CHAPTER

6 Discogenic Pain: Intradiscal Therapeutic Injections and Use of Intradiscal Biologic Agents

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CHAPTER OVERVIEW

Chapter Synopsis: Discogenic pain is a complex process with multiple components. After an annular tear of the intervertebral disc, nociceptors and blood vessels invade new areas of the disc that are normally noninnervated and avascular. Cytokine alterations promote nociception, both directly and indirectly, while altered anabolic-catabolic balance compromises the disc's hydraulic load-bearing function, also effecting changes in the intervertebral joints. This chapter assesses the nonsurgical therapies available to combat each of these components of lumbar discogenic pain. Growth factors in the bone morphogenetic protein family show promise in repairing metabolic and even structural disc abnormalities, but nonspecific anabolic effects of any growth factor must be considered. Although this treatment has potential, it is still in development. Intradiscal injection of fibrin sealants has been shown to improve cell proliferation and matrix production. Although still in an early stage, this therapy seems to address all the components of discogenic pain and disease. Many in the field are excited about the potential for stem cell therapy for discogenic disease. Mesenchymal stem cells transform into chondrocytes, which produce collagen and aggrecan to maintain the disc's structural integrity. Several currently available therapies are also considered, including pharmaceutical interventions and therapies to ablate nociceptive structures.

Important Points:

- Intradiscal ablative agents ethanol and methylene blue seem to be effective treatments for discogenic pain, requiring careful use to avoid potential epidural spread, but are readily available for use today.
- Intradiscal fibrin sealants may represent a useful interim step for addressing discogenic pain; studies are underway.
- Use of mesenchymal stem cells could be an emerging restorative agent but requires further research.

Clinical Pearls: Understanding the anatomy and pathophysiology of discogenic pain allows thoughtful consideration of emerging paradigms and techniques for treatment. The specific mechanism of delivery and confinement of any drug or biological modality to an anatomic disc target is critical to the success and safety of any of these techniques.

Clinical Pitfalls: Many published studies report on treatments for degenerated discs, radicular pain, or sciatica and overbroadly refer to these conditions as "discogenic pain." Many techniques applicable for radicular pain have not proven useful for discogenic pain originating from a painful posterior annular tear. Imprecision in nomenclature is frequent, even in contemporary surgical literature. Novel techniques require confirmation of safety and efficacy in human trials before widespread use.

In lumbar discogenic pain the injured intervertebral disc produces pain not only as a primary nociceptive structure but also as a result of reduced disco-vertebral mechanical load-bearing capacity and subsequently altered spinal biomechanics, including increased zygapophyseal joint loading. As a consequence, therapeutic strategies for discogenic pain are directed toward three general objectives: (1) resolution of primary nociception resulting from post-injury neoinnervation and neovascularization of the posterior annular tear; (2) restoring or mitigating the pro-nociceptive anabolic-catabolic imbalance, including restoration of normalized cytokine immunochemistry within the nucleoannular biochemical and cellular milieu; and (3) restoring lost mechanical and hydraulic function, including the loss of intervertebral hydrostatic pressure, intervertebral disc height, and annular integrity. Therapeutic approaches may rely on direct molecular effects, gene induction or suppression, or cellular replacement. This chapter discusses present and emerging clinical intradiscal therapies for discogenic pain within this triad of therapeutic objectives.

The adult lower lumbar intervertebral discs are the largest structures within the human body that have no dedicated primary

arteriovenous vascular supply, except a small marginal circulation to the outermost annulus, since the vascular buds in the vertebral endplates have typically regressed by 10 years of age. As a consequence, delivery of oxygen and glucose, as well as removal of metabolic waste products, is dependent on diffusion of these substances through the vertebral body endplates, producing a nuclear milieu marked by low oxygen tension, low pH, and a predominance of lactate over glucose as a metabolic substrate. Age- and injury-related changes to the vertebral endplate region may further compromise diffusion transport of nutrients and waste, creating an increasingly challenging milieu for the survival and proliferation of nuclear chondrocytes. The possibility of improving diffusion transport across the vertebral endplates by 7% to 11% as measured by magnetic resonance imaging (MRI) with use of nimodipine has been reported by Rajasekaran and associates.[1] The minimal reparative capacity of nuclear chondrocytes following injury to the intervertebral disc is compounded by the absence of the typical macromolecular humoral and cellular responses to injury seen elsewhere in the human body. The spectrum of discal response to injury, including the immunobiochemistry of the intervertebral disc, has been recently reviewed by Freemont.[2]

