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Intervertebral Disc Degeneration: The Role and Evidence for Non–Stem-Cell-Based Regenerative Therapies

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ABSTRACT

The use of non–stem-cell-based regenerative medicine therapies for lumbar discogenic pain is an area of growing interest. Although the intervertebral disc is a largely avascular structure, cells located within the nucleus pulposus as well as annulus fibrosis could be targeted for regenerative and restorative treatments. Degenerative disc disease is caused by an imbalance of catabolic and anabolic events within the nucleus pulposus. As catabolic processes overwhelm the environment within the nucleus pulposus, proinflammatory cytokines increase in concentration and lead to further disc degeneration. Non–stem-cell-based therapies, which include growth factor therapy and other proteins, can lead to an increased production of collagen and proteoglycans within the disc.

Special Issue

Keywords: back pain, intervertebral disc, disc disease, disc compression, regenerative therapies

INTRODUCTION

Low back pain (LBP) is one of the most common causes for patients seeking medical care. The lifetime prevalence is estimated to range from 50%–80%[1,2] and is a leading cause of functional limitation and work absence, imposing a high economic burden on individuals, families, and society.[3] The associated cost of treatment and lost wages due to back pain in the United States has reached $253 billion annually,[4] with a subset of the population progressing to chronic back pain. In addition to the economic implication of LBP, there are substantial effects on the psychological well-being of patients that lead to increased depression and anxiety.[5] There are a variety of etiologies of LBP including myofascial pain, spinal stenosis, facet arthropathy, discogenic pain, and sacroiliac joint dysfunction. Current first-line management of acute and chronic LBP consists of a combination of conservative measures, including exercise therapy, intensive multidisciplinary treatment programs, and nonsteroidal anti-inflammatory drugs.[6] The use of platelet-rich plasma (PRP) and viscous biologics as regenerative therapy for discogenic lower back pain is a growing area of interest and will be the main focus of this article.

Anatomy and Function of Intervertebral Discs

Often a multifactorial condition, LBP can be categorized by the origin of the pain. A common cause includes intervertebral disc (IVD) degeneration, a distinct category of back pain that primarily consists of nociceptive and neuropathic pain. Other commonly used terms to describe this condition include *discogenic disease* or *axial back pain*.[6–9] The IVD lies between the vertebral bodies, serves as the articulating surface between 2 adjacent vertebral bodies, and is the largest avascular tissue in the body.[10] There is a total of 23 IVD (6 cervical, 12 thoracic, and 5 lumbar), which account for about 20%–30% of the total length of the spine.[11] The IVD is a complex structure that is composed of 3 distinct components: the inner nucleus pulposus (NP), the outer annulus fibrosus (AF), and the cartilaginous endplates (CEP). The inner NP is a gel-like structure primarily consisting of type II collagen and large proteoglycans that retain water to help absorb and disperse compressive loads exerted on the spine.[11] Surrounding the NP is a fibrocartilaginous structure known as the AF, which is composed of inner and outer concentric layers of collagen fibers with alternating angles that account for its tensile strength.[12] The final component of the IVD is the CEP, which are thin layers of hyaline cartilage measuring approximately 600-μm thick

positioned on the superior and inferior surfaces of the IVD, between the NP and VEP, also known as *ring apophysis*.[10] It is important to note that the VEP and CEP are two distinct structures, and only the CEP is part of the IVD complex. In addition to functioning as a mechanical barrier between the vertebral bodies and NP, the CEP is also the principal means for nutrient transport into the disc from the adjacent vasculature.[10,13]

The IVD is largely avascular with a limited number of microvessels present during adulthood. In the early stages of skeletal development, the vascular channels transverse the CEP and supply the majority of the IVD, with the exception of the NP. As the skeletal body continues to mature, the vessels start to retract and migrate towards the outer parts of the AF and the bone-cartilage junction.[11] At this stage, the inner AF and NP rely on diffusion for nutrient consumption.

The initial onset of discogenic disease can often be asymptomatic, as subtle changes in the matrix of the nucleus pulposus (NP) and annulus fibrosus (AF) take shape.[14] As a result, pain in discogenic disease is more often definitively seen with late IVD degeneration, a stage at which imaging can assist with diagnosis of disc-space narrowing, internuclear calcification, osteophyte formation, and endplate sclerosis.[15–17] The flexibility of the spinal column can be credited to the elastic IVD that lie between solid vertebrae. Mechanical forces can elicit flexion, extension, lateral, and rotational loads upon the spine. Excessive magnitude, vectors, or duration of forces can cause disc degeneration, because structural changes related to the matrix within IVD can malfunction, ultimately compromising the mechanical properties of the spinal column altogether.[18,19]

Mechanisms of IVD Degeneration

Disc degeneration is broadly understood to be a product of an imbalance between matrix anabolism and catabolism. Excess catabolic processes result in activation of proinflammatory cell signaling has been shown to weaken and replace matrix and collagenous components of the NP and AF. Therefore, intervention of disc cell necrosis and/or apoptosis has become the mainstay of many therapeutic modalities within this field of management. This can be achieved through upregulation of the underlying proteins and cytokines involved in stimulating disc cell growth, or replacement of necrotic cells in late-stage catabolism.[20,21]

Protein Growth Factors in IVD Homeostasis

To understand the treatment modalities involved in discogenic pain, a review of the underlying molecular components of anabolism and catabolism is necessary. At the core of this process lies proteins and growth factors. Some of the key components of this molecular cascade will be highlighted in this section.

