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The Spine Journal 5 (2005) 494–502

THE SPINE JOURNAL

Topical high molecular weight hyaluronan reduces radicular pain post laminectomy in a rat model

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Received 24 March 2004; accepted 8 December 2004

Abstract

BACKGROUND CONTEXT: A controversy exists about the mechanism of causation of the post-laminectomy pain syndrome. Some believe that epidural scarring, and attendant spinal nerve and nerve root scarring and tethering to the disc or pedicle at the site of surgery contributes to post-laminectomy pain in such patients. However, clinical outcome studies on this question are inconclusive and the assertion remains controversial. Definitive studies to help resolve the question are needed. Previously our laboratory has reported on a preclinical post-laminectomy model that mimics the postoperative proliferative fibrotic response grossly, as well as by biochemical assessment of the collagen content within the spinal canal. The post-laminectomy fibrotic response was attenuated in that study by application of a topical antifibrotic (high molecular weight hyaluronan gel) or by insertion of an absorbable roofing barrier (0.2-mm-thick Macropore sheet material) over the laminectomy defect before wound closure. The question remains of relevance of the attenuation of the fibrotic response to post-laminectomy chronic pain syndromes.

PURPOSE: The purpose of this study is to evaluate the effect of therapeutic attenuation of proliferative scar within the spinal canal post laminectomy on the pain-related behavioral response in a preclinical rat model.

STUDY DESIGN/SETTING: An established L5-L6 rat laminectomy model with a unilateral L5-6 disc injury was employed to assess postoperative proliferative fibrosis of the L5 spinal nerves using quantitative biochemical hydroxyproline assessment of the collagen content in four experimental groups. These observations were correlated with gross descriptions of spinal nerve scarring or tethering. Associated manifestations of a sensory pain-related response in the L5 spinal nerve receptor area of the hind paws was studied using standard tactile allodynia assessment with the von Frey hair technique. The tactile allodynia findings were supplemented by weekly descriptors of behavioral pain manifestations.

METHODS: Bilateral laminectomies at L5 and L6 and a unilateral right disc injury (L5-6) were performed on 35 male adult Sprague-Dawley rats, weighing 400+ grams (approved by the VA Institutional Animal Care Use Committee). The study consisted of four groups: 1) normal nonoperative control; 2) a sham-operated group; 3) an untreated laminectomy–disc injury group; and 4) a laminectomy–disc injury treatment group in which 0.1 cc topical high molecular weight hyaluronan (HMW HA) gel was layered over the dura and into the laminectomy canal before closure. Before animals were entered into the study, they were checked for the presence of abnormal response to the tactile testing procedure of the L5 sensory receptor area. Animals exhibiting anomalous responses were excluded from the study. Behavioral testing for tactile allodynia was performed at weekly intervals post laminectomy beginning at 3 weeks. Pain-related behavior was characterized at weekly intervals. A behavioral test cage with a wire mesh floor allowed for tactile allodynia testing.

FDA device/drug status: not approved for this indication (Healon/Topical High MW Hyaluronan).

Support in whole or in part was received from the VA Merit Review under grant #0003. Nothing of value received from a commercial entity related to this research.

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1529-9430/05/$ – see front matter
doi:10.1016/j.spinee.2004.12.003

Graduated von Frey hairs whose stiffness increased logarithmically from 0.41 to 15 g were used for tactile allodynia tests. The animals were killed 8 weeks postoperatively for analysis. Thedissected spinal nerve and nerve root specimens were studied biochemically for hydroxyproline content to estimate total collagen in and around the L5 neural structures. Statistical analyses were performed using analysis of variance and a Fisher comparison *t* test.

