL transected with PSGAG and GH (PG+GH,n=6). The PG and PG+GH dogs received 2mg/kg PSGAG (Adequen) IM three times a week beginning at the time of surgery. The GH and PG+GH dogs were implanted with osmotic pumps at the time of ACL transection. The pumps were designed to release 4mg/day of GH and PSGAG (PG,n=6), ACL transected with GH (GH,n=6), and ACL transected with PSGAG and GH (PG+GH,n=6). The PG and PG+GH dogs received 2mg/kg PSGAG (Adequen) IM three times a week beginning at the time of surgery. The GH and PG+GH dogs were implanted with osmotic pumps at the time of ACL transection. The pumps were designed to release 4mg/day of GH. Transaction of the ACL was performed via a medial arthotomy. The dogs were permitted unrestricted activity following surgery. Two days following surgery, dogs were exercised on a treadmill for 20 minutes twice weekly, and on alternate days the dogs were allowed free exercise in a large room for 1 hour/day. Sternal and serum samples were obtained at 0, 4, 8 and 8 weeks post-op for determination of IGF-1 levels. Lameness scoring was performed weekly and included gait evaluation, range of motion and force plate studies. At the end of 8 weeks, the dogs were euthanized.

Cartilage: Histology and biochemistry tests were performed on the medial femoral condyle. Osteochondral samples were cut from weight-bearing area of the medial condyle for histology. The tissues were decalcified in 10% formic acid and stained with Haematoxylin/Eosin or Safranin-O/Light Green. The tissues were decalcified in 10% formic acid and stained with Haematoxylin/Eosin or Safranin-O/Light Green. The total Mankin score was used for statistical evaluation of treatments. The average Ha for the cranial site (0.388±0.106MPa) was significantly less than that for the TRANS group. Active collagenase was elevated in all treatment groups over the control (CONT 0±0). The highest collagenase levels were in the TRANS (0.136±0.039EU/gm) and GH (0.107±0.065EU/gm). Dogs. Addition of PG reduced collagenase levels in the PG (0.044±0.029) and GH (0.019±0.019).

There were no consistent trends in the uronic acid or hydroxyproline data. For the tibial cartilage, GH showed significant differences due to location (p=0.006). The average Ha for the cranial site (0.388±0.106MPa) was significantly less than the cranial site (0.463±0.092MPa). Within a treatment group, CONT and PG+GH showed no differences in Ha between cranial and caudal sites. The PG (P=0.011) and GH (P=0.035) were significantly different and TRANS (P=0.051) almost reached statistical significance. Ha's for cranial and caudal sites were evaluated separately using a one factor ANOVA. For the cranial site, there were significant differences in Ha due to treatment. CONT was significantly greater than PG (P=0.001) or TRANS (P=0.008). There were no difference between CONT and PG+GH (P=0.122) or between CONT and GH (P=0.051). GH was significantly greater than PSAG (P=0.0329).

Discussion: Following ACL transection there is a significant reduction in the stiffness of the cartilage and the hardness of the subchondral bone as early as 8 weeks following the injury. The results clearly show that the cranial and caudal sites respond differently to the ligament transection. The cranial site undergoes significant reduction in Ha as a result of ACL transection. Treatment of the dogs in this study with PG effected a reduction in active collagenase production and preservation of subchondral bone stiffness but did not ameliorate a softening of the cartilage as determined by creep indentation tests. Treatment with GH either alone or with PG was able to reduce but not prevent the cartilage soften. This was not mediated through a reduction in active collagenase production.

References:


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