Bone morphogenetic protein-2 (BMP-2) stimulates synthesis of the disc extracellular matrix.[22] As a member of the transforming growth factor β (TGF-β) superfamily of proteins, it helps regulate bone and cartilage formation. With this role, BMP-2 is often targeted for therapeutic intervention in degenerative disc disease.[23–26] Animal models have shown that proteins in the BMP class can upregulate proteoglycan synthesis; specifically, the use of recombinant BMP-2 on human disc cells has resulted in increased collagen and proteoglycan production within the nucleus pulposus.[27–29]

Growth differentiation factor (GDF) is a member of the BMP family. Whereas many members of this family promote activity at the bone, GDF has been shown to induce the formation of cartilage and tendon tissue instead.[30] In chondrocytes and NP cells in vitro, GDF has been shown to have the anabolic effects of upregulated proteoglycan (PG) and collagen production in NP and AF cells.[31,32] However, GDF has properties to equally promote catabolic processes via signaling pathways. The GDF signaling begins at heteromeric transmembrane serine-threonine kinase receptor complexes with type I and type II receptor molecules.[33] Receptor binding ultimately leads to activation of SMAD kinase pathways. With subsequent downstream integrin activation, this cascade promotes inflammatory cytokine signaling. The GDF can provide an important link between the anabolic and catabolic processes of disc degeneration, often making it a well-studied target for therapeutic interventions of discogenic pain. The balance between anabolic and catabolic processes suggests GDF is central to homeostatic maintenance of the IVD.[34]

The TGF-β family was initially described[35] in 1983. The first member of this group of cell regulatory proteins, TGF-β1, is a secreted polypeptide involved in proliferation, growth, and cell differentiation.[36] Similar to previous in vitro models of GDF, studies of TGF-β activation have shown its anabolic effects such as increased PGs and type II

collagen deposition that help maintain bone homeostasis, promote tissue repair, and regulate chondrocyte activity.[37–39] TGF-β activation is shown to be mediated by α_v and multiple β integrin subunits.[40,41] Similar integrin expression in cells of the NP suggest how integrin-mediated activation of TGF-β is important for IVD homeostasis and anabolic processes.[42,43] Hiyama et al[44] related the downstream signaling effects of TGF-β with BMP-2 and found that both regulate β1,3-glucuronosyl transferase-1 expression and chondroitin sulfate synthesis in NP cells, promoting anabolic processes within matrix cells. TGF-β3 is a specific growth factor that has been shown to play a role in transformation of IVD structure via cell differentiation.[45] In vitro models with supplemented TGF-β3 were associated with elevated levels of activated ERK1/2 and enhanced expression of receptors TGF-βRI and TGF-βRII, which showed elevated expression of matrix genes and PG incorporation.[46]

Cessation of the Catabolic Cascade and Inflammation

The balance between anabolic and catabolic processes allows for multiple treatment approaches in IVD. Whereas growth factors are the most commonly approached target in literature, cessation of the catabolic cascade is an alternative to achieve anticatabolic effects that achieve disc regeneration and maintain homeostasis.

Much of disc degeneration can be attributed to destruction of matrix components via overexpression of proteases such as matrix metalloproteinases and ADAMTS. Cytokines are responsible for activation and regulation of these proteases and their subsequent effects.[47] Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine that is upregulated in IVD degeneration, and its effect has been well studied in vitro. Wang et al[48] showed that a blockade of TNF-α–induced upregulation of ADAMTS-4 and ADAMTS-5 reversed cytokine-mediated collagen degradation in human IVD in vitro. Tobinick and Davoodifar[49] studied Etanercept, a TNF-α antagonist, and found a significant improvement in discogenic pain in patients at all follow-up intervals ($P < .0001$). The cytokine interleukin-1 (IL-1) acts similarly to TNF-α as a proinflammatory agent involved in cell apoptosis. Therapy focused on blocking IL-1 is widely studied as a means to help prevent inflammation-mediated damage that leads to disc degeneration.[50] Hoyland et al[51] were able to investigate and compare TNF-α and IL-1 on matrix degeneration and found that inhibition of IL-1 was more effective than inhibition of TNF-α in reducing degradation in normal or degenerated discs.

