A ROLE FOR ANTI-FIBROTICS IN THE PREVENTION OF EPIDURAL FIBROSIS

*Waters, S.N.; *Massie, J.B.; *Amiel, D.; **Akeson, W.H.
*Department of Orthopaedic Surgery University of California, San Diego, San Diego, CA. **VA San Diego Health Care System, La Jolla, CA. La Jolla, CA, (858)552-8585 x3841, Fax: (858)552-4350, wakeson@ucsd.edu

Introduction: Epidural fibrosis is thought to be a major cause of poor results in patients post laminectomy. Scar formation in the spinal canal causes chronic pain through inflammation and fibrosis of neural tissue. In addition to persistent pain, it increases the risk and technical difficulty of subsequent procedures. The so-called post operative “Laminectomy membrane” is adherent to the dura, binding it to the overlying paraspinal muscles. Scar may tether nerve roots preventing normal gliding within the spinal canal, thus contributing to pain postoperatively. Numerous investigators have attempted to decrease scar formation and improve postoperative outcomes. In this study, decreasing scar formation post laminectomy remains elusive. The purpose of this study was to establish a small animal laminectomy model with a disc injury, which reliably produces scar and can be used for subsequent studies for other therapeutic scar neutralizing agents. The efficacy of therapeutic applications of the concepts of fetal healing is now underway (1,2). A high level of hyaluronan is one component of fetal healing (1). The anti-fibrotic properties of hyaluronan have been well documented by other investigators (3,4). Here we present the application of high molecular weight hyaluronan, HA (3.6 x 10^6 daltons), and Adcon-L, an anti-adhesion barrier gel to the epidural space post laminectomy, on the animal model developed.

Materials and Methods:

Animals

46 male Sprague-Dawley rats weighing between 400-500 grams were used and divided into four experimental groups. This research was approved by the Veterans Administration institutional animal care and use committee.

Surgical Procedure

The lamina from L4 to L7 was carefully exposed under general anesthesia using sterile conditions. A bilateral laminectomy was performed on L5 and L6, which included the removal of the spinous processes, laminae, and ligamentum flavum. This was performed using surgical loops. The underlying dura matter and nerve roots were carefully exposed. Once the laminectomy was completed, inserting a 26-gauge needle into the L5-L6 the disc space and gently manipulating the nerve roots created bilateral disc injuries of the L5-L6 disc. This was performed using an operative microscope (Carl Zeise, Inc.). Hemostasis was obtained and the wound was irrigated with saline. A small amount of bone wax was applied to the exposed edges of the laminectomy. Prior to closure two of the groups received 0.1 cc of an anti-fibrotic agent, applied locally. The wounds were closed in layers. All animals were sacrificed at three weeks post operatively.

Groups and Treatments

The rats were divided into four groups. One group of rats served as normal controls, without surgery. The second group underwent laminectomy as previously described, but was untreated. The other two groups consisted of a laminectomy followed by treatment with HA and Adcon-L.

Biochemical Analysis

The L5 nerve roots were dissected free bilaterally using an anterior approach. The nerve roots were excised including the portion of the nerve root within the foramen (1.0 cm total length). The dura was exposed using an anterior approach. The dura from the caudal aspect of the body of L4 to the cephalad aspect of the body of L7 was removed (1.5 cm total length) including all attached scar. The samples were analyzed biochemically by extracting the fat, then vacuum drying and determining the amount of total collagen and the percent of collagen from the hydroxyproline content. The amount of total collagen was expressed in milligrams and the percent collagen was expressed as percent of fat free dry weight. Total collagen was the index of scar measurement.

Statistical Analysis

Statistical analysis of the experimental groups consisted of a one-way ANOVA and Fisher’s multiple comparisons t-test using Statview. All data were expressed as the mean +/- standard error. A p value of <0.05 was considered significant.

Results:

Total Collagen:

In the dura of the untreated rats total collagen increased more than two fold post laminectomy (P= 0.0009). Treatment with HA and Adcon-L significantly reduced scar formation in the dura (P= 0.016 and 0.007 respectively). In the nerve roots the amount of total collagen was not significantly changed by treatment with HA or Adcon-L treated nerve roots.

Percent Collagen:

For both dura and nerve roots the percentage of collagen post laminectomy increased significantly (p = 0.0008 and 0.005 respectively). The collagen percentage in the dura decreased significantly after a single application of HA and Adcon-L (p = 0.02 and 0.06 respectively). Percentage of collagen in nerve roots was not altered significantly by the single application of either Hyaluronan or Adcon-L.

Discussion: This study demonstrates that this is a valid experimental model for the production and subsequent study of epidural fibrosis in a rat laminectomy model. We are also able to moderate scar formation around the dura post laminectomy with the single application of HA or Adcon-L. We have also identified a quantitative measure of scar formation by biochemical measurement of the scar. The advantage of this model is the ability to obtain quantitative data on scar formation by the direct measurement of the total collagen and percent collagen in resected specimens. The application of anti-fibrotics from the growing list of candidate antibodies or peptidomimetic molecules could now be assessed utilizing this model.

References:


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