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Basic Science

Detrimental effects of discectomy on intervertebral disc biology can be decelerated by growth factor treatment during surgery: a large animal organ culture model

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Abstract

BACKGROUND CONTEXT: Lumbar discectomies are common surgical interventions that treat radiculopathy by removing herniated and loose intervertebral disc (IVD) tissues. However, remaining IVD tissue can continue to degenerate resulting in long-term clinical problems. Little information is available on the effects of discectomy on IVD biology. Currently, no treatments exist that can suspend or reverse the degeneration of the remaining IVD.

PURPOSE: To improve the knowledge on how discectomy procedures influence IVD physiology and to assess the potential of growth factor treatment as an augmentation during surgery.

STUDY DESIGN: To determine effects of discectomy on IVDs with and without transforming growth factor beta 3 (TGFβ3) augmentation using bovine IVD organ culture.

METHODS: This study determined effects of discectomy with and without TGFβ3 injection using 1-, 6-, and 19-day organ culture experiments. Treated IVDs were injected with 0.2 μg TGFβ3 in 20 μL phosphate-buffered saline+bovine serum albumin into several locations of the discectomy site. Cell viability, gene expression, nitric oxide (NO) release, IVD height, aggrecan degradation, and proteoglycan content were determined.

RESULTS: Discectomy significantly increased cell death, aggrecan degradation, and NO release in healthy IVDs. Transforming growth factor beta 3 injection treatment prevented or mitigated these effects for the 19-day culture period.

CONCLUSIONS: Discectomy procedures induced cell death, catabolism, and NO production in healthy IVDs, and we conclude that post-discectomy degeneration is likely to be associated with cell death and matrix degradation. Transforming growth factor beta 3 injection augmented discectomy procedures by acting to protect IVD tissues by maintaining cell viability, limiting matrix degradation, and suppressing NO. We conclude that discectomy procedures can be improved with injectable therapies at the time of surgery although further in vivo and human studies are required. © 2014 Elsevier Inc. All rights reserved.

Keywords: Intervertebral disc; Discectomy; Herniation; TGFβ3; Organ culture; Growth factor

FDA device/drug status: Not approved (TGF beta 3).

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The disclosure key can be found on the Table of Contents and at www.TheSpineJournalOnline.com.

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Introduction

Lumbar intervertebral disc (IVD) herniation is a common spine disorder with a lifetime occurrence as high as 40% [1]. Although most lumbar IVD herniations improve over time or with nonoperative therapy, a proportion of patients require surgical intervention [2,3], and some patients may develop a recurrent herniation requiring additional intervention [4]. The US Medicare system spends an estimated $300 million annually on lumbar discectomies [5], and although clinical studies have demonstrated benefits with surgical intervention [2,6,7], the long-term sequelae are unclear and may present with additional clinical problems [8–10]. Costs of managing post-discectomy low back pain were estimated with $4,934 per surgery [10], and, therefore, are a significant health-care burden. The development of cost-effective strategies to prevent or reduce the severity of post-discectomy degeneration may dramatically improve outcomes and reduce health-care costs. There remains little information on the effects of discectomy on the biology of the remaining IVD or on strategies to augment discectomy procedures to limit post-discectomy degeneration.

Although removal of pathologic IVD fragments during discectomy alleviates radicular symptoms, the remaining tissue and enlarged hole in the annulus fibrosus (AF) may promote or accelerate degenerative changes resulting in long-term clinical problems [8,9,11]. Imaging studies suggest that degenerative changes such as loss of IVD height, facet joint arthritis, and end plate changes are likely to occur within months after discectomy [12], and these changes are significantly associated with functional disability and low back pain [8–10]. The concept of accelerated degeneration after injury is also supported by in vivo studies where experimentally induced annular puncture leads to significant changes in the biomechanical properties of IVDs [13–15] resulting in decreased glycosaminoglycan content and increased expression of catabolic and inflammatory mediators [16,17]. It is obvious that the puncture of a healthy IVD creates a different situation from discectomy where the IVD is herniated and often degenerated. Yet, deeper knowledge is required to understand the effects of discectomy with its profound impact on the remaining IVD tissue and to investigate opportunities to develop biological treatments to improve outcomes after discectomy.

Injection of growth factors has been shown to have dose-dependent effects on improving both the structural and biomechanical properties of IVDs including reversing IVD degeneration [18,19] in animal models. Intradiscal injections of osteogenic protein-1 in an annular puncture animal model partly restored IVD height, increased proteoglycan content, and was correlated with improved elastic and viscous moduli of the IVD [20]. Several studies demonstrated that transforming growth factor beta (TGFβ) increases proteoglycan synthesis and expression of extracellular matrix (ECM) genes in the IVD. Transforming growth factor beta 3 has the capability to maintain the phenotype of IVD cells in organ culture [21] and endogenous TGFβ activity limits proinflammatory cytokine expression, suggesting an important role in maintaining the IVD homeostasis [19,20,22–28]. Masuda and An [18] suggested that identifying biological agents that can modify both symptoms and IVD structure would be highly desirable for the treatment of IVD degeneration.

Intervention during discectomy surgery would allow an immediate treatment that could inhibit catabolic responses and slow or arrest progressive degeneration. Although some studies exist about the effectiveness of growth factor treatment for vertebral body fusion and IVD implants [29–31], to our knowledge, nothing is known about the effect of growth factor injection during discectomy. Our broad aim is to improve the knowledge on how discectomy procedures influence IVD physiology and assess the potential of growth factor injection at the time of surgery, and we specifically evaluate the effects of TGFβ3 injection into the discectomy site during surgery using a bovine organ culture model. This study assessed the effects of discectomy with and without TGFβ3 augmentation cell viability, structural, and protein measurements.

Materials and methods

Tissue harvest and culture of IVDs

Skeletally mature bovine tails were obtained from a local abattoir, and four caudal IVDs were prepared from each tail. Vertebrae were cut proximal and distal to vertebral end plates with a histologic band saw (Exakt 310; Exakt, Norderstedt, Germany), and IVD dimensions (height, width, weight) were measured. Blood clots and bone debris were removed by flushing the end plates with water using an orthopedic irrigation system for debridement (Inter Pulse; Stryker, Kalamazoo, MI, USA). Intervertebral discs were then rinsed in ethanol, 1× phosphate-buffered saline (PBS) containing 3% penicillin/streptomycin and 1.5% fungizone, and PBS and assigned to the following groups: Day 0 control, cultured control (control), discectomy (injured), and discectomy+TGFβ3 (treated). To exclude IVD level–dependent differences in cell metabolism rates [32], the different groups were randomly distributed among the harvested caudal levels.

Discectomies were created on the dorsal side by performing a cruciate cut with a #15 scalpel to the center of the IVD. Tissue was loosened and removed using a discectomy curette and a standard IVD Rongeur (Fig. 1). Depending on the size (diameter=23.36±2.59 mm, volume=5.15±1.2 cm^3), an average of 18.8±11.8 μg tissue per IVD was removed. After discectomy, 0.2 μg TGFβ3 in 20 μL PBS+bovine serum albumin was injected into the injury site of treated IVDs with a high-precision syringe (Hamilton; Reno, NV, USA, Fig. 1D and E). Intervertebral discs were loaded in

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