Another therapeutic target of the catabolic cascade is platelet-derived growth factor (PDGF). Presciutti et al[52] showed that PDGF is associated with inhibited cell apoptosis, cell proliferation, matrix production, and messenger RNA expression of critical extracellular matrix genes when studied in vitro. Similar in vitro studies showed PDGF stimulated both PG synthesis in NP cells and IVD cell proliferation.[53,54]

With the growing literature support for growth factor administration for improved outcomes in degenerated IVD and matrix homeostasis, administration of PRP has become a mainstay of study and clinical therapeutic intervention in recent years.[55] PRP is an autologous blood concentrate and often directly administered into the IVD for management of LBP. The advantage of PRP is its concentrated mix of growth factors and cytokines, therefore promoting tissue regeneration and repair.[56,57] The use of PRP in IVD repair has been widely studied in vitro, with promising results. Overall, in vitro studies showed PRP was effective at stimulating cell proliferation and increased PG and collagen synthesis.[58–60] The anti-inflammatory effects of PRP were also highlighted by recent studies. PRP was found to be associated with suppressed aggrecan and type II collagen, stimulation of matrix metalloproteinases-3 and cyclooxygenase-2 expression, and diminished cytokine (IL-1, TNF-α) response and gene expression.[61–63]

CLINICAL STUDIES OF BIOLOGICS FOR INTRADISCAL INJECTION

In the literature, there are few studies discussing the use of regenerative therapies for discogenic LBP (Table 1). Currently, the bulk of studies include preliminary designs to assess efficacy of the treatment model. Levi et al[64] conducted a prospective trial with 22 patients with discogenic LBP proven by clinical means, imaging, and exclusion of other structures. Patients were injected once with PRP at 1 or multiple intervertebral levels. Pain scores assessed with a visual analog scale (VAS) and function by the Oswestry Disability Index (ODI) were recorded at 1-, 2-, and 6-month follow-up visits. For this study, Levi's team used a strict categorical success criteria

Table 1. Clinical studies on regenerative therapies for IVD.

Authors (Year Published)	Study Title	Regenerative Therapy Used	Disease	Study Design	No. of Participants	Treatment Arms	Outcome Measures	Length of Follow-Up	Results	Comments
Levi et al (2016)[64]	Intradiscal PRP injection for chronic discogenic low back pain: preliminary results from a prospective trial	PRP	Discogenic LBP	Prospective, observational	22	Single treatment of intradiscal injection of PRP at 1 or multiple levels	VAS, ODI	1, 2, 6 mo	Strict categorical success criteria was used (at least 50% improvement in VAS and 30% decrease in ODI at follow-up). Categorical success rates were 14%, 32%, and 47% at 1, 2, and 6 mo, respectively.	No randomization, no control. Preliminary study findings
Akeda et al (2017)[65]	Intradiscal injection of autologous serum isolated from PRP for the treatment of discogenic low back pain: preliminary prospective clinical trial	PRP	Chronic LBP	Prospective clinical trial	14	1-dose PRP injection	VAS, RDQ, x-ray, MRI	4, 8, 16, 24, 32, 40, and 48 mo	Mean pain scores decreased significantly at 1 mo and were sustained throughout follow-up period. VAS (7.5 baseline, 3.2 at 6 mo, and 2.9 at 12 mo) RDQ (12.6 baseline, 3.6 at 6 mo, and 2.8 at 12 mo)	Small sample size. No randomization. No control
Navani et al (2015)[66]	PRP injections for lumbar discogenic pain: a preliminary assessment of structural and functional changes	PRP	Lumbar discogenic pain	Prospective, observational	6	Single injection of autologous PRP	VPS, MCS, PCS, SF-36	2, 4, 8, 12, 16, 20, and 24 wk	50% of the VPS scores of all patients decreased by 3 mo, and low pain levels were maintained until the 6-mo follow-up. SF-36 also improved in both physical and mental scores	
Lutz et al (2017)[67]	Increased nuclear T2 signal intensity and improved function and pain in a patient 1 y after an intradiscal PRP injection	PRP	Discogenic LBP	Single case report	1	Single injection of autologous PRP	MRI	6 wk, 1 y	1-y follow-up MRI showed increased T2 nuclear signal intensity at L4-5 and L5-S1. No change in the crescentic fissure in the outer annulus adjacent to the left neural foramen at L4-L5. Patient indicated significant improvement in his low back pain and a return to participation in several athletic activities including running	
Comella et al (2017)[69]	Effects of the intradiscal implantation of stromal vascular fraction plus PRP in patients with degenerative disc disease	PRP mixed with stromal vascular fraction	Degenerative disc disease	Prospective clinical trial	15	Single 1 mL of SVF/PRP suspension injection	VAS, PPI, ODI, BDI, Dallas pain questionnaire, and SF-12 scores	2 and 6 mo	statistically significant improvements in flexion, pain ratings, VAS, PPI, and SF-12 questionnaires	Small sample size. Several patients lost to follow-up. Lack of placebo control
Tuakli-Wosornu et al (2016)[70]	Lumbar intradiskal PRP injections: a prospective, double-blind, randomized controlled study	PRP	Lumbar discogenic pain	Prospective, double-blind, randomized Controlled study	47	Intradiscal PRP vs contrast agent after provocative discography	FRI, NRS, 36-item short form health survey, modified NASS Outcome questionnaire	1, 4, 8 wk, 6 mo, and 1 y	Significant improvement in pain (NRS), function (FRI), and patient satisfaction (NASS outcome questionnaire) in patients who received intradiscal PRP compared with controls at 8 wk. PRP group maintained significant improvements in FRI scores through 1 y.	Limited follow-up interval for control group. No data collection on cell counts. No radiological follow-up

Table 1. Continued.