The posterior annulus of the lumbar intervertebral disc is normally innervated only in its outermost third, with innervation of the middle or inner thirds or of the nucleus limited to pathologically painful states. Mechanical injury to the posterior annulus may tear the posterior annular lamellae, with the result that multiple torn lamellar defects overlap one another in order to combine as radial fissures. The fissure can be confined to the middle or outer annulus, but in painful states, more commonly extends from the nucleoannular junction into or through the posterior annulus. Small tears in the outer annulus appear to accompany neovascularization and neoinnervation of the normally avascular and noninnervated middle and inner third of the annulus. Annular tears and nuclear degeneration may result in compromise of the native broad distribution of loading forces across the intervertebral disc, leading ultimately to a preponderance of load bearing along the annular rim or limbus region, further exacerbating annular wall stress during mechanical loading.

Normal nuclear chondrocytes maintain the hygroscopic nuclear matrix by producing collagen II, aggrecan, and a regulatory protein, SOX-9, with resultant hydrostatic pressure that allows optimal load bearing by distribution of that load across the annulus and vertebral endplates by the intact disco-vertebral unit. While the loss of annular integrity is usually cited as the initiating event in discogenic pain, there is evidence that repetitive mechanical loading stress produces pro-nociceptive changes in the function of nuclear cells.[3] Interestingly, it appears that some moderate degree of dynamic cyclical mechanical stress is associated with improved production of collagen and glycosaminoglycan by cells in the annulus fibrosus and nucleus pulposus as compared to cells undergoing either no cyclic loading or those undergoing high compressive stress.[4] Homeostatic functioning of the nuclear cells also depends upon a delicate balance between cytokine interleukin-1 (IL-1) and its associated receptors and receptor antagonists. Disruption of the IL-1 system can initiate biochemical changes, including a transition from nuclear collagen II to collagen I production, induction of matrix metalloproteinases, and cellular apoptosis. Although tumor necrosis factor (TNF)-α initiates inflammation and pain when applied to a somatic nerve root or to a sciatic nerve, antagonists of TNF-α (such as etanercept) have not proven useful in the treatment of discogenic pain.[5,6] TNF-α may also play a role in promoting sensory neoinnervation of the injured disc.[7] Members of the transforming growth factor (TGF)-β superfamily, which includes the bone morphogenetic protein (BMP) family and SOX-9, have been experimentally demonstrated to result in stimulation of collagen and proteoglycan production as well as the proliferation of nuclear cells; however, the relative stimulatory potency of the different BMPs varies.[8] BMP-7 (also called *OP-1)* has been shown to produce restoration of disc height and water content after initiation of degenerative changes using a rabbit stab injury model.[9] BMP-2 has been used experimentally to achieve intradiscal fusion. Concerns common to most BMPs include avoiding the formation of locally unwanted new bone or blood vessels and maintaining a specific locus of action with predictable termination or modulation of effect so unopposed anabolism does not produce distant or anatomically widespread adverse effects such as proliferative hyperostosis or neoplasm.

The cost of BMPs and injectable growth factors remains a concern. One alternative strategy is to seek inexpensive drugs that stimulate BMP production. Zhang and associates[10] have demonstrated that injection of intradiscal simvastatin (Zocor) in a PEG-PLGA-PEG gel stimulates BMP-2 and produces improvement in nuclear morphology and anabolic changes in a rat model. Although these growth factors and modulators represent an exciting and potentially transformative treatment for human discogenic pain, research using nonbipedal animal models may not translate to effective human treatments; and much additional research will be required to define optimal combinations of pharmacologic moiety and carrier. Human clinical trials with sufficiently lengthy follow-up to answer concerns regarding long-term potential for efficacy or harm will also be necessary.