RESULTS: The major observations on the untreated preclinical post-laminectomy rat model previously described by this laboratory were confirmed. All untreated animals developed a tail contracture concave toward the right (disc injury side) consistent with asymmetrical lumbar muscle spasm. Only one animal in the HA gel treatment group had a tail contracture. It was of mild degree and occurred in an animal that demonstrated slightly increased right L5 tactile sensitivity. Gross inspection of the dissected specimens demonstrated spinal nerve scarring and tethering to the disc and pedicle greater on the right than the left in untreated animals, findings that were markedly reduced in the treatment group. Collagen content of the L5 spinal nerve and nerve roots with attached scar were significantly lower in the HA gel treatment group than in the untreated laminectomy group ($p=.0014$). Pain behavioral testing of the L5 receptor area of the right hind paw in the untreated laminectomy group showed markedly increased sensitivity to tactile allodynia testing compared with the corresponding limb of the control group ($p=.0001$), to the corresponding limb of the sham group ($p=.0001$), and compared with the HMW HA gel treatment group ($p=.0010$). Comparisons of the pain behavioral data between the sham and the post-laminectomy HA gel treatment group and the control animals lacked statistical significance.

CONCLUSION: This study supports the concept of a relationship between perineural fibrosis and radicular neuropathy in the model described, and emphasizes the role of disc injury and spinal nerve retraction in the post-laminectomy fibrotic process. Furthermore, it shows promise for preliminary assessment of interventions with other anti-inflammatory agents, for characterization of the neurochemical profile of the post-laminectomy pain state, and for exploration of newer pharmaceutical agents potentially useful in the prevention or management of the post-laminectomy syndrome. Post-laminectomy scar is but one of many potential causes of the post-laminectomy pain syndrome. Furthermore, a cautionary note must be emphasized as in all studies using preclinical models, conclusions drawn from the studies cannot be extended directly to patients without confirmatory clinical follow-up studies.

Keywords: Spine; Laminectomy; Disc injury; Epidural fibrosis; HA gel; Tactile allodynia

Introduction

Recurrence of pain after spinal decompression surgery is experienced by significant numbers of patients [1,2–5]. Many of these patients undergo additional surgical procedures in an effort to alleviate their musculoskeletal and radicular symptoms. Although it is a common belief that a frequent cause of post-laminectomy pain is epidural scar formation with resultant spinal nerve scarring and tethering at the surgical site [6], documentation of this belief is lacking and controversy about its relevance prevails. Still, repeat surgical procedures after failed laminectomy are recognized to be associated with increased risk because of the danger of dural tears, increased bleeding, or spinal nerve injury attendant to the difficult dissection through a scar bed. Furthermore, attempts by repeat laminectomy to correct the post-laminectomy pain syndrome are frequently complicated by further proliferative scarring. Repeat spinal procedures, unfortunately, also have a high failure rate [7,8].

Authors of one magnetic resonance imaging study of post-laminectomy patients concluded that patients who have excessive epidural scar at the site of surgery are more likely to develop recurrent pain than patients without excessive scar [9]. Others could find no correlation between magnetic resonance imaging evidence of scar and postsurgical pain syndromes [10–13]. Thus, the controversy continues.

Preclinical models are widely used to study disease mechanisms and to guide drug development or surgical intervention development. A natural extension of this approach is to seek help from experimental modeling for questions posed above. Evidence from preclinical models may provide insights into some unanswered post-laminectomy clinical questions by offering experimental constructs not possible to perform in clinical studies. Here we present data comparing the pain behavioral responses in post-laminectomy groups with high and low levels of post-laminectomy fibrosis.

The term “scar wars” has been coined to describe surgical research aimed at reducing proliferative scar with antifibrotics in a variety of postsurgical applications [14]. In this context, numerous investigators have explored strategies to decrease scar formation in a multitude of postsurgical venues [15–25]. In the case of the problem of post-laminectomy proliferative scarring, corticosteroid administration was found marginally useful in one experimental model [26], but the high concentration required locally was associated with an unacceptable rate of postoperative infection. Preclinical and clinical programs using a proprietary gel product (ADCON-L) as an antifibrotic have been presented and