Authors (Year Published)	Study Title	Regenerative Therapy Used	Disease	Study Design	No. of Participants	Treatment Arms	Outcome Measures	Length of Follow-Up	Results	Comments
Derby et al (2004)[74]	Comparison of intradiscal restorative injections and IDET in the treatment of LBP.	Dextrose	Discogenic LBP	Pilot study	109	IDET vs 50% dextrose intradiscal injection therapy	VAS, satisfaction rate, and flare-up before and after the procedures	6–18 mo	Significant decrease in VAS for pain relief in both groups ($P = .01$). Patients receiving injections were more satisfied. 35.8% of IDET patients reported worse pain, whereas no restorative injection patient reported worsening of pain. Higher rates of postprocedure flare-ups in restorative injection group vs IDET (81% and 68.9%, respectively).	No placebo control. Small sample size. Short follow-up interval.
Miller et al (2006)[75]	Treatment of painful advanced internal lumbar disc derangement with intradiscal injection of hypertonic dextrose	Dextrose	Degenerative disc disease	Prospective consecutive patient series	76	Biweekly hypertonic dextrose injections (50% dextrose and 0.25% bupivacaine)	11-scale NPS	18 mo	33 patients (43.4%) achieved sustained improvement. Average improvement in NPS of 71% at 18 mo. Average of 3.5 injections/patient.	No placebo control. Small sample size. Short follow-up interval.
Stagni et al (2012)[79]	A minimally invasive treatment for lumbar disc herniation: DiscoGel chemonucleolysis in patients unresponsive to chemonucleolysis with oxygen-ozone	DiscoGel	Lumbar disc herniation	Prospective, observational	32	Single DiscoGel chemonucleolysis injection	Modified MacNab criteria, questionnaire and direct patient interview by outside observer	6 mo	The treatment was successful (improvement in pain) in 24 of 32 patients (75%). Of the remaining 25%, recourse to surgery was seen in 3 cases (9.3%). No complications. No difference was observed in patients that underwent discolysis in more than one level vs those treated at a single level.	No control group, small sample size. Short follow-up
Kuhelj et al (2019)[81]	Efficacy and durability of radiopaque gelified ethanol in management of herniated discs	DiscoGel	Degenerative disc disease and/or herniation	Prospective, observational	83	Single percutaneous image-guided intradiscal injection of DiscoGel	VAS, physical activity, use of analgesics, patient satisfaction, and willingness to repeat treatment	1, 6, 12, 24, and 36 mo	89.8% of respondents had significant reduction in VAS after 1 mo ($P < .001$). 96.6% of patients were seriously to moderately disabled prior to treatment, which was reduced postprocedurally to 30% after 1 y	Small sample size. High number lost to follow-up (25%)
Hashemi et al (2020)[82]	Effectiveness of intradiscal injection of radiopaque gelified ethanol (DiscoGel) vs percutaneous laser disc decompression in patients with chronic radicular LBP	DiscoGel	LBP and radiculopathy secondary to lumbar IVD herniation	Prospective, observational	72	DiscoGel vs PLDD	NRS, ODI, and progression to secondary treatment	6 and 12 mo	Significant reduction in mean NRS and ODI scores from the total cohort (8.0 and 81.25%, respectively) to DiscoGel group (4.3 and 41.14%, respectively) and PLDD group (4.2 and 52.86%, respectively). ODI score in DiscoGel group was significantly lower at 12 mo	Small sample size. No randomization. No control or comparison with conservative treatment

Table 1. Continued.

Authors (Year Published)	Study Title	Regenerative Therapy Used	Disease	Study Design	No. of Participants	Treatment Arms	Outcome Measures	Length of Follow-Up	Results	Comments
Papadopolous et al (2020)[83]	Comparison of the efficacy between intradiscal gelified ethanol (DiscoGel) injection and intradiscal combination of pulsed radiofrequency and gelified ethanol (DiscoGel) injection for chronic discogenic LBP treatment. A randomized double-blind clinical study	DiscoGel	Discogenic LBP	Randomized, double blind, controlled trial	36	DiscoGel (group A) vs DiscoGel in combination with pulsed radiofrequency (group B)	VAS, RDQ, Lanss score, and quality of life score (EQ-5D)	1, 3, 6, 12 mo	no significant difference in pain score between the 2 groups (P = .084), except in 6th and 12th mo. Group B showed a statistically significant difference, compared with group A regarding RDQ, Lanss score, and EQ-5D score (secondary objectives)	No placebo control. Small sample size