Modulation of discogenic pain by a series of three intradiscal injections given at 2-month intervals using a solution of chondroitin sulfate, glucosamine, carboxycellulose, dextrose, and a cephalosporin antibiotic has been pioneered by Eek. Derby and Eek[11] published results of a prospective trial of chondroitin sulfate and glucosamine (35 patients) vs. intradiscal electrothermal treatment (IDET) (74 patients) in 2004. Some of the patients in each group had prior surgery or IDET treatment, and others had more than one level of identified discogenic pain generation on discography. As a treatment, they mixed 0.5% chondroitin sulfate and 20% glucosamine in 12% dimethylsulfoxide (DMSO) and 2% bupivacaine and then diluted this with equal quantities of contrast agent and 50% dextrose prior to injection. Postoperative flare of pain was seen in the majority of both treatment groups, with much briefer flare (9 days) seen in the mixture-treated group. Average visual analog scale (VAS) decrease of 2.2/10 for the mixture and 1.7/10 for IDET was reported. The results of this research are difficult to analyze due to the confounding factors of prior IDET or surgery as well as to the inclusion of patients with multilevel disc disease. The possible modest efficacy of this approach does not recommend further use at this time in light of superior results demonstrated with other modalities described later in this chapter.

In the field of orthopedic regenerative medicine, there is little that surpasses the excitement surrounding the use of stem cells, typically of mesenchymal origin, for repair of injured joint structures, including the intervertebral disc.[12] Mesenchymal stem cells (MSCs) can be induced to proliferate a chondrocyte phenotype by TGF-β.[13] Type II collagen can also induce and maintain chondrocytic lineage in a bovine model.[14] Interestingly, adult MSCs spontaneously differentiate into a chondrocytic lineage when inserted into disc nuclear tissue in vitro; so it is unclear whether any additional step is truly necessary to induce desired cellular differentiation.[15]

It has been demonstrated that MSCs can be harvested from the intervertebral disc, bone marrow, or the knee. These cells can be grown in culture before implantation, but viability of transplanted MSCs has been demonstrated only in animal models. Wuertz and associates[16] reported enhancement of matrix biosynthesis and nuclear cell proliferation in low-glucose environments; but low pH environments, similar to that of the degenerated disc, reduced both biosynthetic activity and the proliferation of MSCs. Sobajima and colleagues[17] demonstrated stem cell survival and engraftment in a rabbit model. In the knee the use of scaffolding may be superior to monolayer tissue culture for harvesting, but substantial challenges are related to specific details of culture technique, which are beyond the scope of this chapter. Particular note is made of the frequent use of animal models such as rabbit spine, ox tail, or ovine models, in which there is little or none of the repetitive axial loading that has been demonstrated to alter the production of collagen and aggrecan in chondrocyte tissue culture. Differences in epiphyseal and growth plate architecture and the effect of animal age on observed responses have been discussed in a comprehensive review of the limitations of animal models for study of discogenic pain.[18] Issues relevant to successful human therapeutic application include identification of optimal tissue source, ease of cellular harvesting, choice of implantation carrier, and assurance of clinically significant long-term viability of cellular transplants in the harsh disc nuclear environment. Research must also quantify the potential for malignant transformation of transplanted MSCs.

Platelet-rich plasma contains multiple cytokines and has been used for treatment of a variety of musculoskeletal pain processes by administration as prolotherapy. It has been postulated that intradiscal administration of platelet-rich plasma (PRP) may be beneficial in the treatment of discogenic pain, although the specific cytokines or factors contained in PRP that may effect this benefit remain unstudied.[19] Nonetheless, a randomized clinical trial of intradiscal PRP has been initiated by Lutz in 2009. No further information is available on this modality at the time of this writing.