Abbreviations: BDI, Beck Depression Inventory; CC, chondrocyte; FRI, functional rating index; IDET, intradiscal electrothermal therapy; IVD, intervertebral disc; LBP, lower back pain; LMF, lumbar multifidus muscle; MCS, mental component summary; MODQ, Modified Oswestry Disability Questionnaire; MSC, mesenchymal stem cells; NASS, North American Spine Society; NPS, numerical pain score; NRS, numerical rating scale; PSI, patient satisfaction index; ODI, Oswestry Disability Index; PBS, phosphate-buffered saline; PCS, physical component summary; PG, proteoglycan; PLDD, percutaneous laser disc decompression; PLRP, platelet leukocyte rich plasma; PPI, present pain intensity; PPP, platelet-poor plasma; PRP, platelet-rich plasma; RDQ, Roland-Morris Disability Questionnaire; SF-12, short form; SF-36, Short Form; SIJ, sacroiliac joint; VAS, visual analog scale; VPS, verbal pain score.

of at least 50% improvement in VAS and 30% decrease in ODI at follow-up. Categorical success rates were 14%, 32%, and 47% at 1, 2, and 6 months, respectively.

Akeda et al[65] conducted a prospective clinical trial for the treatment of discogenic LBP with PRP in patients with at least 1 symptomatic disc proven by provocative discography and/or disc block. Similar to the investigation by Levi et al, a single PRP injection was administered at the start of the study, and patients were then seen at 4, 8, 16, 24, 32, 40, and 48 months for follow-up assessment. Efficacy of this treatment was assessed with VAS for back pain and the Roland-Morris Disability Questionnaire (RDQ) for back pain–related disability at baseline and at each follow-up. X-ray and MRI were also used for radiologic assessment. This preliminary study reported pain scores that decreased significantly at 1 month, which was sustained throughout the follow-up period. The VAS (7.5 baseline, 3.2 at 6 months, and 2.9 at 12 months; $P < .001$) and RDQ (12.6 baseline, 3.6 at 6 months, and 2.8 at 12 months; $P < .001$) scores are provided. However, mean T2 values in imaging did not significantly change after treatment, suggesting that the chronic progression of disease seen in imaging should be further analyzed.

Navani and Hames[66] performed a case series study with 6 patients with chronic discogenic low back and leg pain who tried and failed conservative treatments. A single intradiscal PRP injection was administered and patients were followed up to 24 weeks. Verbal pain scale scores for all patients decreased at least 50% by 3 months. The 36-item short form (SF-36) also improved in both physical and mental scores. Lutz[67] also took a case series approach to expanding the clinical scope of intradiscal LBP, with an assessment of radiological changes of disc degeneration. This study followed a 42-year-old patient with moderate to severe disc space narrowing and degenerative disc disease at L4-L5 and L5-S1 discs. PRP injections were administered and the patient was seen 6 weeks later showing less pain and improved range of motion. One-year follow-up with MRI showed increased T2 nuclear signal intensity. The negative correlation between the progression of degenerative disc disease and T2 signal intensity is well established.[68] In comparison with the study performed by Akeda et al,[65] imaging findings in this case provide an important component to follow in future studies.

Comella et al[69] performed a prospective clinical trial on 15 patients with degenerative disc disease. In contrast to the trials previously outlined, this study used stromal vascular fraction obtained from a mini-lipoaspirate procedure of fat tissue, which was suspended in PRP for intradiscal injection. Significant improvements of VAS (5.6→3.6) and Present Pain Index (2.6→1.8) were seen at 6 months ($P <$ .001). Statistically significant improvements in flexion, pain ratings, and 12-item short form questionnaires were seen too.

Preliminary studies such as these suggest improved discogenic LBP outcomes with respective therapies, although it is important to note that across these studies we found a small sample size and lack of control or placebo groups. Akeda et al[65] did not have randomization, whereas Levi et al[64] noted that without discography as a patient selection criterion in their trial, significant bias existed. Similarly, Comella et al[69] noted several patients lost to follow-up. Randomized controlled trials are the next step to evaluate the efficacy of these therapies for discogenic LBP and long-term outcomes.

Tuakli-Wosornu et al[70] performed a prospective, double-blind, randomized controlled study assessing the efficacy of intradiscal PRP versus a contrast agent (control) in lumbar discogenic pain. A total of 47 subjects participated in the study after provocative discography. Functional rating index (FRI), numerical rating scale (NRS), SF-36 health survey, and the North American Spine Society (NASS) questionnaire were outcome measures. Length of follow-up was 1, 4, and 8 weeks, and subsequently 6 and 12 months, with a 92% follow-up rate at 8-week time points or longer. Significant improvement in pain (NRS), function (FRI), and patient satisfaction (NASS outcome questionnaire) was seen in patients who received intradiscal PRP compared with controls at 8 weeks ($P <$ .001). The PRP group maintained significant improvements in FRI scores through 1 year. Although the findings in this study suggest encouraging outcomes, it is worth noting that the follow-up interval for this control group was only 8 weeks. PRP and control group outcomes were not compared after 8 weeks, ultimately limiting the scope of the longitudinal analysis of this PRP group. Tuakli-Wosornu et al[70] further highlight that radiological assessment would strengthen future clinical trials.

With only 1 double-blind randomized controlled trial, the clinical evidence of intradiscal therapy of PRP for treatment of discogenic LBP remains insufficient. However, existing studies do support that intradiscal injection of PRP for degenerative disc disease results in a statistically significant improvement in various outcomes measures such as VAS, NRS, and ODI. More randomized controlled trials are necessary to evaluate whether PRP is effective for treating degenerative disc disease and affects long-term prognosis.

Prolotherapy in Intradiscal Pain Management

Prolotherapy for discogenic pain management involves injection of a solution that creates an inflammatory response to repair connective tissue. Commonly used agents include hypertonic dextrose, phenol, or sodium morrhuate. Although these solutions are in the same class of therapy, each uses different mechanisms to elicit their desired response. Dextrose, often the mainstay of prolotherapy due to its well-studied properties of water solubility and safe entry, is an osmotic agent that irritates local tissue to recruit inflammatory cells and the subsequent cascade. Irritants such as phenol damage cell membranes, whereas chemotactic agents such as sodium morrhuate can directly activate the inflammatory cascade.[71–73] The literature examining intradiscal prolotherapy for spine pain includes 2 studies, both reporting positive results.

Derby et al[74] performed a pilot study comparing intradiscal electrothermal treatment (IDET) with dextrose intradiscal injection therapy. A total of 109 patients with discogenic back pain were followed for 6–18 months after a single procedure. Pain relief was statistically significant for both procedures, marginally better for injections (2.2 VAS) than for IDET (1.27 VAS; $P = .01$). Postoperative satisfaction surveys showed that patients receiving injections were significantly more satisfied, and 35.8% of patients in the IDET group actually reported worsening of pain, whereas no patients receiving dextrose reported this. However, postprocedure flare-ups were more frequent in the restorative injection group (81%) than after IDET (68.9%) and were more severe (VAS: 7.9 and 6.1, respectively). Multiple outcome measures in this study point towards biologic intradiscal intervention having similar clinical efficacy as IDET, with an improved cost-benefit ratio. Notably, the intradiscal intervention used was also a mixture of hypertonic

dextrose, glucosamine/chondroitin, and dimethylsulfoxide; therefore, a direct analysis of prolotherapy was more difficult to establish from this study.

Miller et al[75] observed 76 patients in a prospective case series receiving biweekly hypertonic dextrose injections for degenerative disc disease. Each patient was injected 3.5 times on average. Of the patients, 43.4% reported sustained improvement and an average improvement in NPS of 71% at 18 months, compared with pretreatment measures. Similar to Derby et al,[74] a lack of placebo control and randomization is notable in this study. Degenerative disc disease should also be monitored with longer follow-up times to reflect its chronic disease course.

The efficacy of prolotherapy as an intervention for discogenic disease has much more room for analysis within the literature. Two existing studies suggest that intradiscal injection of dextrose solutions may be useful in the management of pain arising from degenerative disc disease. Randomized controlled trials and trials with placebo groups are still necessary to evaluate this further.

Application of Radiopaque Gelified Ethanol for Clinical Studies of Discogenic Disease

As the utility of minimally invasive percutaneous treatment in intervertebral discogenic pain grows, one modality recently made available is radiopaque gelified ethanol (DiscoGel, Gelscom, France). Introduced in 2007, DiscoGel is a sterile viscous intradiscal solution consisting of gelified ethanol with tungsten in suspension. More viscous than absolute ethanol, it is used as a treatment for pain from lumbar discs that fail conservative treatment with an absence of neurological deficit. As DiscoGel is injected into the nucleus pulposus, it decompresses the intradiscal space. Tungsten is added to slow the progression of the gel in the disc, leading to a more controlled substance diffusion. The resulting osmotic gradient allows for water to shift from the periphery to the center of the disc, facilitating disc decompression and reduction of intradiscal pressure.[76–78]

Recent studies have emerged specifically addressing the efficacy of DiscoGel in LBP management. Prospective observational studies currently make up the bulk of this research domain. Stagni et al[79] performed a single DiscoGel chemonucleolysis injection on patients with lumbar disc herniation. A total of 32 individuals met the criteria, which specifically targeted patients who had poor therapeutic outcome following intradiscal oxygen-ozone (O_2-O_3) therapy performed at least 6 months before DiscoGel treatment. The O_2-O_3 chemonucleolysis is an alternative minimally invasive treatment with the best cost-benefit ratio and lowest complication rate (<0.1%) in treatment of herniated discs.[80] The treatment was successful (pain lessened) in 24 of 32 patients (75%) after 6 months. Of the remaining 25%, recourse to surgery was seen in 3 cases (9.3%). Notably, no difference was observed between patients who underwent discolysis in more than 1 level and those treated at a single level. This study found that their results with DiscoGel are comparable to therapeutic success rates of O_2-O_3 chemonucleolysis, suggesting its efficacy in cases refractory to O_2-O_3 therapy. A randomized controlled trial is still necessary to compare these modalities and their prognosis directly, with longer follow-up intervals.