Chymopapain (Chymodiactin) chemonucleolysis had been reported for many years and was popular in the United States in the 1970s when, due to frequent allergic reactions and reports of rare fatal anaphylactic reactions, it was withdrawn from clinical practice. Since that time, various investigators have considered a variety of substances for intradiscal injections that lyse or denature protein, including collagenase, ethanol, osmic acid, phenol, and 50% dextrose. Unfortunately, the chymopapain literature addresses efficacy in the context of lumbar disc herniation and radicular pain, but no reports address use of this modality specifically for axial discogenic pain. Furthermore, there is no evidence that chymopapain restores nuclear homeostasis or annular integrity.

As of this writing, several direct pharmaceutical modalities are presently available or in clinical trials for direct treatment of human discogenic pain. The following paragraphs review the available evidence supporting or questioning efficacy and safety.

Intradiscal steroids, theoretically effecting improvement in discogenic pain by suppression of inflammation, have been used for almost a half century for treatment of discogenic pain with varying success. Retrospective analyses dominated the literature until a rigorous double-blinded randomized controlled trial by Khot and associates failed to show efficacy.[20] Fayad and colleagues[21] reported improved efficacy of intradiscal steroids in patients with Modic I changes at 1 month. At 3 and 6 months, pain scores were not significantly different from baseline in any group, regardless of Modic categorization. If readers wish to consider this class of medications, avoidance of use of methylprednisolone (Depo-Medrol) is recommended because of its potential for intradiscal calcification.[22] At this time there is no evidence for improved long-term outcome with intradiscal steroid use and only weak evidence for a short-term effect.

One of the simplest pathways for treatment of discogenic pain involves chemical oxidation or denaturation of putative algogenic structures, which includes neurolysis. This class of treatments addresses neither restoration of nuclear homeostasis nor restoration of annular integrity. Discussion of intradiscal ozone, ethanol, methylene blue, and intradiscal 50% dextrose follows.

Intradiscal ozone is commercially available although not used in the United States. Therapeutic effectiveness is putatively associated with peroxide formation and oxidative injury. While free radical formation is possible, this mechanism appears less likely to be the predominant source of reputed efficacy. Administration must be carefully controlled to avoid gaseous emboli formation and adjacent structure injury caused by overwhelming of local tissue superoxide dismutase and catalase defenses. While the technique appears popular in Italy and India, no published literature addresses discogenic pain in the sense of internal disc disruption, addressing only applications in the treatment of radicular pain. Whereas original clinical series were reported for herniated nucleus pulposus and radicular pain[23,24] using concentrations of 27 mcg/mL, better outcomes were observed by concomitant infiltration of the nerve root with local anesthetic and steroids, with a reported 78% successful outcome at 6 months. Curiously, Gautam and colleagues[24] reported improved results with concomitant percutaneous intradiscal radiofrequency lesioning, a technique that, performed alone, has been shown to be entirely unhelpful for treatment of discogenic pain.[25] Unfortunately, serious complications, including basilar stroke,[26] epidural abscess,[27] and fulminating sepsis resulting in death[28] have been reported with this intradiscal ozone. As of this writing, no evidence supports the use of intradiscal ozone as being efficacious in the treatment of discogenic pain due to painful posterior annular tears.

Ethanol has been a traditional choice for regional anesthetic neurolytic block for many years. Intradiscal ethanol has been used by Riquelme and associates.[29] They reported a series of 118 patients in which discography was performed to identify the nucleoannular junction with subsequent injection of 0.4 mL of absolute ethanol at the junction of the middle and lateral thirds of the disc resulting in 98% of patients improved at 6 months. They did not inject full-thickness posterior annular tears (Dallas grade 5) because of concerns for potential epidural and dural structural injury, and no complications were noted in the series. These procedures were performed under propofol general anesthesia. It is unclear whether the patients had a diagnosis of discogenic pain since most of the patients treated had sciatica and no data on the proportion of patients with predominantly axial pain were included. Avoidance of spread into the epidural space or onto the dural surface by confinement of the drug to the target tissue has spurred use of a gel carrier using ethylcellulose, which has shown preliminary success in 91% of 221 patients studied by Theron and associates.[30] After injection of 0.4 to 0.8 mL of the gelled ethanol intradiscally with gentamicin for antibiotic prophylaxis, patients also underwent mandatory facet joint injection with triamcinolone, unilaterally or bilaterally, in this reported series. Successful use of gelified ethanol for treatment of 90% of cervical disc herniations without adverse effect has also been reported by Theron and associates.[31] They used tungsten or tantalum dust to opacify the gel, but both ethylcellulose and ethanol are relatively inexpensive and commercially available. These results are encouraging, but additional clinical studies will be necessary to determine the proper place of this moiety in treatment of discogenic pain.