A prospective observational study was performed by Kuhelj et al[81] in 2019, using DiscoGel injection in lumbar disc herniations. Among their 82 initial participants, 89.8% of study respondents had a significant reduction in VAS after 1 month, with mean VAS scores of 8.5→4.5 for the lumbar spine group ($P < .001$). Of the patients, 96.6% were seriously to moderately disabled prior to treatment, which reduced postprocedurally to 30% after 1 year. One major drawback of this study, however, was a poor rate of follow-up (25% of patients). This study also highlights that many trials within radiopaque gelified ethanol injection are focused on immediate or short-term follow-up, reporting results up to 1 year. Discal degeneration is a chronic, progressive disease that has permanent effects on quality of life, justifying the need for further studies to establish a care model for long-term results.

Hashemi et al[82] presented a prospective observational study comparing DiscoGel with percutaneous laser disc decompression (PLDD) in patients with LBP and radiculopathy secondary to lumbar IVD herniation, the first study of its kind. A total of 72 participants with either intervention were followed up to 12 months. Overall, a significant reduction in mean NRS of the preoperative total cohort (8.0) to DiscoGel (4.3) and PLDD groups (4.2; $P = .001$). Mean ODI scores also showed a significant decrease from the total cohort (81.25%) to the DiscoGel (41.14%) and PLDD groups (52.86%; $P = .001$). This study began to offer a more direct comparison

between current treatment modalities but still lacked randomization and control. Hashemi et al[82] further suggested that a comparison with conservative treatment would aid in understanding long-term efficacy.

A randomized, double-blind controlled trial was performed by Papadopolous et al[83] in 2020. This study compared DiscoGel (group A) with DiscoGel in combination with pulsed radiofrequency (group B). During the follow-up period, a significant difference in pain (VAS) was found at 6 and 12 months. Overall, group B showed a statistically significant difference compared with group A regarding the study's secondary objectives, such as the Roland-Morris Disability Questionnaire, Lanss score, and quality of life (EQ-5D). Although this study monitored progress up to 12 months with a small sample size, the randomization marks it as the first of its kind regarding radiopaque gelified ethanol for intradiscal disease. The suggestion of improved outcomes through augmentation of DiscoGel treatment with pulsed radiofrequency should be studied in the future with prolonged follow-up intervals.

The application of radiopaque gelified ethanol has grown over the past decade. Clinical studies continue to emerge, but the intervention still lacks a library of randomized controlled trials necessary to evaluate the long-term treatment advantages and efficacy as a minimally invasive percutaneous treatment.

Evidence of Safety in Intradiscal Injection

As the application of interventional discogenic pain management modalities grows, follow-up studies have been used to monitor compilations or side effects (Table 2). Potential risks related to intradiscal injection procedures include bleeding, pain at the injection site, osteomyelitis/discitis, nerve injury, or allergic reactions to steroids or dye.[84,85] Early evidence suggests positive outcomes with low adverse effects across a variety of procedure types and biologics, particularly when compared with surgical alternatives across similar patient populations. Orozco et al[86] performed a pilot study in 2011 on 10 patients with chronic degenerative disc disease treated with autologous expanded bone marrow mesenchymal stem cells (MSC) injected into the NP. Significant improvements were seen in pain (VAS) and disability (ODI) at the 3-, 6-, and 12-month follow-up periods ($P < .001$), with no major adverse effects recorded. Despite this study showing no change in disc height on MRI follow-up, there was increased T2 signal within the disc at 1-year follow-up, suggesting this modality promoted disc hydration alongside a favorable side effect profile.

Phase 1 studies allow monitoring of safety and efficacy for intradiscal injection across a variety of treatment arms and biologics. Tschugg et al[87] performed a phase 1 study in 2016 assessing the safety and efficacy of an autologous disk chondrocyte transplantation of Novocart Disc Plus (NDplus; Aesculap, Tuttlingen, Germany) across 24 patients while using immunological markers as a treatment arm. No indications of harmful material extrusion or immunological consequences were observed across the 6-week follow-up period. C-reactive protein and IL-6 markers were not significantly elevated at any point, and there were no imaging abnormalities such as fractures, significant foraminal stenosis or degenerative spinal stenosis. Kumar et al[88] reflected similar outcomes in their single-arm phase 1 clinical trial in 2017, which assessed the safety and tolerability of intradiscal implantation of adipose tissue–derived MSCs (AT-MSCs) for chronic discogenic LBP. Ten patients composed 2 groups with low- or high-dose AT-MSCs and hyaluronic acid derivative intradiscal injection. No procedure or stem cell–related adverse events occurred during the 1-year follow-up period, whereas VAS (pain), ODI (disability), and SF-36 scores significantly improved in both groups ($P = .002$). In 2012, Coric et al[89] performed a single-arm prospective cohort study evaluating the safety of NuQu allogeneic juvenile chondrocytes delivered percutaneously for the treatment of lumbar spondylosis with mechanical LBP in 15 patients. Mean ODI, NRS, and SF-36 summaries all improved significantly from baseline at a 12-month follow-up, and 8 patients sustained radiological improvement in disc contour and height at 12 months. No patient experienced neurological deterioration, disc infections, or serious or unexpected adverse events during the follow-up period.