Methylene blue is often thought to be a reducing agent, but at physiologic pH is more likely to function as an oxidizing agent. Intradiscal use has been studied by Peng and associates in a pilot study and then in a formal randomized controlled trial.[32,33] They report use of a simple and inexpensive technique, mixing 1 mL of methylene blue in 2 mL of lidocaine (Xylocaine) 1% and injecting this mix into the putatively painful lumbar intervertebral disc nucleus immediately after completion of (positive) discography. Use of methylene blue raises concern since direct neurotoxicity of this drug has been reported in both intrathecal and epidural applications.[34] However, their results bear thoughtful consideration since there were neither reported complications nor patient injuries. Their randomized controlled trial of 72 patients showed that 91% of the patients studied were satisfied by this treatment at 2 years, with an average pain reduction of 52 on a 101-point numerical rating scale and mean reduction in Oswestry scores of 36 compared with placebo. Reduction in the use of medications was also demonstrated. These outcomes have been envied by researchers worldwide, but wide adoption of this technique must await duplication of these results by other researchers.

Miller, Mathews, and Reeves[35] reported using 50% dextrose, a preparation known to be neurotoxic, on patients with positive concordant discography and transient response to two epidural steroid injections. Forty-three percent of patients improved by 71/100 on VAS. Single injections were insufficient, and the average patient required 3.5 injections. Since many patients with discogenic pain have exclusively axial symptoms and most do not respond to epidural steroid injection, the highly selected nature of Miller's population limits inferences that may be drawn.

One technique that appears to meet all three goals for treatment of discogenic pain involves use of an injectable fibrin sealant. Fibrinogen and thrombin are delivered in a dual syringe and mixed at a Y connector to form an elastic coagulum that is injected into the disc. Fibrin has been shown to improve cell proliferation and matrix production in vitro by Sha'ban and colleagues.[36] Human use of injectable fibrin sealants has been reported following nucleoplasty or IDET by Derby and Kim[37] and as a stand-alone treatment by Yin and associates.[38] Proposed mechanisms for efficacy include (1) fibrin glue sealing a mechanically defective posterior annular rent; (2) improving annular integrity to promote improved mechanical load sharing and reduction of annular wall shear forces; (3) preventing algogenic substances from reaching the sensitized or neoinnervated annular defect; and (4) improving nuclear cell function, including improved aggrecan and collagen production. U.S. Food and Drug Administration phase III clinical trials have demonstrated clinical efficacy of the patented clinical product. Greater than 50% reduction in both back and leg pain was demonstrated at 12 weeks. A single case of discitis was the only reported complication in the clinical series reported by Yin and Pauza. A multicenter randomized controlled phase III trial began in 2009 and is underway in the United States.

In summary, multiple biological and pharmaceutical modalities for intradiscal treatment of discogenic pain are available and under development. Treatments using ethanol and methylene blue appear to be simple, presently available, and promising. These approaches only address pain and do not address restoration of hydrostatic forces and annular integrity. Intradiscal fibrin sealants may represent a useful interim step for addressing discogenic pain in comprehensive fashion. Use of BMPs, simvastatin, and mesenchymal stem cells appear to be emerging as agents capable of addressing the entire triad of goals for resolving discogenic pain, but their use will require much further research and development before incorporation in routine clinical practice.

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