The evidence of safety across interventional administration of allogeneic cell sources is growing. Early studies show encouraging outcomes, particularly when compared with side effect profiles and risks of alternative surgical modalities available. Randomized controlled trials across prolonged follow-up periods exceeding 1 year would help evaluate the long-term safety of minimally invasive

Table 2. Clinical studies on regenerative therapy safety and efficacy for IVD.

Authors (Year Published)	Study Title	Therapy Used	Disease	Study Design	No. of Participants	Treatment Arms	Outcome Measures	Length of Follow-Up	Results	Comments
Orozco et al (2011)[86]	Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study	MSC	degenerative disc disease	Pilot, phase 1 trial	10	Single transplantation of autologous expanded bone marrow MSCs into the NP	VAS, ODI	3, 6, 12 mo	No major AEs recorded. VAS and ODI outcomes significantly improved across all follow-up intervals. 85% of total improvement occurred within initial 3 mo.	Small sample size, no randomization, no control.
Tschugg et al (2016)[87]	A prospective randomized multicenter phase 1, phase 2 clinical trial to evaluate safety and efficacy of NOVOCART disk plus autologous disk chondrocyte transplantation in the treatment of nucleotomized and degenerative lumbar disks to avoid secondary disease: safety results of Phase 1—a short report	NDplus	degenerative disc disease	Prospective, randomized phase 1 trial	24	Sequestration and transplantation	Inflammatory markers IL-6 and CRP, MRI	2, 6, 24, 36 h and 6 wk	No change in CRP after implantation, IL-6 showed minor elevations and peaked at 42 h. No significant difference in markers between cohort and experimental groups. MRI showed no space-occupying effects, osteochondrosis, fractures or stenosis.	Short follow-up intervals.
Kumar et al (2017)[88]	Safety and tolerability of intradiscal implantation of combined autologous adipose-derived mesenchymal stem cells and hyaluronic acid in patients with chronic discogenic low back pain: 1-year follow-up of a phase 1 study	AT-MSC	chronic discogenic LBP	Prospective, single-arm phase 1 trial	10	Single injection of AT-MSC and HA derivative	AE, SAE, VAS, ODI, SF-36, MRI	1 wk, 1, 3, 6, 9, 12 mo	No AEs or SAEs reported. Success was reported as >50% improvement in outcomes measure baselines. Seven patients reported success at 6 mo, 6 patients reported successful improvement in VAS, ODI at 12 mo. No cases of degeneration or fractures on MRI, increase in water content seen in 3 cases at 12 mo.‘	Small sample size, no randomization, no control.
Coric et al. (2012)[89]	Prospective study of disc repair with allogeneic chondrocytes	NuQu allogenic chondrocytes	Lumbar spondylosis	Prospective, cohort	15	Single injection of juvenile chondrocytes	ODI, NRS, SF-36, MRI	1, 3, 6, 12 mo	Mean ODI, NRS, and SF-36 summaries all improved significantly from baseline at 6 and 12-mo follow-up visits. Radiological improvement in disc contour and height at 12 mo in 8 participants. No major adverse effects reported (neurological decline, infection)	Not blinded, no control.

Abbreviations: AE, adverse effect; AT-MSC, adipose-tissue derived mesenchymal stem cells; HA, hyaluronic acid; LBP, lower back pain; MSC, mesenchymal stem cells; NDplus, NOVOCART Disc Plus; NP, nucleus pulposus; NRS, numerical rating scale; NuQu, NuQu allogeneic juvenile chondrocyte; ODI, Oswestry Disability Index; SAE, serious adverse effect; SF-36, short form; VAS, visual analog scale.

percutaneous modalities and autologous and allogeneic cell sources.

CONCLUSIONS

The literature supporting non–stem-cell biologics such as PRP and viscous intradiscal solution for degenerative disc disease continues to grow. The clinical application of such therapies and their efficacy spearheads the focus of recent research trends. Currently, widespread literature supports that these therapies may be beneficial for LBP management in discogenic disease. However, further prospective, randomized, controlled studies with an emphasis on follow-up beyond 1 year are necessary to bolster the incorporation of such modalities into standard practice.

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